The experience of long-term survival following allogeneic blood and marrow transplant (BMT) in New South Wales (NSW), Australia.

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

Faculty of Medicine

University of Sydney

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Declarations

Statement of originality

This is to certify that to the best of my knowledge the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I, Gemma Dyer, certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Statement of authorship

This thesis is a thesis by publication, with eleven papers presented as eleven of the thesis chapters. I certify that I am the first and corresponding author for seven of these papers (Chapters 6-12) and, and co-author for the remaining four papers (Chapters 5, 13-15). I have included in the appendix (Appendix A) a signed written statement from each co-author for each paper, and my supervisor, attesting to my contribution to each paper.

[redacted]

Gemma Dyer ***Date***

Supervisor statement of authorship

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements are correct.

[redacted]

Professor Ian Kerridge ***Date***

Synopsis

Background

Allogeneic blood and marrow transplant (BMT) is widely used for the treatment of life threatening malignant and non-malignant diseases in both adults and children. While it provides many patients with their best (and sometimes only) opportunity for long-term survival it is associated with significant mortality and morbidity. Over the past two decades significant improvements in outcomes post-BMT and advances in supportive care, immunobiology, chemoradiotherapy and donor selection have led to significant changes in BMT practice worldwide. These include an increase in frequency of BMT (relative to the population) for almost all indications, increased use of unrelated donors (versus related donors), and an increase in the age of patients eligible for BMT (largely a result of the introduction of reduced intensity conditioning for BMT). In Australia in 2016, 635 patients underwent allogenic BMT. Of these 42% were over 60 years of age and just over 70% were alive at one-year post-transplant. While this represents significant improvement over historical outcomes of BMT, long-term survivors experience significant long-term and late-effects of transplant including ongoing acute and chronic graft versus host disease (GVHD), increased risks of infections, chronic illnesses and secondary malignancies. Long-term BMT survivors also report twice as many medical problems compared to case matched controls, are 3.5 times more likely to develop a severe/life-threatening condition than siblings (this increases up to 4.7 times in those with GVHD) and have higher rates of hospitalisations and late mortality.

Despite increased recognition of the physiological and psychosocial adverse effects that confront survivors of BMT, and the publication of international recommendations for screening and preventative care post-BMT, little is known about the challenges faced by Australian BMT survivors. The aim of this study was to obtain comprehensive data regarding the late sequelae of BMT in an Australian setting, and to use that data to identify gaps in service provision provided to this vulnerable and high-risk group.

Methods

This study employed a cross-sectional descriptive survey design using both quantitative and qualitative methods to examine the physiological and psychosocial impacts of BMT and the quality of life (QoL) of allogeneic BMT survivors. The survey consisted of seven instruments; six validated instruments including the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4) survey, the Chronic Graft Versus Host Disease (GVHD) Activity Assessment – Patient Self Report (Form B), the Lee Chronic GVHD Symptom Scale, the Post Traumatic Growth Inventory,

the Fear of Recurrence Scale and the DASS 21, and one instrument, the Sydney Post-BMT Survey, purpose designed for the study. In total, participants were asked 518 questions which required a combination of tick box, free text and Likert scale responses and took approximately one hour to complete.

Eligible study participants were all allogeneic BMT survivors (age>18 years) who had undergone an allogenic transplant at one of the four adult allogeneic BMT sites in New South Wales (NSW) between January 2000 to December 2012, were at least 12 months post-BMT, could read and write English and had no objection to participating in the study. Participants who agreed were sent study packs in the mail and given the option to self-complete or complete the survey via a phone interview.

Main findings

Of the 669 BMT recipients alive at study sampling, 583 were contactable and agreed to receiving a study pack. Surveys were completed and returned by 441 (66% of total eligible, 76% of those contacted), while 17 (3%) explicitly declined after receiving the survey and 125 (21%) did not return the survey nor respond to a second round of phone calls.

Respondents consisted of 250 (56.7%) males and 191 (43.3%) females with a median age of 49 years. A total of 86.8% identified as being of Australian/European ethnicity and 72.2% lived in a major city. Most respondents (46.3%) were between 2-6 years post-transplant and (53.4%) has an underlying diagnosis of acute leukaemia. Many (66.9%) reported being in CR1/CR2 at the time of transplant, over half (56.9%) had a sibling donor, 86.4% received peripheral blood stem cells and almost half (48.7%) received myeloablative conditioning for their BMT, with 28.6% receiving T-cell depletion of some form.

Overall, the BMT survivors who responded to this study described extensive long-term adverse health related effects of BMT. In order of frequency, the BMT survivors reported chronic medical conditions including chronic GVHD (69.3%), iron overload (34.5%), osteoporosis/osteopenia (29.1%), cataracts (28.9%), hypertension (28.9%), hypercholesterolaemia (23.9%), recurrent upper respiratory tract infections (22.9%), diabetes mellitus (14.3%), any spinal/hip fracture (4.3%), hypothyroidism (4.1%), avascular necrosis (3.6%) and hyperthyroidism (1.3%). Second malignancies were experienced by more than a quarter of survivors, with skin cancer reported by 23%, oral cancer by 6% and 'other malignancies' by 4.9%. The most frequently reported infections were influenza-like-illness (38.4%) and herpes zoster (27.9%). Vaccination and health screening uptake were incomplete; only 31.8% of survivors had completed the re-vaccination schedule following BMT, 66.1% regularly saw a dentist or had an oral health check, 52.3% had a skin check, 63.4% had a pap smear, 53.3% had a mammogram,

32.4% had a bowel cancer check, and 36.2% had a prostate check. Almost half were overweight/obese, a third were inactive and over 50% of those >5 years post-transplant reported gastrointestinal symptoms which affected nutritional status.

BMT survivors also reported a range of adverse psychosocial impacts of transplant. Full-time employment fell from 65% pre-transplant to 32.5% post-transplant, the proportion of those in the lowest household income strata increased from 21% to 36% and almost 30% experienced anxiety and depression. Sexual dysfunction was reported by 66% of females and 51% of males. Complementary and alternative medicine (CAM) therapy was used by 54.1% and the median number of specialists involved in survivor's care was three, with the most common being dermatologists (60.3%), ophthalmologists (43.6%) and respiratory physicians (28.2%).

When asked about preferences for long-term care and follow-up, approximately 75% wished to have their follow-up in their transplant centre or in an expert facility linked to their transplant centre.

Conclusions

While significant progress has been made in BMT much of this has been in relation to patient selection, donor identification, conditioning chemo-radiotherapy, GVHD prophylaxis and treatment and supportive care for the prevention and management of acute complications of BMT, far less progress has been made in the prevention and management of long-term and late effects of allogeneic BMT. And despite publication of international and Australian guidelines for post-BMT care, long-term follow-up (LTFU) is often not standardised or readily accessible and as a consequence, many BMT survivors, their carers and families, do not receive the comprehensive care they need. The results of this research – which provides the most comprehensive account of allogeneic BMT survivorship in a contemporary Australian cohort – reveal the high incidence and broad range of physiological and psychosocial complications that adversely affect the health and functional status of BMT survivors.

While many of these results are similar to the extant international literature on the experience of survival following BMT and/or cancer therapy, some findings provide important and unique insights into the experience of BMT survival. Financial insecurity and occupational vulnerability is a clear and very real issue for long-term survivors of BMT, a significant number do not return to work due to ill-health (Paper 6, Chapter 10), there is unlikely to be a 'one size fits all' model of care (MOC) which suits all BMT survivors and BMT centres (Paper 2, Chapter 6), and currently available 'standard' measures of post-BMT QoL may not adequately ask the questions we need to ask in order to gain a rich picture of the challenges of survivorship (Paper 10, Chapter 14).

The results of the study reported in this thesis are critically important, both because they provide a comprehensive account of the experience of survival post-BMT and because they inform the development of policy, strategies for patient education and preventive practice, and the design and delivery of health care for long-term BMT survivors. In this regard it is critical that these results are translated into policy and practice as to not do so would further disadvantage this highly vulnerable group.

Acknowledgements

A number of people and groups need to be thanked for their assistance in seeing this thesis through to completion.

To the core research team: Dr Lisa Brice, Dr Nicole Gilroy and Prof Ian Kerridge - thank you for all your time and support in showing me the ropes.

To all the members of the New South Wales (NSW), Agency for Clinical Innovation (ACI), BMT LTFU working group, but specifically to my co-authors (in no particular order); Mrs Masura Kabir, Mrs Louisa Brown, Mrs Megan Hogg, Mrs Gillian Huang, Dr John Kwan, Prof David Gottlieb, A/Prof Stephen Larsen, Dr Matt Greenwood, Prof Christopher Ward (associate supervisor), Dr Grace Gifford, Mr Jeff Tan, Dr John Moore, Mr Julian Lindsay, Mrs Christina Poon, Mrs Jennifer Smith, Dr Jennifer Bradford and A/Prof Mark Schifter. Thank you for your input and patience – it's been a long road!

To the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) team: Mrs Leonia Wilcox, Mr Steven Tran, Dr Ian Nivison-Smith and Donna Aarons – thank you for always willingly answering all my data queries.

To the ACI BMT Network – thank you for supporting this research and funding survey printing and postage. This research would not have been possible without this assistance.

To the Northern Blood Research Centre (NBRC) who part-funded a number of publications for this study as well as my trip to Valencia, Spain to present my poster at the European Blood and Marrow Transplant (EBMT) conference (detailed in poster presentations below).

To my work colleagues in the team at eviQ, Cancer Institute NSW (CINSW), who have listened to me talk about this thesis for the past five years and dutifully read the papers when I circulated them post publication. A particular thank you to my manager Julia Shingleton who has always been supportive and generous with providing conference and study leave, and also part-funding for national conference attendance to present my work at a number of the annual Australian and New Zealand Haematology (HAA) and the Clinical Oncology Society of Australia (COSA) conferences (detailed in oral and post presentations below).

To my supervisors Prof Chris Ward (associate supervisor) and Prof Ian Kerridge (again - as my primary supervisor). Thank you for your enduring patience, I hope you know how much I have appreciated your time and support over the years. I have learnt so much, and I very much hope this is not the end of our working relationship.

To all the patients and carers who completed this (lengthy) survey. You have provided immeasurable assistant in furthering the care of BMT survivors now and into the future. I don't think a thank you is enough.

And lastly, to my family. To my mum and step-father who cleaned, cooked and baby sat as much as they could so I could have time to write. And to my husband Chris, my son Henry and my soon to be born little girl – no more PhD related stress and neglect, I promise!

Outcomes arising from this thesis

Publications

The following publications are presented in Part III, Chapters 5-15 of this thesis:

1. Gifford G, Gilroy N, **Dyer G**, Brice L, Kabir M, Greenwood M, Larsen S, Moore J, Hertzberg M, Kwan J, Huang G, Tan, Brown L, Hogg M, Ward C, Kerridge I. "The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia". *Blood and Marrow Transplantation* 2016;51(10):1361-8.
2. **Dyer G**, Gilroy N, Brown L, Hogg M, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Huang G, Tan J, Ward C & Kerridge I. "What They Want: Inclusion of Blood and Marrow Transplantation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia." *Biol Blood Marrow Transplant* 2016;22(4):731-743.
3. **Dyer G**, Gilroy N, Bradford J, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. "A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia." *Br J Haematol* 2016;172(4):592-601.
4. **Dyer G**, Larsen SR, Gilroy N, Brice L, Greenwood M, Hertzberg M, Kabir M, Brown L, Hogg M, Huang G, Moore J, Gottlieb D, Kwan J, Tan J, Ward & Kerridge I. "Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)." *Cancer Med* 2016;5(7):1702-16.
5. **Dyer G,** Larsen SR, Gilroy N, Brice L, Kabir M, Hogg M, Brown L, Hertzberg M, Greenwood M, Moore J, Gottlieb D, Huang G, Tan J, Ward C, Kerridge I. "Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia". *Australian Journal of Cancer Nursing* 2017:18(2):16-23.
6. **Dyer G,** Brice L, Gilroy N, Kabir M, Hertzberg M, Greenwood M, Larsen SR, Moore J, Gottlieb D, Huang G, Hogg M, Brown L, Tan J, Ward C, Kerridge I. "Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia". *Bone Marrow Transplant* 2018;53(7):926-31.
7. **Dyer G,** Brice L, Schifter M, Gilroy N, Kabir M, Hertzberg M, Greenwood M, Larsen SR, Moore J, Gottlieb D, Huang G, Hogg M, Brown L, Tan J, Ward C and Kerridge I. Oral health and dental morbidity in long-term allogeneic blood and marrow transplant survivors in Australia. Aust Dent J. 2018;63(3):312-9.
8. **Dyer G,** Gilroy N, Brice L, Kabir M, Gottlieb D, Huang G, Hogg M, Brown L, Greenwood M, Larsen S, Moore J, Hertzberg M, Tan J, Ward C, Kerridge I. "A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia" *Transplant Infectious Diseases,* In press (accepted 10th December 2018).
9. Lindsay J, Kabir M, Gilroy N, **Dyer G,** Brice, L, Greenwood M, Moore J, Hertzberg M, Larsen S, Kwan J, Brown L, Hogg M, Huang G, Tan J, Gifford G, and Kerridge I. "Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia". *Cancer Med.* 2016;5(12):3606-14.
10. Brice L, Gilroy N, **Dyer G**, Kabir M, Greenwood M, Larsen S, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Brice L, Huang G, Ward C. & Kerridge, I. "Haematopoietic stem cell

transplantation survivorship and QoL: is it a small world after all?" *Support Care Cancer*. 2017;25(2):421-7.

11. Smith J, Poon C, Gilroy N, Kabir M, Brice L, **Dyer G**, Hogg M, Greenwood M, Moore J, Hertzberg M, Brown L, Tan J, Huang G, Kwan J, Larsen S, Ward C and Kerridge I. "Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia". *Support Care Cancer.* 2017;25(1):137-44.

For Chapters 6-12 I am the principal author and I was responsible for co-designing the study, recruiting study participants, collecting and cleaning data, interpreting the results and drafting the manuscript.

For Chapters 5 and 13-15, I was responsible for co-designing the study, recruiting study participants, collecting and cleaning data, interpreting the results, and drafting the manuscript, but I was not the principal author.

A signed Statement of Contribution from all authors for all papers is in Appendix A.

Presentations

The following local, national and international presentations were given during my candidature:

Oral presentations:

1. **Dyer G,** Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan M, Brown L, Hogg M, Huang G, Tan J, Ward C and Kerridge I. Aug 2017. The experience of survival following allogeneic blood and marrow transplant (BMT) in NSW – what were the financial and occupational impacts?? St Vincents Hospital, Haematology Multidisciplinary Education session, **Sydney, NSW**.
2. **Dyer G,** Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan M, Brown L, Hogg M, Huang G, Tan J, Ward C and Kerridge I. Nov 2016. The occupational and financial impact of Blood and Marrow Transplantation (BMT) on long-term survivors of BMT in NSW, Haematology Society of Australia and New Zealand, the Australian & New Zealand Society of Blood Transfusion and the Australasian Society of Thrombosis and Haemostasis (Collectively HAA), 2016 Annual Scientific Meeting, **Melbourne, VIC** (Presented in the Presidential Symposium)
3. **Dyer G,** Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C and Kerridge I. Oct 2016. The occupational and financial impact of Blood and Marrow Transplantation (BMT) on long-term survivors of BMT in NSW, Victorian Comprehensive Cancer Centre (VCCC) Survivorship Conference, **Melbourne, ViC.**
4. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C and Kerridge I. Aug 2016. *The experience of survival following Blood and Marrow Transplant in NSW, Australia,* NSW Pharmacists Interest Group (Oncology and Haematology), **Sydney, NSW**
5. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Nov 2015. *The experience of survival following Blood and Marrow Transplant in NSW,* Clinical Oncology Society of Australia (COSA), **Hobart, TAS**.
6. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Oct 2015. *Secondary Cancers, Health Behaviour **and** Cancer Screening Adherence in survivors of Allogeneic Blood and Marrow Transplant (BMT) in NSW.* Cancer Institute NSW (CINSW), 2015 Innovations in Cancer Treatment and Care Conference, **Sydney, NSW**.
7. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Oct 2015. *The experience of survival following Blood and Marrow Transplant in NSW, Australia* , Cancer Institute NSW (CINSW), 2015 Innovations in Cancer Treatment and Care Conference, **Sydney, NSW**.
8. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Sept 2015. *Secondary Cancers, Health Behaviour and Cancer Screening Uptake in survivors of Allogeneic Blood and Marrow Transplant (BMT) in NSW*, University of Sydney Cancer Research Network and Lifespan Research Network, Cancer-Lifespan Research Symposium, **Sydney, NSW**.

9. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. July 2015. *The Experience of Survival following Allogeneic BMT in NSW; Cancer Screening Adherence, Sexuality and Fertility, Preferences for Long Term Care Delivery and Vaccination Adherence and Quality of Life*, NSW Agency for Clinical Innovation (ACI), BMT Network Senior Nurses Forum, **Sydney, NSW**.
10. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. July 2015. *The Experience of Survival following Allogeneic BMT in NSW; Cancer Screening Adherence, Sexuality and Fertility, Preferences for Long Term Care Delivery and Vaccinations post BMT,* CINSW, Research Forum, **Sydney, NSW**.
11. **Dyer G**. 2012. *Dancing in the Dark: Challenges to the design and delivery of long-term care following Blood & Marrow Transplantation, (*NSW ACI, Network to Network Australasian Clinical Networks 2012 Conference, **Sydney, NSW**.
12. **Dyer G**. 2012. *BMT Long Term Follow Up – Beyond Survival*, NSW ACI, BMT Network Annual Scientific Forum, **Sydney, NSW**.

Poster Presentations:

1. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. April 2016. *The experience of survival following Blood and Marrow Transplant in NSW, Australia,* European Blood and Marrow Transplant 42nd Annual Meeting, **Valencia, Spain**
2. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Nov 2015. *The Experience of Survival following Allogeneic BMT in NSW; physiological and psychological complications, and the functional status of survivors in Australia*, Clinical Oncology Society of Australia (COSA), 2015 Annual Scientific Meeting, **Hobart, TAS.**
3. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Oct 2015. *Secondary Cancer, Cancer Screening Adherence, Health Behaviours in Survivors of Allogeneic Blood and Marrow Transplant (BMT) in NSW,* Haematology Society of Australia and New Zealand, the Australian & New Zealand Society of Blood Transfusion and the Australasian Society of Thrombosis and Haemostasis (Collectively HAA), 2015 Annual Scientific Meeting, **Adelaide, SA**
4. **Dyer G**, Gilroy N, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. Oct 2015. *BMT Survivor Preference for Long Term Care in NSW,* HAA, 2015 Annual Scientific Meeting, **Adelaide, SA**

Ethical approval

The primary data collection reported in the results chapters of this thesis received approval from human research ethics committee:

Northern Sydney Local Health District Human Research Ethics Committee

The experience of survival following blood and marrow transplant in Sydney, Australia (HREC/12/HAWKE/209, NSLHD 1207-217M) (Appendix B):

- Site authorisation (Royal North Shore Hospital, 1307-222M)
- Site authorisation (Royal Prince Alfred Hospital, X13-0129)
- Site authorisation (Westmead Hospital, SSA/13/WMEAD/134)
- Site authorisation (St Vincents Hospital, SVH13/137)

List of Tables

Table 1: The publication status and journal of results chapters included in this thesis.

Table 1.1: Indications and disease status for BMT.

Table 3.1: Abbreviated summary recommendations for screening and prevention of late complications in long-term BMT survivors by time after transplant.

Table 3.2: BMT LTFU models of care employed across NSW at study commencement (2012).

Table 16.1: BMT LTFU Models of care employed across NSW at study completion (2018).

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List of Appendices

Appendix A: Statement of contributions for each publication presented in this thesis

Appendix B: Human research ethics committee approval letter for the study

Appendix C: Sydney post-BMT study invitation letter, Patient information sheet (PIS), Informed consent form (ICF)

Appendix D: Sydney post-BMT study survey instrument

Appendix E: Sydney post-BMT study clinical data form

List of Abbreviations

ABMTRR	Australasian Bone Marrow Transplant Recipient Registry
ACI	Agency for Clinical Innovation
ACTH	Adrenocorticotropic hormone
AIH	Australian immunisation handbook
Allo-graft	Allogeneic blood and marrow transplant
Allo-HSCT	Allogeneic haematopoietic stem cell transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AML	Acute myeloid leukaemia
APC	Antigen presenting cells
APN	Advanced Practice Nurse
ASBMT	American Society of Blood and Marrow Transplantation
AVN	Avascular necrosis
BMD	Bone mineral densitometry
BMI	Body mass index
BMT	Blood and marrow transplant, bone marrow transplant
BOS	Bronchiolitis obliterans syndrome
CALD	Culturally and linguistically diverse
CAM	Complementary and alternative medicine
cGVHD	Chronic graft versus host disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CNC	Clinical nurse consultant
CNS	Central nervous system
CNSp	Clinical nurse specialist
COP	Cryptogenic organising pneumonia
CR	Complete remission (can be CR1, CR2 and CR3+)
CRV	Community acquired respiratory virus
CVD	Cardiovascular disease
DASS21	Depression, anxiety and stress scale
DLI	Donor lymphocyte infusions
DM	Diabetes mellitus
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-barr virus
ECG	Echocardiography
ESRD	End stage renal disease
FACT	Foundation of Accreditation of Cellular Therapies
FACT –BMT	Functional assessment of cancer therapy - bone marrow transplant
GCSF	Granulocyte colony stimulating factor
GGT	Gamma-glutamyl transferase
GH	Growth hormone
GHPS	Gated heart pool scan

GI	Gastrointestinal
GP	General Practitioner
GVHD	Graft versus host disease (can be acute or chronic)
Gy	Gray
HBV	Hepatitis B virus
HCT	Haematopoietic cell transplant
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPC	Haematopoietic progenitor cells
HPCT	Haematopoietic progenitor cell transplant
HPV	Human papillomavirus
HSCT	Haematopoietic stem cell transplant
HSV	Herpes simplex virus
HTN	Hypertension
ICF	Informed consent form
IOM	Institute of medicine
IQR	Interquartile range
IST	Immunosuppressive therapy
IUGR	Intrauterine growth restriction
JACIE	Joint Accreditation Committee of the International Society for Cellular Therapy Europe
KCS	Keratoconjunctivitis sicca syndrome
LFTs	Lung function tests
LH	Liverpool Hospital
LHD	Local health district
LTFU	Long-term follow-up
MA	Myeloablative
MDR-GNB	Multi-drug resistant gram-negative Bacilli
MDT	Multidisciplinary team
MOC	Model of Care
MSAC	Medical Services Advisory Committee
NATA	National association of testing authorities, Australia
NIP	National immunisation program
NMA	Non-myeloablative
NP	Nurse Practitioner
NS	Nephrotic syndrome
NSW	New South Wales
ONJ	Osteonecrosis of the jaw
OR	Odds ratio
OTC	Over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical benefits scheme
PCP	Pneumocystis jiroveci pneumonia
PET	Positron emission tomography
PHN	Primary health network
PIS	Patient information sheet

PML	Progressive multifocal leukoencephalopathy
PNS	Peripheral nervous system
POF	Primary ovarian failure
PTLD	Post-transplant lymphoproliferative disorder
QoL	Quality of life
RIC	Reduced intensity conditioning
RNSH	Royal North Shore Hospital
RPA	Royal Prince Alfred Hospital
SCC	Squamous cell cancer
SOS	Sinusoidal obstruction syndrome
SVH	St Vincents Hospital
TBI	Total body irradiation
TB	Tuberculosis
TKI	Tyrosine-kinase inhibitor
TMA	Thrombotic microangiopathy
VMO	Visiting medical officer
VPD	Vaccine preventable disease
VZV	Varicella zoster virus
WBMT	Worldwide network for blood and marrow transplantation
WH	Westmead Hospital

Notes on key terms and nomenclature

Blood and marrow transplant (BMT) is a complex medical procedure in which haematopoietic stem cells are used to repopulate the haematopoietic system in patients after conditioning chemotherapy and/or radiotherapy has been administered(1). It can be autologous (the recipient is transplanted with their own cells) or allogeneic (the recipient is transplanted with cells from another person). This thesis presents research on allogeneic BMT survivors only.

The procedure was originally termed bone marrow transplant as haematopoietic stem cells had not been clearly described or characterised in either bone marrow or peripheral blood. It was presumed that haematopoietic transplant required cells from bone marrow, and harvesting bone marrow from the iliac crest was the only available method to retrieve haemopoietic progenitor cells (HPC) at the time (circa 1960s). As advances in cellular biology and pharmacology made clear that stem cells existed in many forms in different tissues, that haematopoietic progenitors were present not only in bone marrow but also in umbilical cord blood, and that haematopoietic stem cells could be mobilised into peripheral blood following administration of chemotherapy and growth factors, new terms were formulated; blood and marrow transplant (BMT), haematopoietic stem cell transplant (HSCT), haematopoietic progenitor cell transplant (HPCT), haematopoietic cell transplant (HCT), allo-graft.

These terms are synonymous and can be used interchangeably. For continuity, throughout this thesis the term BMT (blood and marrow transplant) has been used. In the manuscripts arising from this research the term most commonly used by the target journal has been utilised.

1. Bosi A, Bartolozzi B, Guidi S. Allogeneic stem cell transplantation. Transplant Proc. 2005;37(6):2667-9.

Thesis overview and structure

The research described in this thesis used a cross sectional survey design to examine the long term and late effects of survival following adult allogenic BMT in New South Wales (NSW). The study was conducted with the goal of describing the experience of survival following BMT and to improve the care provided to long-term survivors. The study had the following aims:

1. to describe the incidence and range of late complications of BMT and their association with the health and functional status of survivors;
2. to address limitations in BMT survivorship literature – particularly with regards to the financial, occupational and psychosocial impact of BMT;
3. to identify gaps in service provision provided to this vulnerable and high-risk patient group;
4. to provide better information to patients contemplating BMT, and to their families and guardians, regarding the possible long-term sequelae of BMT; and
5. to support clinical and health policy decision-making around BMT through the provision of more comprehensive data regarding late sequelae of BMT in an Australian setting

The research was conducted across four adult allogenic BMT centres across the state. At the time this represented all adult allogeneic sites in NSW who cared for long-term survivors of BMT. (There are now five centres). This research was completed by publication and is presented as a combination of chapters and stand-alone manuscripts. Accordingly, there is a degree of repetition throughout the results chapters in the background, methods and limitations sections of each manuscript (Chapters 5-15). Also, in addition to the discussion contained within each manuscript, a synopsis follows each paper which expands on the discussion points, provides an update in evidence (where relevant), and relates the findings to the implications that the data has on the education and care provided to long-term BMT survivors. The references forming part of each manuscript appear within the published article, while any additional references used in the synopsis are listed at the conclusion of the synopsis. Together, the manuscripts address the overall aims of the research outlined above and provide a comprehensive account of the experience of survival following BMT in NSW.

Chapter 1 provides a brief overview of BMT. It includes an overview of the history of BMT, a description of the developments in clinical application of BMT, conditioning regimens, therapeutic protocols and supportive care, and subsequent improvements in survival rates of BMT.

Chapter 2 provides an overview of the issues associated with survival following BMT by presenting a review of the national and international literature on the long-term and late effects of BMT by body system.

Chapter 3 provides an overview of the recommendations for BMT long-term follow up (LTFU) and a description of health care service provision for survivors of BMT in NSW. This chapter also outlines the aims of this thesis.

Chapter 4 presents the research methods used in this thesis including a description of the research sample, setting, instruments and data analysis.

Chapters 5 presents a published manuscript titled, 'The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia'. This manuscript provides an overall summary of the late effects of long-term survival following BMT in NSW.

Chapters 6 presents a published manuscript titled, 'What They Want: Inclusion of Blood and Marrow Transplantation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia'. This manuscript reports on BMT survivors preferred model of care (MOC) for the delivery of long term follow up (LTFU).

Chapter 7 presents a published manuscript titled, 'A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia'. This manuscript reports on the reproductive and sexual health of our long-term BMT survivors.

Chapter 8 presents a published manuscript titled, 'Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)'. This manuscript reports on the incidence of secondary cancers in long-term survivors of BMT and their subsequent adherence with Australian cancer screening guidelines.

Chapter 9 presents a published manuscript titled, 'Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia'. This manuscript reports on BMT survivor's engagement in high-risk health behaviours known to contribute to chronic non-communicable conditions.

Chapter 10 presents a published manuscript titled, 'Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia'. This manuscript reports on the long-term impact of allogeneic BMT on survivors' work status and household income.

Chapter 11 presents a published manuscript titled, 'Oral health and dental morbidity in long-term allogeneic blood and marrow transplant survivors in Australia'. This manuscript reports on the incidence and range of oral and dental disease occurring in long-term survivors of BMT.

Chapter 12 presents an in press manuscript titled, 'A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia'. This manuscript reports on the incidence of infectious diseases and the rate of re-vaccination adherence post-BMT.

Chapter 13 presents a published manuscript titled, 'Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia'. This manuscript reports on the use of complementary and alternative medicine (CAM) therapies in long-term survivors of BMT.

Chapter 14 presents a published manuscript titled, 'Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all?'. This manuscript provides a qualitative account of the lived experience of BMT survivorship.

Chapter 15 presents a published manuscript titled, 'Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia'. This manuscript reports on issues relating to nutrition, body weight and body image in long-term survivors of BMT, and their impact on survivors' quality of life (QoL).

Chapter 16 synthesises the main findings of the results chapters and discusses their implications for how LTFU care and education provided to BMT survivors might be improved. It presents the thesis conclusions and identifies key areas for future research, education, policy and healthcare reform.

Table 1 details the thesis results chapters and their publication status.

Table 1 The publication status and journal of results chapters included in this thesis

Chapter	Title	Publication status	Journal
5	The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia	Published	*Bone marrow transplantation*
6	What They Want: Inclusion of Blood and Marrow Transplantation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia	Published	*Biology of blood marrow transplantation*
7	A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia	Published	*British journal of haematology*
8	Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)	Published	*Cancer medicine*

9	Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia	Published	*Australian journal of cancer nursing*
10	Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia	Published	*Bone marrow transplantation*
11	Oral health and dental morbidity in long-term allogeneic blood and marrow transplant survivors in Australia	Published	*Australian dental journal*
12	A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia	In press	*Transplant infectious disease*
13	Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia	Published	*Cancer medicine*
14	Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all?	Published	*Supportive care in cancer*
15	Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia	Published	*Supportive care in cancer*

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PART I: Background and Literature Review

Chapter 1: History and Progress in Allogeneic BMT

Chapter 2: Long-term and Late Effects of BMT

Chapter 3: BMT Long-term Follow-up Service Provision in NSW

Chapter 1: History and Progress in Allogeneic Blood and Marrow Transplant

1.1. Chapter overview

This chapter provides an overview of allogeneic BMT. It includes a brief outline of the history of allogeneic BMT including a description of the developments in its application, conditioning regimens and supportive care, and subsequent improvements in survival rates following BMT.

1.2. Introduction

Allogeneic BMT is now established as a standard of care for a number of malignant and non-malignant diseases in adult and children. The notion that BMT could be used to replace a damaged or defective bone marrow is almost 80 years old, having been considered as a possible strategy to 'rescue' those exposed to ionising radiation during World War II(1). The history of the clinical development of BMT however, goes back 50 years, and has resulted from progress in immunobiology, pharmacology, pathology, and virology and, somewhat ironically, by a series of parallel socio-political events including the development of the pharmaceutical and nuclear weapons industries(2).

The emergence of allogeneic BMT

In 1975 Professor Donnall Thomas *et al* published an article in the New England Journal of Medicine describing renewed enthusiasm in the potential development of a new therapy; allogeneic bone marrow transplant (BMT)(3). This therapy, which involved infusing donor bone marrow into a recipient to colonise their failing bone marrow, was primarily developed for the treatment of immunological deficiencies, leukemias and victims of radiation accidents. Proof of concept was initially reported by George Mathé almost two decades previously when 5 (of 6) physicists accidently exposed to lethal doses of total body irradiation (TBI) at the Vinca Nuclear Centre in Belgrade, Yugoslavia in 1958 received human adult bone marrow which rescued them from 'radiation sickness'(4). Following successes in preventing the death of laboratory animals exposed to radiation(5), and Mathés' experience, clinical BMT appeared feasible and between 1959 and 1962, 154 transplants were performed worldwide(6). But while these cases established the safety of intravenous infusions of bone marrow and the possibility of successful engraftment of donor marrow, survival beyond 4-5 weeks post-transplant proved impossible(7). Consequently, enthusiasm for BMT as a potential treatment option for patients with bone marrow failure, immunodeficiency or cancer waned during the 1960s(6). It wasn't until Thomas' ground-breaking work in the late 1960s, particularly in identifying the importance of human leukocyte antigen (HLA) typing in recipient-donor matching, that genuine progress in allogenic transplantation was made. Over the next thirty years rapid progress was made in BMT(8, 9) and in 2012 the one millionth BMT was celebrated(10). Improvements in immunobiology,

chemoradiotherapy, supportive care and donor selection continue to improve the outcomes of BMT, with more and more patients becoming candidates for transplantation and surviving long term.

A brief of history of allogeneic BMT

1970s

Following translation into the clinic in the early 1970s BMT was a myeloablative (MA) procedure of 'last resort' for the treatment of acute leukaemia and aplastic anaemia, which used cyclophosphamide(11) and/or TBI(12) as conditioning and was performed only in patients who were young (less than 45 years of age) medically fit, and had a HLA-identical sibling. While this extended the lives of some recipients by months or even years, very few survived –a 1977 report documented that only thirteen of 100 patients with acute myeloid leukaemia (AML) survived more than one year, with most recipients dying of infection and acute GVHD(12). It was also in this decade, in 1975, that the first BMT was performed in Australia, in New South Wales (NSW)(13).

1980s

During the late 1970s and early 1980s an enormous amount of work was done internationally to better understand the causes of graft failure and GVHD, and to develop safe strategies for the prevention and treatment of GVHD. In the early 1980s randomised studies provided clear evidence for GVHD prophylaxis(14) – until that time a major cause of treatment failure and death – and methotrexate and cyclosporin became the agents of choice to prevent GVHD. At the about the same time, interest in T-cell depletion of the graft to prevent GVHD increased(15), leading to exploration of different conditioning protocols including busulfan plus cyclophosphamide(16) and TBI plus etoposide(17). Following progress in the development of immunosuppressive therapies and HLA typing, the application of BMT was further extended from those with HLA identical sibling donors to unrelated or mismatched donors including haplo-identical and HLA-matched unrelated donor transplants(18). (The first HLA-matched unrelated donor BMT for leukaemia was performed on ten year old Laura Graves on the 4th September 1979(19). She survived for two years before dying as a result of leukemic relapse. The first unrelated BMT for aplastic anaemia was less 'successful', it was performed in an eighteen year old male in 1972. Unfortunately he died of graft failure two months post-BMT(20)).

1990s

During the 1990s numerous advances were made in BMT, particularly in relation to the use of alternative stem cell sources, transplant conditioning and antimicrobial prophylaxis and treatment. Notable advances included the application of ganciclovir to prevent and treat cytomegalovirus (CMV) infection(21) – until that time a major cause of death post-BMT – and the development of

haematopoietic growth factors (particularly granulocyte colony stimulating factor (GCSF)), which enabled dose intensification of chemotherapy, facilitated haematopoietic reconstitution and enabled peripheral blood stem cell harvesting for use in allogeneic and/or autologous BMT(22). During this time cord blood stem cells were also identified as an alternative source of haematopoietic progenitors for BMT(23) – thereby increasing the number of patients, particularly among ethnic minorities, who could be candidates for BMT. Although initial outcomes following cord blood transplantation were compromised by high rates of graft failure, infection, relapse and chronic GVHD (cGVHD)(24), outcomes rapidly improved with broader application. Finally, recognition of the degree to which transplant outcomes were determined by T-cell immunocompetence, rather than by transplant conditioning intensity stimulated the introduction of reduced intensity conditioning (RIC) and non-myeloablative (NMA) conditioning for transplantation, the use of post-BMT donor lymphocyte infusions (DLI) to induce graft versus malignancy effects and the incorporation of donor chimerism assessment in post-BMT care(25, 26). The impact of these developments was profound as they allowed the age criteria for BMT to be raised to over 60 years, enabled transplantation in those with significant co-morbidity and enabled the development of programs for outpatient allogenic BMT(27).

2000s

While scientific and clinical innovation continued to improve outcomes following BMT and broaden its application, the expansion of BMT internationally and progress in its safety and efficacy also resulted from the development of systematic processes and structures to support it. The expansion, standardisation and integration of bone marrow/stem cell donor registries worldwide, and the expansion and standardisation of tissue typing, have substantially improved donor-recipient matching and BMT outcomes(28). At the same time, the adoption of quality standards as determined by the Foundation for the Accreditation of Cellular Therapies (FACT) in the US (founded in 1996) and the Joint Accreditation Committee of the International Society for Cellular Therapy Europe (JACIE) in Europe (founded in 1997) improved the collection, processing and administration of haemopoietic stem cell therapies(29).

Contemporary application of allogeneic BMT

Improvements in immunobiology, chemoradiotherapy, supportive care, donor selection and quality management have resulted in a significant change in BMT practices and survival worldwide. The American Society of Blood and Marrow Transplant (ASBMT) report that there are now ninety indications for which BMT is considered standard of care, or standard of care with clinical evidence available (but no large scale clinical trials), and standard of care for rare conditions (in which clinical trials are not feasible), and eighteen indications for which evidence for BMT is developing(30) (Table

1.1). BMT is now routinely offered for patients with lymphoid malignancies, myeloma, haemoglobin disorders, solid tumours, storage disorders and inborn errors of metabolism(31). Older patients who were previously ineligible for BMT now regularly undergo the procedure - of the 635 allogenic BMTs performed in Australia in 2016, 42% were over age 60(32). Increasing numbers of BMTs use stem cells from unrelated donors (rather than related donors) or haplo-identical donors.

As the indications for BMT have expanded, so too has the number of people who undergo the procedure. By 2012, over 400,000 allogenic BMTs had been performed worldwide(10). The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) records that 10,482 allogeneic BMTs were performed in Australia (since the registry began in 1992)(33). This increase in frequency is understandable as survival outcomes have improved considerably. From an initial zero percent survival beyond 4-5 weeks(3), the ABMTRR now report that one-year transplant related mortality (TRM) has decreased from 24.3% to 18.9% for unrelated BMTs, and from 12.1% to 11.6% for HLA-identical sibling transplants. They also report figures for one-year survival rates just over 70% (for all allogeneic BMTs (Figure 1)) and ten-year survival rates of up to 77% (depending on the primary disease and donor type)(33).

1.3. Summary

Allogeneic BMT is now clearly established as optimal care for adults and children with a range of malignant and non-malignant disorders. With improvements in donor selection, supportive care, chemoradiotherapy, immunobiology and quality management(34, 35) more and more people are undergoing this life saving procedure, and more and more recipients are living long term. While this represents remarkable progress, it does not come without consequence, as survival following BMT is associated with significant morbidity and mortality(36, 37). The long term and late effects of BMT are discussed in the next chapter, followed by a description of the international long-term follow up (LTFU) screening and preventive care guidelines and a discussion regarding current health care service provision provided to BMT survivors in NSW in Chapter 3.

Table 1.1: Indications and disease status for BMT(30)

Indication and Disease Status	Allogeneic BMT	Autologous BMT
Acute myeloid leukemia		
CR1, low risk	N	C
CR1, intermediate risk	S	C
CR1, high risk	S	C
CR2	S	C
CR3+	C	C
Not in remission	C	N
Acute promyelocyte leukemia		
CR1	N	N
CR2, molecular remission	C	S
CR2, not in molecular remission	S	N
CR3+	C	N
Not in remission	C	N
Relapse after autologous transplant	C	N
Acute lymphoblastic leukemia		
CR1, standard risk	S	C
CR1, high risk	S	N
CR2	S	C
CR3+	C	N
Not in remission	C	N
Chronic myeloid leukemia		
Chronic phase 1, TKI intolerant	C	N
Chronic phase 1, TKI refractory	C	N
Chronic phase 2+	S	N
Accelerated phase	S	N
Blast phase	S	N
Myelodysplastic syndromes		

Indication and Disease Status	Allogeneic BMT	Autologous BMT
Hodgkin lymphoma		
CR1 (PET negative)	N	N
CR1 (PET positive)	N	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Diffuse large B-cell lymphoma		
CR1 (PET negative)	N	N
CR1 (PET positive)	N	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	C	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Follicular lymphoma		
CR1	N	C
Primary refractory, sensitive	S	S
Primary refractory, resistant	S	N
First relapse, sensitive	S	S
First relapse, resistant	S	N
Second or greater relapse	S	S
Transformation to high grade lymphoma	C	S
Relapse after autologous transplant	C	N

Low/intermeditate-1 risk	C	N
Intermediate-2/high risk	S	N
Therapy related AML/MDS		
CR1	S	N
Myelofibrosis & myeloproliferative diseases		
Primary, low risk	C	N
Primary, intermediate/high risk	C	N
Secondary	C	N
Hypereosinophilic syndromes, refractory	R	N
Plasma cell disorders		
Myeloma, initial response	D	S
Myeloma, sensitive relapse	C	S
Myeloma, refractory	C	C
Plasma cell leukaemia	C	C
Primary amyloidosis	N	C
POEMS syndrome	N	R
Relapse after autologous transplant	C	C
T-cell lymphoma		
CR1	C	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	C	S
First relapse, resistant	C	N
Second or greater relapse	C	C
Relapse after autologous transplant	C	N
Lymphoplasmacytic lymphoma		
CR1	N	N

Mantle cell lymphoma		
CR1/PR1	C	S
Primary refractory, sensitive	S	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Solid tumours		
Germ cell tumour, relapse	N	C
Germ cell tumour, refractory	N	C
Ewing's sarcoma, high risk	N	C
Breast cancer, adjuvant high risk	N	D
Breast cancer, metastatic	D	D
Renal cancer, metastatic	D	N
Non-malignant diseases		
Severe aplastic anaemia, new diagnosis	S	N
Severe aplastic anaemia, relapse/refractory	S	N
Fanconi's anaemia	R	N
Dyskeratosis congenita	R	N
Sickle cell disease	C	N
Thalassemia	D	N
Hemophagocytic syndromes, refractory	R	N
Mast cell diseases	R	N
Common variable immunodeficiency	R	N
Wiskott-Aldrich syndrome	R	N

Primary refractory, sensitive	N	C
Primary refractory, resistant	R	N
First or greater relapse, sensitive	R	C
First or greater relapse, resistant	R	N
Relapse after autologous transplant	C	N
Burkitt's lymphoma		
First remission	C	C
First or greater relapse, sensitive	C	C
First or greater relapse, resistant	C	N
Relapse after autologous transplant	C	N
Cutaneous T-cell lymphoma		
Relapse	C	C
Relapse after autologous transplant	C	N
Plasmablastic lymphoma		
CR1	R	R
Relapse	R	R

Chronic granulomatous disease	R	N
Multiple sclerosis	N	D
Systemic sclerosis	N	D
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn's disease	N	D
Polymyositis-dermatomyositis	N	D
Chronic lymphocytic leukemia		
High risk, first or greater remission	C	N
T-cell prolymphocytic leukemia	R	R
B-cell, prolymphocytic leukemia	R	R
Transformation to high grade lymphoma	C	C

N, not generally recommended; C, standard of care, clinical evidence available; S, standard of care; R, standard of care, rare indication; D, developmental.

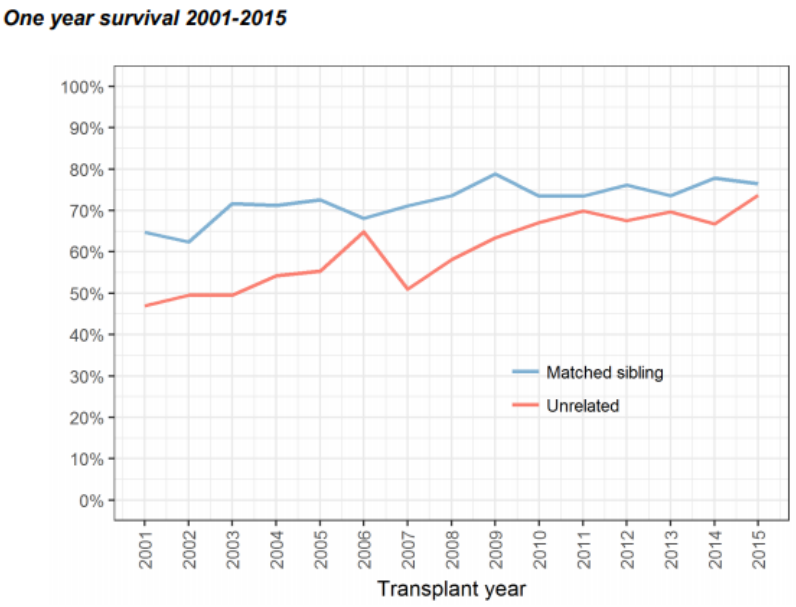

Figure 1: One-year survival for all Australian and New Zealand allogeneic BMTs performed in recipients aged 16+(33)

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Chapter 2: Long-term and Late Effects of BMT

2.1. Chapter overview

Chapter 2 provides an overview of the long-term and late effects of allogeneic BMT including their incidence, and risk factors by body system.

2.2. Long term and late effects of allogeneic BMT

Over the past two decades increasing attention has been devoted to the long term and late effects of cancer therapy, with increasing recognition of the substantial morbidity and mortality experienced by survivors of cancer therapy. A wealth of quantitative and qualitative literature has documented the experience of survival following cancer, described the unmet needs of cancer survivors and supported the development of survivorship programs(1-5).

Following research done in patients with solid cancer and leukaemia, and extensive evidence in childhood cancer survivors, over the last decade there has been a burgeoning literature on the long-term and late physical and psychosocial effects of BMT and their impact upon BMT survivors. The literature demonstrates that survivors experience twice as many medical problems compared to case matched controls, are 3.5 times more likely to develop a severe/life-threatening condition than siblings (this increases up to 4.7 times in those with GVHD)(6, 7), and have higher rates of hospitalisations and late mortality(8). In numerical terms, the fifteen-year cumulative incidence of a BMT survivor experiencing any chronic health condition is 71% and of a severe/life-threatening condition or death due to these chronic conditions is 41%(9). The collective impact is profound with BMT survivors experiencing a 30% lower life expectancy than a matched population cohort(10, 11). While many survivors rate their QoL highly at two years post-transplant, many BMT recipients experience considerable difficulty coping with the short, medium and long term physical and psychological sequelae of BMT and with the uncertainties of their prognosis.

Late complications are generally defined as any complication occurring from three months post-transplant and are often separated into ‘delayed’ (3mths to 2 years), ‘late’ (2-10 years) and ‘very late’ (>10 years)(12). These complications, which occur as a consequence of exposure to chemo-radiotherapy and the impact of chronic GVHD (cGVHD) (and its treatment) affects every body system. Major complications of BMT include: cardiac impairment(13), endocrine dysfunction(14), compromised fertility(15), compromised lung and respiratory function(16), renal impairment(17), liver dysfunction(18, 19), skeletal disorders(20, 21), cGVHD(22, 23), immunodeficiency and

infection(24, 25), secondary malignancies(26, 27), ocular side effects(28), neurocognitive effects(29), compromised functional status(30, 31), unemployment or underemployment(30), and compromised QoL(32). Each of these complications are further detailed below.

2.3. Cardiac and circulatory disease

All forms of vascular disease, including cardiovascular, cerebrovascular and peripheral vascular disease, occur with greater frequency in BMT survivors(33). Cardiac dysfunction also frequently occurs in survivors of BMT including cardiomyopathy, congestive heart failure (CHF), valvular dysfunction, ischaemic heart disease (acute myocardial infarction (AMI) or angina), arrhythmia and pericarditis(34).

In a large study of late mortality post BMT it was found that 3% of treatment related deaths were related to cardiac toxicity. This was found to represent a more than two-fold greater risk of premature death than the general population(11). Cardiovascular death, in a separate cohort study of two-year post BMT survivors, had an adjusted incidence rate difference of 3.6 per 1000 person-years. Survivors were also found to have an increased cumulative incidence of ischemic heart disease, cardiomyopathy or heart failure, stroke, vascular diseases, and rhythm disorders and an increased incidence of related conditions that predispose toward more serious cardiovascular disease (CVD) (hypertension (HTN), renal disease, dyslipidaemia, and diabetes mellitus (DM))(35).

The leading transplant related risk factors for cardiac toxicity following BMT are cumulative exposure to anthracyclines, TBI or chest irradiation as part of the treatment of the primary malignancy or conditioning regimen, cGVHD, age at BMT and cardiac co-morbidity. Gender, non-cardiac co-morbidities and standard cardiovascular risks are also contributing factors(36). A clear relationship between post-transplant cardiovascular risk factors and late coronary and CVD in long-term survivors has been demonstrated(13, 37). These late cardiac events may appear years and even decades after BMT, with the cumulative incidence being reported as high as 22% twenty-five years after BMT.

Established risk factors for CVD, such as HTN, dyslipidaemia, DM, smoking and physical inactivity are associated with a higher risk of complications post-transplant due to the high prevalence of metabolic syndrome reported among BMT survivors(33, 38). Allogeneic BMT recipients have showed a 2.2–fold increased risk of metabolic syndrome, compared to age and gender matched controls(39, 40), increasing their risk of CVD. Prevalence of dyslipidaemia ranges from 8.9% to 56%, depending on the presence of comorbid conditions or other risk factors(41, 42). It has also been found that BMT

survivors were 3.65 times and 2.06 times more likely to report DM and HTN respectively, when compared to siblings(43).

Importantly, two or more cardiovascular risk factors (obesity, dyslipidaemia, HTN, and DM) after BMT is associated with a 5.2-fold increased risk of late CVD, pre-HCT chest radiation exposure is associated with a 9.5-fold greater risk of coronary artery disease and the presence of multiple post-BMT cardiovascular risk factors is associated with a 19.5-fold risk of late cerebrovascular disease(44, 45).

2.4. Endocrine dysfunction

Endocrine dysfunction occurs commonly post-BMT as a result of conditioning chemoradiotherapy prior to BMT, cumulative chemo/radiation exposure – including from treatment prior to BMT, cGVHD and prolonged corticosteroid exposure(46, 47). Endocrine dysfunction can be either primary, as a consequence of endocrine organ failure, or secondary to hypothalamic-pituitary axis dysfunction.

Endocrine complications of BMT, which are often more profound in patients transplanted in childhood or adolescence, include short stature(19%)(46), hypogonadism (25%), hypothyroidism, hyperthyroidism, hypoadrenalism, osteoporosis, infertility, weight problems (both over- and underweight) and other metabolic risks including dyslipidaemia and DM(47, 48). Thirty-four to thirty-nine percent have one or more indicators of metabolic syndrome(39, 49).

Hypothalamic-pituitary dysfunction

Hypothalamic-pituitary dysfunction commonly occurs following BMT as a complication of cranial irradiation or TBI, and results in gonadal dysfunction, hypothyroidism, adrenal failure and growth hormone (GH) deficiency. Survivors who are irradiated with doses greater than 18 Gray (Gy) are at greatest risk, but hypothalamic-pituitary dysfunction can occur at lower doses(48).

Adrenal insufficiency is particularly important because unrecognised ACTH deficiency resulting in secondary adrenal insufficiency can be life-threatening and may be easily misdiagnosed or underdiagnosed because it often presents in a ‘non-specific’ fashion (for example, fatigue).

While GH deficiency is of little clinical significance in adults, children and adolescents who undergo BMT frequently have compromised growth and growth velocity – depending upon their pre-transplantation therapy and whether their transplant conditioning includes TBI(46, 48).

Gonadal dysfunction

Gonadal dysfunction is highly prevalent in BMT survivors occurring in up to 92% of males and 99% of females(46). Conditioning chemotherapy (particularly alkylating agents), TBI and cGVHD contribute to the risk of gonadal dysfunction post BMT(47, 48). While the clinical manifestations of gonadal dysfunction are highly dependent on the BMT recipient's age and gender, potential effects include pubertal failure, infertility, sexual dysfunction, osteoporosis, fragility fractures and a range of troublesome symptoms including menopausal symptoms (in women), hot flushes, night sweats, mood disorders, insomnia, lack of concentration, arthralgia, impaired sexual function and cognitive impairment(50).

Thyroid disease

Thyroid disease occurs commonly after BMT including clinical hypothyroidism, subclinical/compensated hypothyroidism, hyperthyroidism, autoimmune thyroid disease, benign thyroid nodules and thyroid cancer.

Clinical hypothyroidism occurs with a two-fold greater incidence in BMT survivors when compared to sibling controls(51), and has been reported in up to 50% of patients whose conditioning includes TBI and up to 11% in those who receive MA conditioning with busulfan and cyclophosphamide(33). Subclinical/compensated hypothyroidism generally occurs 4-7 years post-BMT but may be present in 7% - 15% of patients in the first year after transplantation(46). Hyperthyroidism is less common in long term survivors of BMT, generally occurring earlier post-BMT with 15% of survivors at 12-18 months post BMT being affected(47, 48). Autoimmune thyroid disease also commonly occurs post-BMT as a consequence of passive transfer from the donor and immune dysregulation associated with cGVHD(52, 53).

The incidence of both thyroid nodules and thyroid cancer is substantially increased in BMT survivors, particularly in those who have had head and neck irradiation prior to BMT and TBI conditioning. The risk of malignancy is higher in those patients exposed to radiation at a younger age(54).

Metabolic disease

Obesity, DM and dyslipidaemia all occur with greater frequency in BMT survivors. DM, in particular, occurs in up to 20% of survivors, with studies demonstrating that BMT survivors have an odds ratio (OR) of 3.65 of developing DM compared to their siblings when controlled for age, sex, race and body mass index (BMI)(47, 48, 55). TBI containing transplant conditioning, cGVHD, prolonged corticosteroid exposure and/or weight gain (corticosteroids, mobility), and non-Caucasian ethnicity all contribute to

these metabolic risks(43). Abdominal irradiation performed pre-transplant also increases the likelihood of pancreatic, endocrine and exocrine insufficiency post-BMT(56).

2.5. Genital disease and sexual function

Genital disorders, sexual dysfunction and infertility are some of the most common and confronting challenges facing long-term survivors of BMT. These complications occur as a result of a range of interrelated factors including genital cGVHD, immunosuppression, human papillomavirus (HPV) infection, premature ovarian and testicular failure, interruption to the sexual response cycle, disruption of identity, relationship breakdown, social isolation and psychological morbidity including anxiety and depression post BMT. The impact of these complications is profound – dramatically compromising the QoL, social functioning and relationships of many of those affected(50).

Genital cGVHD

Genital cGVHD is commonly reported post-BMT, with international studies suggesting that up to 50% of women surviving BMT experiencing some degree of vaginal cGVHD and 13% of men experiencing cGVHD of the penis(57-59). In women, genital cGVHD can affect the vulva and vagina and may present with lichen planus-like changes including erosions, leukokeratosis and vaginal scarring/stenosis. Vulvovaginal cGVHD may be asymptomatic (thus delaying diagnosis and treatment) or cause a range of symptoms including vaginal dryness, burning, itching, difficulty with urination, dyspareunia, cyclic pain and amenorrhea (due to haematocolpos/haematometra)(60). In men, penile cGVHD may cause balanoposthitis, phimosis, lichen sclerosis-like changes, Peyronie's disease and erectile dysfunction(59).

Primary ovarian failure

Primary ovarian failure (POF) is almost ubiquitous following BMT – occurring in up to 90% of women who undergo BMT during their reproductive years – principally as a consequence of conditioning chemotherapy, TBI and cGVHD(60, 61). Post-transplant ovarian failure results in infertility in most-BMT survivors of reproductive age, increases the likelihood of osteoporosis and fragility fractures and causes a range of bothersome symptoms, including hot flushes, night sweats, mood disorders, insomnia, lack of concentration, arthralgia, impaired sexual function and cognitive impairment(50).

Male gonadal failure and impaired spermatogenesis

The vast majority of men (approximately 90%) will develop azoospermia, oligospermia and sperm motility problems as a consequence of high-dose conditioning chemotherapy, TBI and cGVHD(62). While some men (up to 25%) will show some evidence of recovery (particularly those who are aged <30 years at the time of transplant)(63) many will remain hypogonadal and infertile.

Genital secondary cancers and HPV infection

As with other viral infections, HPV occurs with a greater frequency in BMT survivors than in the general population. In those infected, HPV can cause genital warts, cervical, vaginal, vulvar and anal intraepithelial neoplasia and anogenital squamous cell cancer (SCC). The risk of cervical SCC in female BMT survivors is reported to be thirteen times greater than that of the general population(64). Genital malignancy also occurs with much greater frequency in male BMT survivors, with premalignant or malignant conditions reported in 8.4% of men with genital lichen sclerosis(65).

Sexual dysfunction

Up to 80% of long-term BMT survivors will experience some form of sexual dysfunction(50, 66). Sexual symptoms include decreased interest, erectile dysfunction, anejaculation, retrograde ejaculation and anorgasmia. A range of physical and psychosocial factors contribute to the likelihood and severity of sexual dysfunction post BMT, including: gonadal insufficiency, genital disease, altered body image, illness and debility, relationship dysfunction, and anxiety and depression – all of which can impact upon sexual desire, libido, arousal and orgasm(59, 67).

Fertility and reproduction

Almost all patients will become infertile following BMT, with up to 90% of patients who undergo BMT during their reproductive years developing primary ovarian or testicular failure as a consequence of high-dose conditioning chemotherapy, TBI, high dose steroids, severe infection, cGVHD, older age, long-term immunosuppression and pre-BMT therapy (particularly alkylating agents and pelvic irradiation)(60). Hypothalamic-pituitary dysfunction and secondary hypogonadism, thyroid dysfunction and effects on other reproductive organs (for example, the uterus) may also contribute to subfertility and infertility.

While some patients – particularly those aged less than 30 years at the time of BMT and those who did not receive TBI as part of their conditioning therapy – will regain some gonadal function, the vast majority of women will enter premature menopause and the vast majority of men will have persistent azoospermia, oligospermia and sperm motility problems(60, 63).

A small number of women (0.6%) will successfully achieve a pregnancy and have a child following BMT(68, 69). While children born to survivors of BMT do not have higher than expected rates of cancer or genetic disorders, female survivors experience a range of adverse pregnancy outcomes including increased rates of intrauterine growth restriction (IUGR), low birth rate, preterm delivery, spontaneous abortion (due to decreased uterine volume), placental abruption, uterine rupture and caesarean section deliveries compared with the general population(70-72).

2.6. Lung and respiratory dysfunction

Late onset post-BMT pulmonary complications occur in up to 60% of BMT recipients(73) – principally as a consequence of cGVHD. Pulmonary disease is a major cause of increased morbidity and mortality including bronchiolitis obliterans syndrome (BOS), cryptogenic organising pneumonia (COP), idiopathic pneumonia syndrome and sinopulmonary infections(74, 75). Asthma has also been reported post-BMT from atopic asthmatic donors(76).

BOS is reported to occur in 14% of long-term survivors of BMT who develop cGVHD(77) and prognosis is poor (a 13% five-year survival rate has been reported)(78). COP has been reported in up to 10.3% of unrelated donor transplants(79) but has a much better prognosis than BOS, up to 80% will be cured(80).

In addition to cGVHD, other risk factors for lung disease post-BMT include pre-existing lung disease, a history of pneumonitis, infection, smoking history, MA conditioning chemotherapy, radiation exposure – including TBI and pre-transplant thoracic radiotherapy – advanced disease at BMT, hypogammaglobulinaemia, and prolonged immune compromise(33, 46).

2.7. Renal impairment

Chronic kidney disease (CKD) has been reported in 5-65% of survivors of allogeneic BMT(81, 82). It typically presents as one of three distinct clinical entities: thrombotic microangiopathy (TMA), nephrotic syndrome (NS), and idiopathic or GVHD-related CKD(83). Radiation nephritis may also occur following TBI. One retrospective study of 266 patients demonstrated that the cumulative incidence increases between five and ten years after BMT(84), and in another report, a case matched control study, it was shown that BMT survivors who develop CKD are at increased risk of mortality compared to non-BMT survivors, with mortality approaching 90% for those who progress to end stage renal disease (ESRD) requiring dialysis(85). For these reasons kidney transplantation is sometimes performed for ESRD after BMT(86).

Risk factors for the development of CKD in BMT survivors include pre-BMT renal disease, primary diagnosis (e.g. myeloma), older age at BMT, transplant-related renal toxicity resulting from sinusoidal obstruction syndrome (SOS), haemorrhagic cystitis, endothelial damage from acute and/or chronic GVHD and infection, treatment related renal toxicity resulting from chemotherapy exposure, TBI, calcineurin inhibitors and antimicrobial drugs, polyoma BMT virus nephropathy, and increased rates of chronic illness post-BMT including HTN and DM(56, 83, 87).

2.8. Liver dysfunction

Late liver complications have been reported in up to 72% of BMT survivors(88), most commonly as a consequence of cGVHD, reactivation of viral hepatitis (HBV and HCV), prior SOS, iron overload from transfusions and/or ineffective erythropoiesis and/or hepatotoxic medications(46, 88, 89). Hepatic cGVHD occurs in 90% of patient with cGVHD(88) and may manifest with asymptomatic elevation of serum alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), slowly progressive cholestatic jaundice or acute hepatocellular injury(90).

Infection with HCV is also associated with greater morbidity and mortality in BMT survivors. Cirrhosis and end-stage liver disease related to chronic HCV infection has been reported to occur in approximately 35% of long-term survivors. A faster rate of progression to end stage disease has also been reported in BMT recipients when compared to case matched controls(90); the 20-year cumulative incidence for death due to liver complications is 6.1%, and for severe liver complications (death from liver failure, cirrhosis and liver transplantation) it is 11.7%(91).

Long-term survivors also appear to have an increased incidence of gallstones and gallstone complication. This is likely related to myeloablative conditioning causing calcium bilirubinate microlith formation. Chronic cyclosporine or tacrolimus use can also lead to biliary symptoms and acute pancreatitis(90).

2.9. Skeletal disorders

BMT survivors have an increased risk of bone disease post-transplant, with osteopenia and osteoporosis incidence ranging between 3–70%(92, 93) and fractures reported in 8%(94). When compared to age and sex matched general population controls, female BMT survivors have an eight-fold increased risk of fracture and males have a seven- to nine-fold increased risk of fractures in those aged 45-65 years(94).

Multiple risk factors contribute to bone loss following BMT, including conditioning chemo-radiotherapy, GVHD, the use of glucocorticoids and calcineurin inhibitors (especially cyclosporine), gonadal failure, malabsorption, chronic renal dysfunction, malnutrition, vitamin D deficiency, weight loss and immobility. Glucocorticoid therapy, in particular, is associated with a markedly increased risk of bone loss, particularly in the first few months of use. Glucocorticoids also increase fracture risk, with fractures occurring at a higher bone mineral densitometry (BMD) than occurs in postmenopausal osteoporosis(92). In each of these cases, impaired bone mineralisation occurs through a range of different physiological processes including disturbances of calcium and vitamin D homeostasis, osteoblast and osteoclast dysfunction, and growth and gonadal hormone secretion(95). Collectively these contribute to rapid bone loss post-BMT, which is maximal in the first 3–6 months following transplant(96).

Osteonecrosis or avascular necrosis of bone (AVN) (most commonly affecting the hip, knees, ankles and shoulders) also occurs with increased frequency after BMT. Although the literature on AVN in adult survivors of BMT is limited, AVN is reported to occur in 4–19% of survivors with a cumulative incidence of 3–10% at five years post-BMT(95).

A number of risk factors for AVN have been identified, including the use of glucocorticoids, a history of acute lymphoblastic leukaemia (ALL), TBI, excessive alcohol intake, cGVHD, and being female. In BMT patients the risk of osteonecrosis is dependent upon the duration and cumulative dose of glucocorticoids as well as the presence of cGVHD(97). The risk is low (<3%) in patients treated with doses of prednisone less than 15–20mg/day(98).

2.10. Oral and dental disease

Late complications involving the oral cavity are common post BMT. Survivors often report oral pain, dryness, odynophagia, dysphagia and sensitivity (irritation from normally tolerated spices, foods, liquids or flavours) that may limit oral intake and they may have restricted mouth movement. Many of these issues are related to cGVHD, of which the oral cavity is the most commonly affected organ(99, 100). The presence of lichen planus, hyperkeratotic plaques, mucosal erythema, atrophy, mucoceles (due to inflammation and obstruction of the salivary gland ducts), pseudomembranes, ulcers, and restrictions due to peri-oral fasciitis or skin sclerosis are also common, and in some cases are diagnostic of oral cGVHD. Other causes of oral and dental complications post BMT include the late effects of the conditioning regimen, long-term immunosuppression, and medications which can contribute to xerostomia (e.g. antidepressants, anti-histamines, diuretics, muscle relaxants and some analgesics).

The most important risk factors for oral and dental complications include oral cGVHD, irradiation to the head and neck region, long-term immunosuppressive therapy (IST), DM, sicca syndrome, presence of chronic and latent infections, patient age at BMT and adequacy of post-BMT dental care(46, 101).

Oral function is essential for many aspects of normal daily activities and any compromise can profoundly impact QoL, overall health and psychosocial wellbeing(102, 103). cGVHD, in particular, may cause a range of mucosal abnormalities including a marked risk of development of SCC of the oral mucosa and xerostomia(104, 105). These issues further increase risks to oral and dental health by causing significant pain affecting alimentation, and nutritional status and by increasing the risk of dental caries, periodontal disease and oral infections(99, 101, 103).

BMT survivors are also at risk for osteonecrosis of the jaw (ONJ). This occurs following invasive dental procedures such as dental extractions and is associated with the long-term use of anti-resorptive therapies used for the prevention of osteoporosis, whether this is age related or iatrogenic from long-term and/or high dose glucocorticoid use or direct use of anti-absorptive agents in diseases such as multiple myeloma for the management and prevention of hypercalcaemia or lytic bone lesions(106). Long-term bisphosphonate use is associated with ONJ, particularly zoledronic acid and denosumab(107).

2.11. Immunodeficiency and infection

Infectious complications are exceedingly common following allogeneic BMT and are an important cause of life-threatening emergencies and death. In the first year post BMT, infection contributes to death in up to 61% of recipients(108) and in those who survive 15 years post-BMT, infection is the cause of death in 11% of those without cGVHD(11). The major risk factor for late infection causing death post BMT, is however, cGVHD(109).

Immunodeficiency and infection following BMT occur as a consequence of neutropenia, immune ablation and immunosuppression related to disease processes, splenectomy, conditioning chemo-radiotherapy and treatments for cGVHD. Specifically, BMT recipients experience decreased thymic function, restricted T-cell repertoires, decreased CD4 T-cell numbers, decreased regulatory T-cells, decreased B-cells, or increased immature B-cells, decreased splenic size and functional hypersplenism(110-112). Bacterial, fungal and viral infections all occur post BMT and further transplant and patient related risk factors include cord blood, HLA-mismatched or T cell-depleted graft, disease status at BMT, cGVHD with prolonged immunosuppression, older age, and a history of oncogenic viruses(46, 113).

International and national guidelines for prevention and management of post-BMT infection include recommendations for bacterial, viral, fungal, regionally limited/rare infections, infection prevention and control, safe living after BMT, and vaccination post-transplant(114). A large number of pathogens are associated with infection post-BMT including: Streptococcus pneumoniae, Viridans Streptococci, Haemophilus influenzae type b, Bordetella pertussis, Cytomegalovirus (CMV), Epstein-Barr virus EBV), Herpes simplex virus (HSV), Varicella Zoster virus (VZV), community-acquired respiratory viral (CRV) infections including Influenza, Respiratory Syncytial virus, Human Metapneumovirus, Parainfluenza virus, Adenoviruses, Polyomavirus BK and JC, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus (HCV), Herpesvirus 6, 7 and 8, Human Immunodeficiency virus (HIV), Fungal, yeast infections, mould infections, Mycobacterium tuberculosis (TB), Pneumocystis jiroveci Pneumonia (PCP), Toxoplasma gondii, Nocardia infection, Strongyloides stercoralis, Trypanosoma cruzi, Leishmania, Malaria, Legionnella, Methicillin-Resistant S. aureus, VRE, multi-drug resistant gram-negative Bacilli (MDR-GNB), Clostridium difficile, Rotavirus, Norovirus, and Astrovirus.

While immune reconstitution occurs post BMT, full T-cell immunity may take up to two years to be re-established or longer if cGVHD persists. Immunocompetence is defined as the ability to receive live vaccines (re-vaccination) which is an important infection prevention strategy post-transplant(114).

2.12. Second malignancies

One of the most tragic late effects of BMT is the development of a second malignancy. Typically, there are three types of secondary malignancies post BMT; secondary leukaemia and lymphomas, post-transplant lymphoproliferative disorders (PTLD) and secondary solid tumours(115). Most PTLDs occur within the first months after BMT, while solid tumours and leukaemia mostly occur years to decades after transplant and increase in prevalence with time post-BMT(116).

Almost all cancers have been reported post BMT including breast, skin, oropharynx, thyroid, oesophagus, lung, soft tissue, brain, melanoma, liver, anogenital, bone and connective tissue(64, 65, 117-119). B-cell neoplasms and Hodgkin's disease have also been described but are rare(116). Incidence rates for PTLD are up to 8.1%(120), breast cancer has a cumulative incidence of 17% at twenty five years in those who have received TBI(119), and secondary leukaemia or myelodysplasia is reported to be 4% at 7 years post BMT(121) and to be of donor-derived origin in many instances(122). When compared to the general population, survivors of BMT develop new solid cancers at twice the expected rate, with this risk increasing over time, being three-fold at fifteen years post BMT(123) with no plateau(118).

Risk factors for secondary malignancies include younger age at BMT, gender (depending on the malignancy), underlying diagnosis (Fanconi's anaemia), pre-BMT exposure to EBV and HPV, prolonged prior chemotherapy, particularly alkylating agents, TBI, prior irradiation, T-cell depletion of the graft, unrelated or mis-matched donor transplant, prolonged IST post-BMT, exposure to azathioprine post-BMT (particularly for skin cancers), cGVHD, a second BMT and increasing time from BMT(120, 121, 123, 124).

2.13. Ocular side effects

There are three main ocular late effects of allogeneic BMT(33); ocular cGVHD and keratoconjunctivitis sicca syndrome (KCS)/dry eye disease(46, 125, 126); cataract formation; and ischaemic microvascular retinopathy(46). Ocular GVHD, dry eyes and cataracts are the most common ocular complications, occurring in 40-60%, over 50% and 85% of long-term BMT survivors respectively(127-129).

Ocular cGVHD profoundly impacts on BMT survivor's QoL – decreasing their visual acuity and reducing their ability carry out activities of daily living(130). Manifestations include reduced tear flow, KCS, sterile conjunctivitis, corneal epithelial defects and corneal ulceration and can cause a range of symptoms, including dryness, burning, irritation, grittiness, pain, foreign body sensation, blurred vision, photophobia and excessive tearing(33, 125, 126). Other ocular complications of the posterior chamber include haemorrhage, optic disk oedema and infectious retinitis, uveitis, choroiditis and blepharitis(131).

Risk factors for ocular complications include TBI (dose and schedule dependent), cGVHD in other organs, having more than one BMT, older age, DM, prolonged corticosteroid and cyclosporine exposure(33, 128).

2.14. Neurocognitive effects

Neurological complications

Up to 16% of BMT survivors experience neurological complications affecting both the central and peripheral nervous system(CNS and PNS)(132). These include immune-mediated neuropathies, myasthenia gravis, myositis, thrombotic microangiopathy, cyclosporin neurotoxicity, infection including viral meningo encephalopathy and progressive multifocal leukoencephalopathy (PML), metabolic encephalopathies cerebrovascular complications, demyelination, and immune-mediated encephalitis(133, 134). Malignant gliomas, neuroectodermal tumours and meningiomas have also been reported post BMT, as have late infections of the CNS, cerebral vascular lesions and cerebral

angitis(134, 135). Some of these late effects have been reported up to eighteen years post BMT(136). Neurological complications of BMT appear to have a profound impact on survival, with one study reporting a four-year probability of survival of only 12% in those who experience neurological events post BMT(132).

A number of factors contribute to the risk of neurological disease post BMT including TBI, cranial irradiation, intrathecal chemotherapy, younger age at BMT(137), unrelated or mis-matched donor transplant, IST, cGVHD, and exposure to rituximab post BMT (particularly PML)(134, 138) .

Neurocognitive complications

Up to 40% of those who survive five years post-BMT report some form of neurocognitive deficit including reduced short term memory, verbal recall and motor dexterity(139).

Risk factors for neurocognitive decline post BMT include immunosuppression with cyclosporin, TBI, prior cranial irradiation, intrathecal chemotherapy, younger and older age at transplant, and cGVHD. Prolonged hospital admission has also been associated with greater cognitive deficit after BMT(140).

2.15. Chronic graft versus host disease

cGVHD is one of the most common and deleterious effects of BMT, occurring in 30-75% of BMT survivors and profoundly impacting upon survival and QoL post-BMT, with a five year mortality rate of 30-50%(141). cGvHD is a highly complex immune pathology involving donor T and B, and other cells, which causes donor cells to respond to alloantigen presented on host antigen presenting cells (APC), resulting in fibroproliferative changes. It can be mild, presenting with a single organ symptom (such as lichenoid features in the mouth only), or it can be diffuse, severe and prolonged, manifesting as multisystemic immunological disease including systemic lupus erythematosus, Sjogren's syndrome, scleroderma, rheumatoid arthritis, primary biliary cirrhosis, BOS, immune cytopenias, and chronic immunodeficiency(142). In order of frequency, cGVHD affects the skin, mouth, eyes, gut, liver, joints, muscles, vagina, oesophagus, nails, lungs and serosa(142, 143) and can lead to a multitude of long-term and late effects as outlined in this chapter.

Risk factors for more severe or prolonged cGVHD include the use of older BMT recipients and donors, mis-matched and unrelated donor transplant, the use of peripheral blood stem cells, acute GVHD, and the use of DLIs(144, 145).

Importantly, as the treatment of cGVHD involves prolonged and often intense IST, this increases the risk of infection and malignancy. And while 50% of those who develop cGVHD will experience resolution of symptoms within seven years of commencing treatment, approximately 40% will have recurrent malignancy or die within seven years, and the remaining 10% will require continued treatment for an indefinite period of time(143, 146). Unsurprisingly, given the extensive and pervasive physical impact that cGVHD can have, it is the major determinant of QoL and functional status in those who survive more than two years post-BMT(147).

2.16. Compromised quality of life

Although difficult to define QoL comprises broad concepts that affect global life satisfaction, social and personal functioning, achievement of life goals and inter-relationships(148). It is a subjective, multidimensional concept which encompasses psychological, social, physical and contextual or environmental aspects of health and illness. BMT survivors are known to experience significant declines in QoL in the lead up to and in the years following BMT due to the toxicity of chemo-radiotherapy, the complications of BMT, particularly cGVHD, the medications used to prevent and treat these complications, including steroids and immunosuppressive therapies, and the intractable nature of survival with chronic illness(148). Symptoms and issues impacting on BMT survivor QoL include pain, fatigue, insomnia, sexual dysfunction, declines in physical functioning, emotional distress, depression, post-traumatic stress, psychological and neurocognitive functioning declines, issues with schooling, work or returning to work, issues with marital and family roles and social support, caregiver burden and financial toxicity(149, 150).

Risk factors for poorer QoL in the years post BMT include worse pre-BMT physical health, younger and old age at BMT, prior chemo-radiotherapy, depression, being female, low education levels, low social support, greater physical symptoms, unrelated donor transplants, cGVHD and exposure to corticosteroids(151-153).

In studies comparing QoL of BMT survivors to sibling controls, BMT survivors are less likely to be married, more likely to have health related issues preventing them from holding a job, more likely to report difficulty maintaining health insurance and acquiring life insurance and require additional support with school and tertiary studies(33, 36, 154). Over 50% experience depression or subclinical depression and there is some data that depression may negatively impact on survival in the first-year post BMT (155). Over 70% of survivors report moderate to severe symptoms of fatigue for at least five years post-transplant(6) and for those under 40 years, over 30% experience concerns about

fertility(149). The majority of survivors report sexual dysfunction at some point post BMT(150). BMT survivors also have increased rates of suicide compared to the general population(156).

Although many BMT survivors return to work post-BMT (particularly as time increases post-transplant) this is highly dependent on their age at transplant, their pre-BMT employment status, and the development and severity of cGVHD(151, 154). Physical recovery occurs earlier than psychological and 'work recovery', and full physical and psychosocial recovery from BMT may take up to five years (substantially longer than the time estimated by BMT healthcare professionals(157)).

While many survivors have ongoing psychosocial and financial concerns post BMT and many continue to fear the risk of relapse or recurrence of disease post-BMT(6), many survivors also report positive impacts of BMT including a personal strength and appreciation for life, closer interpersonal relationships, reprioritizing "what really matters," renewed faith, and a sense of gratitude(150, 158).

2.17. Summary

Allogeneic BMT survival is associated with a multitude of adverse long term and late effects which affect every body system. Many of these significantly impact the morbidity and mortality of survivors post-BMT and their QoL. While methodological differences (retrospective, prospective, self-report, patient medical record/result review) between studies of long-term survivors, and the heterogeneity of cohorts studied (transplant type (autologous, allogeneic), donor type, conditioning intensity, primary disease and disease status at BMT) make it difficult to elucidate a clear and comprehensive picture of BMT survivorship, it is clear that all survivors require some degree of life long follow-up(159). The publication of international guidelines for BMT long-term follow up (LTFU) illustrate the increasing recognition of the complex health care needs of BMT survivors and the responsibility for transplant services to provide comprehensive preventive care(160, 161).

The next chapter provides an overview of the guidelines for BMT LTFU and details the provision of services available to BMT survivors in New South Wales (NSW).

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Chapter 3: BMT Long-Term Follow-up Service Provision in NSW

3.1. Chapter overview

This chapter provides an overview of the recommendations for long-term follow-up (LTFU) of BMT survivors and the health care services currently available for BMT recipients in NSW, including the provision of LTFU. The final section of this chapter presents the research aims of this thesis.

3.2. International guidelines for LTFU of BMT survivors

Increasing recognition of the long-term and late effects of BMT (as detailed in Chapter 2) has led a number of national and international BMT organisations to develop and disseminate consensus guidelines for screening and prevention of late complications of BMT(1, 2). These guidelines outline the surveillance tests, clinical assessments and preventive care that BMT survivors require at regular intervals, for life. These tests, assessments and preventive care aim to monitor for recurrent and secondary malignancies, cGVHD, infections, respiratory, cardiovascular, renal, musculoskeletal, ocular, oral, gastrointestinal, dermatological and endocrine dysfunction, and psychosocial issues, among others.

The burden of testing and treatment that follows adherence to these guidelines however, both for BMT survivors, their carers and health care teams is immense. Survivors receiving follow-up care according to these guidelines require contact with at least six clinical specialties and need up to thirty-four assessments annually, including health history, clinical examinations, laboratory analysis, diagnostic imaging, psychosocial assessments, health counselling and education (Table 3.1).

Table 3.1: Abbreviated summary recommendations for screening and prevention of late complications in long-term BMT survivors by time after transplant(1)

Recommended screening/prevention	6mo	1yr	Annually
Immunity			
Encapsulated organism prophylaxis	2	2	2
PCP prophylaxis	2	2	
CMV testing	2	2	2
Immunisations	1	1	1
Ocular			
Ocular clinical symptom evaluation	1	1	1
Ocular fundus exam	*	1	*
Oral complications			
Clinical assessment	1	1	1
Dental assessment	*	1	1

Respiratory			
Clinical pulmonary assessment	1	1	1
Smoking tobacco avoidance	1	1	1
Pulmonary function testing	*	*	*
Chest radiography	*	*	*
Cardiac and vascular			
Cardiovascular risk-factor assessment	*	1	1
Liver			
Liver function testing	1	1	*
Serum ferritin testing		1	*
Kidney			
Blood pressure screening	1	1	1
Urine protein screening	1	1	1
BUN/creatinine testing	1	1	1
Muscle and connective tissue			
Evaluation for muscle weakness	2	2	2
Physical activity counselling	1	1	1
Skeletal			
Bone density testing (adult women, all allogeneic transplant recipients and patients at high risk for bone loss)		1	*
Nervous system			
Neurologic clinical evaluation	*	1	1
Evaluate for cognitive development		1	1
Endocrine			
Thyroid function testing		1	1
Growth velocity in children		1	1
Gonadal function assessment (prepubertal men and women)	1	1	1
Gonadal function assessment (post pubertal women)		1	*
Gonadal function assessment (post pubertal men)		*	*
Muco-cutaneous			
Skin self-exam and sun exposure counselling	1	1	1
Gynaecologic exam in women	*	1	1
Second cancers			
Second cancer vigilance counselling		1	1
Screening for second cancers		1	1
Psychosocial			
Psychosocial/QOL clinical assessment	1	1	1
Sexual function assessment	1	1	1
1 = recommended for all transplant recipients			
2 = recommended for any patient with ongoing chronic GVHD or immunosuppression			
* = reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms			

While published guidelines are clearly beneficial in that they optimise, standardise and harmonise the post-transplant care of BMT survivors(3) many questions remain about their translation into clinical practice and the evidence for their utility. While historically BMT units have been responsible for providing pre-, peri- and post-transplant care for BMT recipients, this is changing as more transplants are performed, more patients survive, and more patients become long-term survivors of BMT. While BMT centres are most familiar with long-term and late effects of BMT, and have access to a range of specialist services, new models of care (MOC) are required for BMT LTFU(4, 5).

3.3. Health care and the provision of post-BMT care in NSW

NSW is Australia's most populous state with a population of 7,995,100 (as at 31 March 2018)(6). It is the third largest state/territory covering an area of 800,628 square kilometres which represents 10.4% of Australia's land mass(7). Health care in NSW, as across all Australia, is complex, and consists of public and private providers who deliver multifaceted primary health care, community services, emergency and hospital-based treatments, rehabilitation and palliative care. While public sector health services operate within a complex funding structure administered by both federal and state and territory governments, private hospitals, medical and allied health practices and pharmacies are owned and operated by the private sector (but regulated by government)(8).

NSW's public health care system consists of fifteen local health districts (LHD) (health administration boards which operate public hospitals, institutions, health services and health support services), three speciality networks (Sydney Children's Hospital Network, Justice and Forensic Mental Health Network and St Vincents Health Network) and nine primary health networks (a regional network of general practitioner-led councils and Community Advisory Committees to ensure primary, community and specialist sector services work together across the region)(9).

In total, there are 431 hospitals in NSW. This comprises 226 public hospitals and 205 private hospitals and facilities(10). Of these, only five public hospitals perform adult allogeneic BMT - Westmead Hospital (WH), St Vincents Hospital (SVH), Royal North Shore Hospital (RNSH), Royal Prince Alfred Hospital (RPA) and Liverpool Hospital (LH). All five are located in metropolitan Sydney. This means that BMT recipients who live in regional and rural NSW (2,729,742 people are reported to live outside the Greater Sydney area as at June 2017 (11)) must relocate to Sydney to undergo transplant and for the early post-transplant period (Figure 3.1).

3.4. Early Post-BMT care for survivors in NSW

The care of BMT recipients during transplantation and in the first three months post-BMT is well established. The focus during this period is on monitoring disease status, and surveillance and prevention of early post-transplant complications including acute GVHD and infection. Following this period, provided there is no ongoing necessity for intensive treatment for acute GVHD, infections or other acute issues, the frequency of BMT Specialist follow-up is gradually decreased and the patient is able to return to their home. After a patient has survived 3-12 months post-BMT, the focus of their care changes to monitoring for relapse, and screening for and management of cGVHD and maintenance of good health. During this period many patients are transitioned to long-term and late effects clinics, although this care may also be delivered within standard BMT clinics. Post-BMT care is generally co-ordinated by the BMT specialist and/or more commonly, by BMT advanced practice nurses (APN) (e.g. BMT Co-ordinators, Nurse Practitioners (NP), Clinical Nurse Consultants (CNC), Clinical Nurse Specialist (CNSp)) and is subsidised by Medicare and the Pharmaceutical Benefits Scheme (PBS).

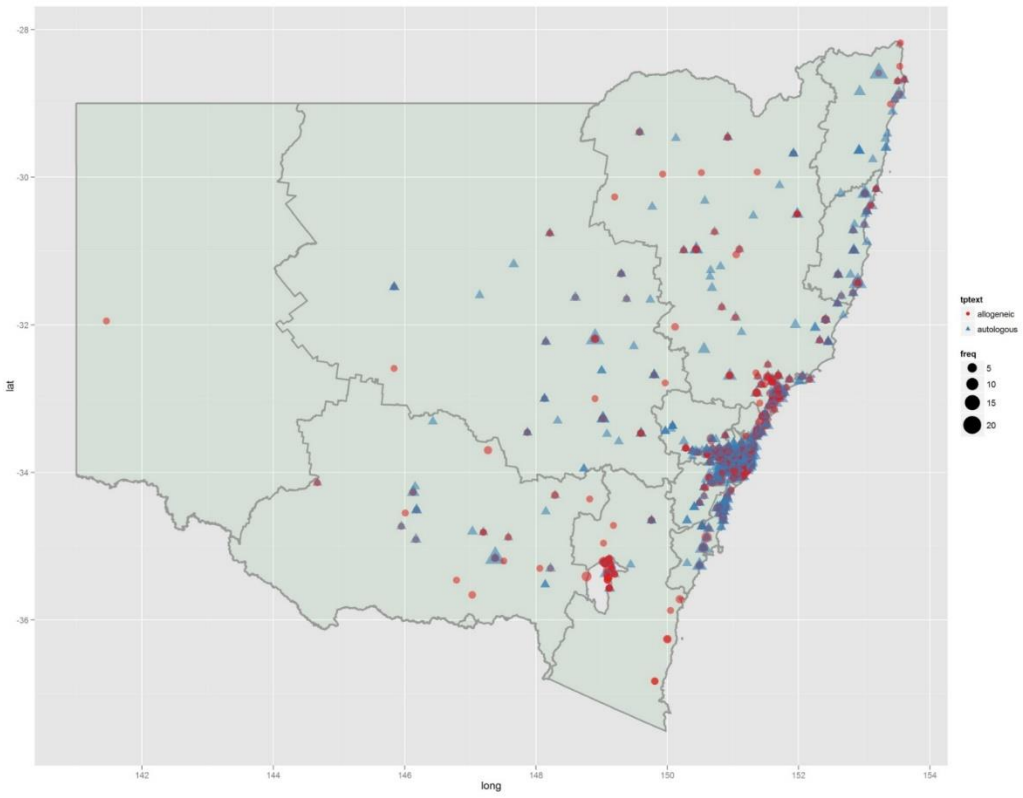

Figure 3.1: Place of residence of BMT recipients in NSW

3.5. Models of care for BMT LTFU

It is increasingly recognised that there is a need for flexible, heterogeneous and sustainable MOCs for BMT LTFU. Rather than describe a single model for delivery of post-BMT care, survivorship guidelines

recognise that delivery of healthcare needs to be personalised and have therefore focussed more on the components of care that need to be addressed in healthcare design and delivery. In this regard it is notable that the Institute of Medicine (IOM) 2005 report titled 'From cancer patient to cancer survivor: Lost in transition' specified that comprehensive survivorship care should be characterised by safety, effectiveness, patient-centeredness, timeliness, efficiency and equity(12). Developing and implementing robust LTFU MOCs to satisfy these essential components is critical, both for BMT centres who are perfoming more and more BMTs and for the health care system that will need to support more and more survivors.

Both nationally and internationally there is no consensus regarding the optimal LTFU MOC(13, 14). In the US, Canada and the UK various MOCs exist and services have typically been based on historical and opportunistic practices, and on cancer survivorship models(15-19). In general terms BMT LTFU care is provided in four different ways:

- *LTFU care provided during routine follow-up in the BMT Clinic:*
  BMT specialist/BMT APN continues to see the survivor in the BMT clinic.

- *LTFU care undertaken as a 'stand-alone' assessment/clinic visit either within the BMT clinic or in a dedicated BMT LTFU clinic:*
  The survivor is transitioned to a dedicated LTFU clinic/team. This is distinct from the early post-BMT clinic, is often held in an alternate space or on a different day, (but may be run alongside the early post-BMT clinic), and may be staffed by a multidisiplinary team (MDT).

- *Collaborative LTFU care shared between the BMT centre and other providers (e.g. sub-specialists, local haematologist, General Practitioner (GP)):*
  The survivor is seen infrequently in the BMT centre (often for purposes of LTFU review and data collection) with the majority of follow-up test, assessments and health care delivered by the surivors local haematologist/GP and by community health care providers.

- *LTFU care with local haematologist/GP:*
  The survivor is transitioned or discharged from the BMT service to the care of their local haematologist or GP with a care plan and recommendations for follow-up.

3.6. BMT LTFU in NSW

At the time of study commencement (2012) there were no national or state guidelines for BMT LTFU, no standarisation or harmonisation in BMT LTFU care, no agreed processes for transitioning adult survivors of childhood BMT to adult health care services, few nurses employed to provide post-BMT care and no nurse practitioners employed in NSW in LTFU. BMT recipients were followed up in a range of different settings, dependent in part upon instiutional culture, on avaiable (human and space) resources and existing MOCs. Some recipients continued to receive co-ordinated care through their BMT centers, some were referred back to their local haematologist and many had no ongoing care and were lost to follow-up 2-5 years post-BMT. The ABMTRR reported at the time there were estimated to be over 1,500 long-term BMT survivors(20) however hospital BMT database estimates were less than 900(personal communication). With the exception of WH there was very limited multidisciplinary care, limited nursing involvement in post-BMT care and limited co-ordination of long-term care. Rural and regional BMT survivors were either required to return to the BMT centre for LTFU (if available) or their care was left to their local haematologist or GP (often without direction from the BMT centre)(Table 3.2).

Informal discussions with BMT survivors and their carers, and with health care providers involved in the follow-up of BMT recipients at the time found that many BMT survivors experienced difficulties accessing and paying for specialist health care services, dealing with fragmentation of care and poor communication between health providers, and navigating between different healthcare providers, between the public and private sector and between the hospital and community health care systems (LHDs and PHNs). Many also experienced significant difficulties as a consequence of loss or reduction of employment and costs related to care being inadequately subsidised by Medicare and/or the PBS.

3.7. Research aims

This research arose directly out of concerns regarding this suboptimal experience of BMT survivors in NSW, a recognition that post-BMT care was inconsistent and fragmented, and often did not satisify recommendations of international BMT LTFU guidelines(1), was not organised in accordance with the principles described by the IOM for cancer survivorship(12) and was not based on a comprehensive, evidence-based understanding of post-BMT survivorship in Australia. (At the time of study commencement the ABMTRR only collected data on date last seen, cGVHD, relapse and/or death).

The aims of the research described in this thesis, therefore, were:

1. to describe the incidence and range of late complications of BMT and their association with the health and functional status of survivors in NSW;

2. to address limitations in BMT survivorship literature – particularly with regard to the financial, occupational and psychosocial impact of BMT;
3. to identify gaps in service provision provided to this vulnerable and high-risk patient group;
4. to provide better information to patients contemplating BMT, and to their families and guardians, regarding the possible long-term sequelae of BMT, and
5. to support clinical and health policy decision-making around BMT through the provision of more comprehensive data regarding the late sequelae of BMT in an Australian setting.

The next chapter presents the research methods used to address these aims. It includes a description of the research sample, setting, and instruments used, and of the data analysis performed.

Table 3.2: BMT LTFU Models of Care employed across NSW at study commencement (2012)

Centre	# Allos/ year 2011	BMT Nursing involvement (FTE)	Clinic type available for post-BMT patients	Delivery mode (Led by and frequency)	Located within	Provider involvement	Referral timepoint to BMT LTFU (if available)
WH	62	Yes (0.5 CNS2)	2 x Post-BMT Clinics 1 early post-BMT 1 LTFU clinic	Routine post-BMT care (BMT LTFU CNS - weekly)	BMT Clinic	BMT LTFU CNS BMT physicians Dermatology Gynaecology Endocrinology Concurrent Respiratory medicine clinic runs in private rooms	3 mo post-BMT
		Yes (0.3 CNC)	Post-BMT Clinic – Satellite Clinic (Newcastle)	Routine post-BM care (Newcastle BMT-Co-ordinator - monthly)	WH pt specific Post-BMT Clinic	BMT-Coordinator BMT Physician from Westmead (rotating physicians on a monthly basis)	3 mo post-BMT

SVH	38	Yes 0.5 CNC2 (funded by the NSW BMT Network)	Post-BMT Clinic	Specialised LTFU Clinic (BMT CNC - monthly)	Specialised LTFU Clinic	BMT LTFU CNC BMT Fellow Social worker (Referral to this clinical was at BMT physician discretion – some preferred to follow-up their patients themselves)	2 years post-BMT
		No (for those BMT physicians who preferred to follow-up BMT patients themselves)	Post-BMT Clinic	Routine post-BMT care (BMT Physician)	Haematology Clinic	BMT Physician Referrals made within and outside SVH as required/per physician discretion	
RNSH	18	Yes 0.5 CNC2 (funded by the NSW BMT Network)	BMT LTFU Clinic	Specialised LTFU care	Specialised LTFU Clinic	BMT CNC BMT Physician Clinical Psychologist Social worker	2 years post-BMT

				(BMT CNC – monthly)			
RPA	21	No	Post-BMT Clinic	Routine post-BMT care (BMT Physician)	Haematology Clinic	BMT Physician Referrals made within and outside RPA as required/per physician discretion	
LH	N/A						Liverpool did not become an allogeneic BMT centre until 2012 so they did not have any long-term survivors at study commencement
CNS, Clinical Nurse Specialist; CNC, Clinical Nurse Consultant; NP, Nurse Practitioner; pt, patient; mo, months							

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PART II: Methods

Chapter 4: Methods

Chapter 4: Methods

4.1. Chapter overview

This chapter outlines the methods that were employed for the research described in this thesis. Due to journal word count restrictions, each manuscript contains a concise methods section (relevant to that manuscript), therefore some additional detail regarding study design and execution is provided here.

4.2. Methods

This study used a cross-sectional survey design that combined quantitative and qualitative methods to examine the long-term and late effects of allogeneic BMT performed on adults and was conducted in NSW. The study included an examination of the sequelae of BMT and their association with a range of sociodemographic, transplant factors and the impact that these had on survivors' experience and QoL. The project also aimed to identify the gaps in service provision provided to this vulnerable and high-risk group.

Design

A cross sectional survey design was employed to collect data to address the aims of this study. This method was chosen because it provides an established method for determining the frequency of an attribute of interest/patterns of morbidity and potential risk factors, in a particular population, at a defined time point, in a timely and inexpensive manner(1, 2). Cross-sectional studies have been used extensively to determine the prevalence of risk factors and to measure the current health status, health practices, knowledge, and attitudes of various populations. The data provided by cross-sectional studies can be used for priority setting for disease control and health service planning, and enable hypothesis generation for future research. In particular, observations made during the cross-sectional surveying can be used to develop hypotheses for testing temporal relationships between risk factors and disease(3). In practical terms, cross-sectional studies also are efficient, affordable and can be conducted across multiple sites and in different settings. For all these reasons a cross-sectional survey was regarded as the most appropriate means for documenting the physical and psychosocial health of BMT survivors in NSW.

Research Setting

This study was conducted in NSW, Australia. Australia has a population of approximately 24.9 million people distributed throughout six states and two territories. NSW is the most populous state with

approximately 7.9 million inhabitants as at March 2018(4). In 2012 (when the study began) 554 BMTs were perform throughout Australia with NSW contributing 216 to this total(5).

At the time of study inception there were five allogeneic BMT centres located in the state (however one centre (LH) only commenced their allogeneic BMT program in 2012 so had no eligible survivors for the study – accordingly only four centres were involved) - all are located in metropolitan Sydney. Therefore, as discussed in Chapter 3, regardless of residential location in NSW, patients who need an allogeneic BMT are required to relocate to the state's capital to receive their treatment at WH, SVH, RNSH, RPA or LH.

All four of the participating hospital BMT centres are National Association of Testing Authorities, Australia (NATA) accredited, operate as referral centres for patients domestically and internationally and all report their BMT outcome data to the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), the Centre for International Blood and Marrow Transplant Research (CIBMTR) and the Worldwide Network for Blood and Marrow Transplantation (WBMT). Each unit has vast experience in the delivery of BMT (BMT was first performed in Australia in 1975(6)) with hospital physicians, nurses and scientists nationally recognised for their work in BMT through significant research output.

Research Sample

Eligible study participants were all BMT survivors (age >18 years) who had undergone an allogeneic transplant at WH, SVH, RNSH, or RPA between January 2010 – December 2012, could read and write English and consented to participate in the study.

This sample time frame was chosen for several reasons: BMT techniques and supportive care have improved vastly over the past four decades (as detailed in Chapter 1) such that the most relevant issues and outcomes, for both future patients and health services, are likely to be identified in those who have undergone BMT in the past decade, and clinical records and contact details were reliably available for this cohort of patients.

Research Procedures

Potential participants were identified from each hospital's BMT database and were phoned by the researchers or advised of the study when attending their BMT Clinic. In each case the study was verbally explained to the patient and the patient was given the option of receiving a study pack in clinic or via the post. Study packs consisted of an invitation letter, Patient Information Sheet (PIS) and Informed Consent Form (ICF) (Appendix C), and the survey instrument (Appendix D). The invitation letter and PIS outlined that the purpose of the study was to examine the physical and psychosocial

impact of BMT and the QoL of allogeneic BMT patients, to identify gaps in services provided to survivors of BMT and to provide better information to patients and health care professionals on the possible late effects of BMT. Participants were also advised that study participation was voluntary, confidential and, due to the nature of the study, unlikely to be of direct benefit to the individual completing the survey. All participants were given the option of completing the survey instruments themselves at home or during their transplant clinic appointment, or completing the survey with the assistance of a member of the research team via a telephone interview. They were also given the opportunity to contact the investigators to address any questions they had and to receive additional help to answer the questionnaires if required. Participants were also given a stamp self-addressed envelope to post the ICF and completed survey back to the research team at the co-ordinating hospital (RNSH).

A total of 669 BMT survivors were eligible for study participation. Following phone contact, study packs were sent and given out in clinic to a total of 583 people (87.1% of eligible). A follow up phone call was made to those survivors who did not return the survey within one month of it being distributed to them. Failure to send the surveys back after this was considered non-response and no further contact was made. In total, the response rate was 75.6% (n=441) of the total number of surveys sent, and 65.9% of total population eligible for participation (Figure 4.1).

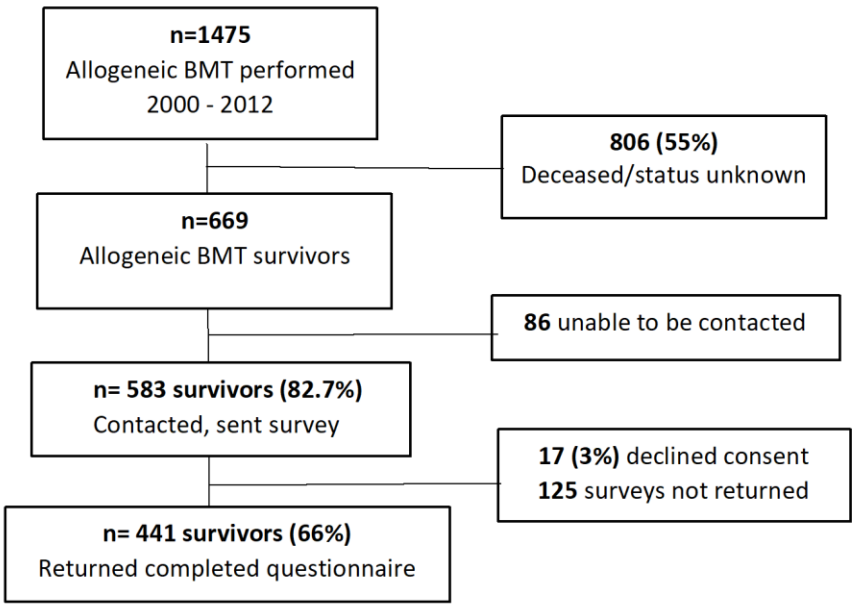

Figure 4.11: Sydney Post-BMT Study Flowchart

4.3. Study Instruments

The survey instrument used in this study consisted of six validated questionnaires and a survey designed by the research team to address areas not explored in other validated survey instruments. This latter survey, the Sydney Post-BMT Survey, was developed following a review of the international BMT literature and following input from relevant health professional and BMT survivors. The validated questionnaires utilised in this study were the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4), the Chronic GVHD Activity Assessment – Patient Self Report (Form B), the Lee Chronic GVHD Symptom Scale, DASS21, The Post Traumatic Growth Inventory, and the Fear of Recurrence Scale. (Full descriptions of these survey instruments are given below). All these instruments were combined into one twenty-page document for ease of completion by study participants (Appendix D). This twenty-page document was then converted into a scannable document which simply required that study participants enter an 'x' in the 'yes', 'no', 'don't know' or appropriate Likert scale box or write free text as indicated by the question. A study specific BMT Clinical Data Form was also developed and used to collate clinical and transplant variables (Appendix E). This form was completed by the researchers, required tick-box responses and was also scannable. The scannable technology was utilised to aid efficiency in the data entry phase of the study.

The Sydney Post-BMT Survey

The Sydney Post-BMT Survey was devised by the research team in collaboration with health professionals involved in the care of BMT patients, including haematologists, infectious disease physicians, BMT nurses, BMT psychologists, and dieticians, in and discussions with transplant survivors attending BMT clinics. It is a 402-question survey covering twenty areas including:

- Demographics (6 questions)
- Medical complications (36 questions)
- Referrals, tests and assessment and time (35 questions)
- Medications and treatments (27 questions)
- Oral and dental health (15 questions)
- Infections (17 questions)
- Vaccinations (30 questions)
- Complementary therapies (17 questions)
- Cancer screening (37 questions)
- Travel history (36 questions)
- Close personal contacts (6 questions)
- Lifestyle (10 questions)
- Diet/Nutrition (19 questions)

- Occupation – Infection risk (11 questions)
- Occupation – works status and functioning (35 questions)
- Fertility and sexual function (41 questions)
- Relationships (3 questions)
- Preference for long term follow up care (8 questions)
- Social, occupational attitudes, physical and psychological concerns (12 questions)
- The three things that have impacted you most (1 question)

The demographics section consists of six questions eliciting date of birth, BMT date, postcode, ethnicity, gender and education. The medical complications section included 36 questions eliciting responses to known medical conditions. The section covering referrals, tests and assessment included 35 questions covering the types of specialist services patients had accessed, and the burden that they experienced as a consequence of seeking medical care. Twenty-seven questions explored use of medications and other therapies. The oral and dental health section asked fifteen questions about oral and dental problems that have developed since BMT. Two sections comprising forty-seven questions explored infection and immunisation status pre and post-BMT.

Complementary and alternative medicine (CAM) therapy use was elicited in seventeen questions while thirty-seven questions explored preventive health behaviour. Travel history, including insurance issues and infection health risk behaviours were explored in thirty-six questions. Six questions asked about BMT survivors living arrangements and close contacts. Lifestyle choices were elicited in ten questions. While nineteen questions asked about diet and nutrition. Post-BMT participation in high-risk occupation was explored in eleven questions and the impact that BMT had on work status and functioning was explored in more detail in thirty-five questions. Fertility and sexual function post-BMT were investigated in forty-one questions and relationship status in three questions. Survey respondents where then asked what type of long term follow up care they would prefer post-BMT in eight questions. Most survey questions asked for binary (yes/no) responses, although some sections allowed for open/free text responses eg. “if yes, how?”.

The final two sections on the survey addressed psychosocial consequences of BMT. The social, occupational attitudes, physical and psychological concerns section consisted of twelve questions – each of which required a five-point ordinal Likert scale response from ‘Not at all’ to ‘Very much’. The final section of the survey asked a single question,” What would you say are the **three things** that have had the most impact on your QoL since your transplant (or that cause you the most distress)?” and provided room for participants to write a free text response. This was the only question in the survey that elicited purely qualitative data.

The Sydney Post-BMT survey was checked for face and content validity for respondent comprehension via piloting with six patients at two of the hospitals under study (RNSH and RPA). Patients were approached at their BMT clinic visit and asked if they would be willing to complete and review the survey and provide any feedback they thought necessary. All six patients approached agreed. Five patients chose to self-complete the survey and send it back to the research team. The sixth patient chose to review the survey by completing it in a one-on-one interview with a member of the research team. All the patients understood that the surveys completed for this pilot would be destroyed once reviewed for validity by the research team, and the data would not be used for publication.

No amendments were made to the survey as a result of this pilot testing. All six patients provided positive feedback in relation to the aims of the survey and none had any objections to the types of questions asked. The PIS however, was amended following this review. Patients were asked to provide an indication of the time taken to complete the survey, which was found to be significantly more than the research team had estimated (originally the PIS indicated the entire survey would take approximately thirty minutes to complete. This was updated to one hour). Data from this pilot testing was not included in the results.

Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4)

The FACT-BMT is a validated questionnaire for measuring QoL in BMT recipients(7). It takes three to five minutes to complete and combines two instruments, the FACT-G and a BMT subscale. The FACT-G is a twenty eight-item self-report instrument that measures QoL (QoL) in cancer patients(8). It consists of five subscales measuring physical, functional, social and emotional well-being and satisfaction with the doctor/patient relationship. The BMT subscale includes twelve items designed to test QoL in BMT patients. The FACT-BMT plus the BMT subscale provides an overall QoL score. Patients rate themselves over the past seven days using five-step Likert scales with responses used to calculate overall QoL and subscale wellbeing scores.

The Chronic GVHD Activity Assessment – Patient Self Report (Form B)

The Chronic GVHD Activity Assessment – Patient Self Report Form B was developed by the NIH Consensus Development Project(9). It is a ten-item questionnaire which asks patients to report on the severity and intensity (out of 10) of skin, oral, ocular and vulvovaginal symptoms as well as perceived global ratings of GVHD. It takes about one minute to complete.

The Lee Chronic GVHD Symptom Scale

The Lee Chronic GVHD Symptom Scale is a thirty-item validated questionnaire for measuring symptoms of cGVHD(10). It consists of seven subscales measuring adverse effects of cGVHD on skin, eyes, mouth, lungs, nutritional status, muscles and joints, vitality and psychological functioning. Patients rate themselves over the past month using five-step Likert scales. It takes about two minutes to complete.

The Post Traumatic Growth Inventory

The Post Traumatic Growth Inventory is a twenty one-item questionnaire which measures post traumatic growth experiences in trauma survivors' lives(11). Tedeschi and Calhoun (1996) identified five major domains of growth which include 1) greater appreciation of life and changed sense of priorities; 2) warmer, more intimate relationships with others; 3) a greater sense of personal strength; 4) recognition of new possibilities or paths for one's life; and 5) spiritual development. It is widely used to assess positive life changes following traumatic events such as cancer, HIV, rape and disasters and other crises(12). Statements including 'I developed new interests', 'I know that I can handle difficult situations' and 'I learned a great deal about how wonderful people are' expressed and the reader is asked to respond using a six-point Likert scale with responses ranging from, 'I did not experience this change' to 'I experienced this change to a very great degree as a result of my crisis'.

Fear of Recurrence Scale

The Fear of Recurrence scale was developed in the early 1990s by the authors of a study looking at QoL in Leukemia patients. It consists of five questions which measure individual's thoughts surrounding recurrence of their disease and includes question such as 'Because cancer is unpredictable, I feel I cannot plan for the future', 'I am afraid of my cancer coming back' and 'I will probably have a relapse in the next five years'. Responses are asked for in the format of a 5-point Likert scale from 'strongly agree' to 'strongly disagree'. In total the five questions are scored out of twenty, and higher scores represent greater fear of recurrence than lower scores(13, 14) .

The DASS 21

The Depression, anxiety and stress scale (DASS 21) is a twenty one-item self-report questionnaire designed to measure the severity of a range of symptoms common to both depression and anxiety(15). It is widely used and has been shown to be valid and reliable in both non-clinical and clinical cohorts(16, 17) Patients are asked to indicate how much a particular statement has applied to them over the past week. It uses a four-point Likert scale which ranges from 'did not apply to me' to

'applied to me very much, or most of the time' for statements such as, 'I found it hard to wind down', 'I felt I had nothing to look forward to' and 'I felt life was meaningless'. Each question is scored out of three for an overall total score out of sixty three. A higher score indicates greater severity of symptoms of anxiety or depression.

Sydney Post-BMT Clinical Data Form

A one-page BMT Clinical Data Form was developed by the research team to collect information regarding date of transplant, date of diagnosis and stage at transplant, transplant conditioning, GvHD prophylaxis, stem cell source and donor type of BMT survivors. It contained ten questions and was completed by the research team. This information was retrieved from the transplant databases of each of the four participating transplant centres once patient consent forms had been received. This information enabled a comparison between clinical variables and late effects of BMT.

Statistical Analysis

Quantitative data

Categorical responses were summarised using frequencies and percentages. Parametric continuous variables were summarised using means and standard deviations, and nonparametric variables using medians, interquartile ranges (IQR) or ranges. ORs and 95% confidence limits, Pearson 2 test or Fisher's exact tests were used for comparative analysis of dichotomous categorical variables. Two sample comparisons of parametric and nonparametric data were determined using the independent t-test, and Wilcoxon Rank Sum tests, respectively. Comparisons of greater than two samples were determined using one-way analysis of variance and Kruskal–Wallis tests, respectively. Multivariable logistic regression and multiple regression analyses were used to adjust for confounders and to ascertain independent associations of explanatory variables with outcomes of interest.

A two-tailed p value <0.05 was used as the level of statistical significance. Statistical analysis was performed using Stata software (Version12.1).

Qualitative data

De-identified responses to the QoL question, 'What would you say are **the three things** that have had the most impact on your QoL since your transplant (or that cause you the most distress)?' were copied verbatim into a word document. The analytical framework used for coding was initially guided by the model of QoL conceived by Ferrell et al(18). The coding organization was performed on NVivo software. The thematic scheme was further refined following multiple readings and line-by-line coding of the text to examine, conceptualize, and categorize physical, psychological, social or spiritual

themes. Thematic analysis was performed independently by two members of the research team with final agreement on categories made after the five core members of the research team (GD, LB, NG, and IK) had independently read and provided commentary on both the codes and the characteristics of each category.

Ethical approval and considerations

Ethics approval was provided by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD HREC Reference: 1207-217M) to conduct the study at the four relevant hospitals across NSW; WH, SVH, RNSH and RPA. Site Specific Governance approval was provided by each hospitals Research Governance Office prior to study commencement. (See the 'Ethical approval' section of this thesis for reference details and Appendix B).

As the majority of the target population for this study (adult survivors of allogeneic BMT) were continuing to receive care in BMT centres including by members of the research team and could, in theory, experience psychological distress as a consequence of completing this survey, the following strategies where employed to reduce the likelihood of harm:

- The research team was readily available (email addresses and phone numbers were provided), to answer any questions or concerns that participants may have had.
- Participants were advised that LB (a clinical psychologist with experience in working with BMT patients) was available should they wish to discuss concerns arising from participation in this study.
- To prevent (perceived or real) coercion potential participants were not approached by their BMT doctor about this study – only by the research team – and all were advised that their care would be not impacted if they did not wish to be involved in the study.
- Prior to completing the survey, potential participants were given a PIS and ICF, which provided information about the study in lay-terms. Potential participants were given a month to consider if they wanted to be involved in the study. If happy to voluntarily proceed, they were asked to return the signed ICF.
- Confidentiality was assured by giving each survey a dedicated study ID and only entering de-identified survey responses into the database for analysis. In addition, only aggregated data was presented so that individual responses could not be identified.
- Data protection was assured by storing the surveys, study documents and electronic files in a secure locked cupboard and computer file in the haematology department at RNSH. Only the researchers had access to this cupboard and password protected computer files. These

documents will be destroyed by shredding and confidentially erasing the files seven years from study closure (1st February 2021).

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PART III: Results

Chapter 5: The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia

Chapter 6: What They Want: Inclusion of Blood and Marrow Transplantation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia

Chapter 7: A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia

Chapter 8: Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)

Chapter 9: Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia

Chapter 10: Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia

Chapter 11: Oral health and dental morbidity in long-term allogeneic blood and marrow transplant survivors in Australia

Chapter 12: A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia

Chapter 13: Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia

Chapter 14: Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all?

Chapter 15: Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia

Chapter 5: The experience of survival following allogeneic haematopoietic stem cell transplantation (allo-HSCT) in New South Wales, Australia

5.1. Chapter overview

This chapter provides an overall summary of the late effects of long-term BMT survival, presenting all the results of this research. It consists of a published manuscript entitled, 'The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia'. The manuscript reports on all domains investigated; demographics, transplant factors, cGVHD, chronic co-morbidities, secondary malignancies, infections and vaccination uptake, health screening, sexual dysfunction, polypharmacy, health professional referrals, preferences for LTFU service delivery, household income and employment, QoL, fear of recurrence and personal growth.

The findings have implications for the rest of the work reported in this thesis as they reveal the extent of long term and late effects occurring in our study sample, and provide a point of reference for further in-depth analysis of the study data.

5.2. Publication details

Gifford G, Gilroy N, **Dyer G**, Brice L, Kabir M, Greenwood M, Larsen S, Moore J, Hertzberg M, Kwan J, Huang G, Tan, Brown L, Hogg M, Ward C, Kerridge I. "The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia". *Blood and Marrow Transplantation* 2016;51(10):1361-8.

5.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

5.4. Manuscript

The published version of the manuscript follows.

Bone Marrow Transplantation (2016), 1–8

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ORIGINAL ARTICLE

The experience of survival following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia

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Allogeneic haematopoietic stem cell transplantation (allo-HSCT) entails long-term morbidities that impair survivors' quality of life through broad physical and psychosocial sequelae. Current data and survival measurements may be inadequate for contemporary Australian allo-HSCT recipients. This study sought to comprehensively describe survivorship in an up-to-date, local setting through validated measurements and a novel questionnaire designed to complement and address limitations of current instruments. All adults who received an allo-HSCT between 2000 and 2012 in New South Wales were eligible and included, if alive, those literate and consenting to the study, which encompassed seven survey instruments. Four hundred and forty-three survivors participated, which is 76% of contactable ($n = 583$) and 66% of eligible survivors ($n = 669$). Chronic GVHD (cGVHD) and co-morbidity rates were similar to published data. Noteworthy results include prevalent sexual dysfunction (66% females, 52% males), loss of income (low income increased from 21 to 36%, $P < 0.001$) and employment (full-time employment fell from 64 to 33%, $P < 0.001$), suboptimal vaccination (31% complete), and health screening (≈50%). Risk factors for poor vaccination and health screening were cGVHD, younger age, less education, rural/regional residence and transplantation < 2 years. This study suggests that improvement in survivorship may necessitate structural changes in the current delivery of health services.

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INTRODUCTION

Over the past two decades, advances in allogeneic haematopoietic stem cell transplantation (allo-HSCT) have led to concomitant increases in the number of people undergoing this procedure and improvement in survivorship. Between 2001 and 2011, 90 000 allo-HSCTs were performed globally,[1] with 4369 of them performed in Australia.[2] With improvements in donor selection, conditioning therapies and supportive care, more recipients are living longer,[3] and up to 85% are expected to be alive at 10 years.[4,5]

Although allo-HSCT provides a clear benefit, it is associated with significant morbidity and mortality.[6] A range of complications may occur anytime post transplant, including 'early' (< 3 months), 'delayed' (3 months to 2 years), 'late' (2–10 years) and 'very late' (> 10 years).[7] Although contemporary allo-HSCT recipients are living longer than historical cohorts, published data suggest that allo-HSCT survivors experience a 30% lower life expectancy than a matched population[6] and may experience a compromised quality of life (QoL) owing to the ongoing physical and psychological sequelae of cumulative therapies,[8,9] failure to reintegrate socially[10,11] and uncertainty of prognosis.[12]

International and local bodies have recognised that research into the health, psychological and functional status of survivors is necessary to identify and address unmet needs of survivors and their families, enable better education and decision-making around BMT and inform the design and delivery of multidisciplinary health services essential to the care of long-term survivors.[13–15] This provides the rationale both for international and national registry studies of survivorship and 'local' studies of the specific experience of allo-HSCT survivors.

This study sought to comprehensively describe contemporary allo-HSCT survivorship in an Australian population with the intention of providing up-to-date information to candidates for allo-HSCT, their families and/or guardians regarding the long-term sequelae of allo-HSCT, supporting local clinical and health policy decision-making around allo-HSCT and optimising the care of survivors. Specifically, the aims of this study were to document the incidence and range of late complications and their association with the health and functional status of allo-HSCT survivors, address limitations in the current literature around survivorship, particularly with regards to the financial, occupational and psychosocial impact of allo-HSCT, and identify gaps in the existing care of survivors in New South Wales (NSW), Australia.

PATIENTS AND METHODS

Patients and procedures

Participants were eligible if they had undergone an allo-HSCT between 1 January 2000 and 31 December 2012 in NSW, Australia's most populous state (population 7.5 million),[16] were > 18 years of age at time of transplant, literate in English and were alive at the time of sampling. Potential participants' identity and phone number were retrieved from the four NSW adult allogeneic transplant centres' databases. Patients were informed about the study in a clinic visit or via a telephone call from one of

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the researchers. Patients who agreed received a study pack at the clinic or through the post, which consisted of an invitation letter, patient information sheet, consent form, the questionnaire and a stamped self-addressed envelope for return of the study instrument. All participants were given the option to complete the questionnaire themselves or via a phone interview with a researcher. To increase recruitment, a second phone call was made to participants who had not returned the survey within a month. This study was approved by the Northern Sydney Local Health District Research Ethics Committee (NSLHD Reference: 1207–217M).

Instruments

Researchers collated information from transplant databases on diagnosis, disease status and date of transplantation, conditioning regimen, GVHD prophylaxis, stem cell source, and donor type for each consenting participant. All other information was obtained from patient's self-reported responses to the questionnaire. Participants completed a 20-page document that amalgamated seven survey instruments: The Sydney Post BMT Study survey (SPBS)—a questionnaire uniquely developed by the research team—and six other instruments previously validated in allo-HSCT populations including the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT–BMT Version 4),[17,18] the Chronic GVHD Activity Assessment–Patient Self Report (Form B),[19] the Lee Chronic GVHD Symptom Scale,[20] the Depression Anxiety and Stress Scale (DASS21),[21] the Post Traumatic Growth Inventory (PTGI)[22] and the Fear of Recurrence Scale.[23]

The Sydney Post BMT Study survey (SPBS) was uniquely designed by the research team to address limitations in existing post-transplant assessments to provide a more comprehensive account of survival. Item construction was informed by a review of the literature, interdisciplinary collaboration among health professionals involved in long-term care of allo-HSCT survivors and consultation with transplant recipients and their carers. There were 402 questions covering 20 domains, including demographics, medical complications, referrals/investigations, pharma- and non-pharmacotherapy, oral/dental health, infections, vaccinations, complementary therapy, cancer screening, travel history, close personal contacts, lifestyle, nutrition, infection risk, work status, fertility and sexual function, relationships, long-term follow-up care, psychosocial concerns and a qualitative question 'What are the three things that have impacted you most?'. The questionnaire used tick box response, short answer questions and 5-step Likert Scale measuring attitudes and other factors. The questionnaire was piloted in clinic and phone interviews to assess face and content validity and to check for comprehension of the survey questions.

Statistical analysis

Exploratory analyses of all demographic data, baseline transplant characteristics, and post-transplant exposures and lifestyle factors were summarised using descriptive statistics. Categorical responses were summarised using frequencies and percentages. Parametric continuous variables were summarised using means and SDs, and non-parametric variables using medians and interquartile ranges. The Pearson Chi-square or Fisher's0 Exact tests were used for dichotomous categorical variables and Pearson's correlation coefficient to assess the relationships between continuous variables. The McNemar test was used to assess for significant differences in the distribution of pre-transplant and post transplant dichotomous variables. Comparisons of means and medians were determined by the independent *t*-test and Wilcoxon Rank Sum tests for two samples; one-way analysis of variance and Kruskal Wallis tests were used when there were >2 samples. Multivariable logistic regression was used to assess for significant associations between explanatory and outcome variables after adjusting for potential confounders. A two-tailed *P* value <0.05 was considered as the level of statistical significance.

Statistical analysis was performed using STATA 12.1 statistical package (StataCorp, College Station, TX, USA).

RESULTS

There were 1475 allo-HSCT performed during the study period. There were 669 recipients alive at study sampling. Of the survivors, 583 were contactable and were sent study packs. Surveys were completed and returned by 443 (66%); while 17 (3%) declined consent and 125 (21%) did not return the survey.

Demographics and transplant characteristics are summarised in Table 1.

Post-allo-HSCT morbidities are detailed for cGVHD (Table 2), chronic morbidities including secondary malignancies (Table 3), and infectious disease (Supplementary Table 1). Summarily, cGVHD was common (69.3%) and self-reported symptoms were moderate-severe in 32.4%. Skin, eye, vagina and mouth were the most symptomatic. The most reported chronic morbidities following allo-HSCT were iron overload (32.5%), osteoporosis/osteopenia (29.1%), hypertension (28.9%) and cataracts (28.9%). Depression and anxiety were reported by 23.3% and 20.6%, respectively. The most frequently reported infections were influenza (38.4%) and herpes zoster (27.9%). A diagnosis of one or more malignancies following allo-HSCT was reported by 24%. The odds for having chronic co-morbidities were compared between those who have cGVHD ($n=301$) and those without cGVHD ($n=133$) (Supplementary Table 2). cGVHD increased the odds of co-morbidities, most significantly for osteoporosis/osteopenia (odds ratio (OR) 1.85, $P=0.01$), cataracts (OR 2.26, $P=0.001$), recurrent upper respiratory tract infections (OR 1.86, $P=0.02$), diabetes mellitus (OR 2.10, $P=0.03$) and anxiety (OR 1.86, $P=0.03$).

Vaccination and health screening uptake are described in Table 4. Assessed screening were the Australian Government's Department of Health national screening for breast carcinoma (women 50–74 years), cervical (sexually active women between 18 and 70 years) and bowel carcinoma (>50 years). Briefly, 52.3% had skin checks, 63.4% and 53.3% of females had papanicolaou (PAP) smear and mammography, respectively, and 66% had regular dental reviews. Only 31.8% had completed transplant vaccinations recommended in the first 12 months post transplant. Allo-HSCT of >2 years was the only variable significantly different between survivors who were not at all vaccinated compared with those who received all inactivated vaccines; survivors >2 years post allo-HSCT were much more likely to be vaccinated than early survivors (adjusted OR 12.2, 95% confidence interval 3.1–49.0, $P=0.001$). Age ($P=0.93$), gender ($P=0.11$), income ($P=0.9$), rural residence ($P=0.71$), marital status ($P=0.26$), education ($P=0.31$) and cGVHD ($P=0.21$) had no effect on vaccination. Polypharmacy was common, 10% were on five and 21% were on six or more medications; Supplementary Table 3 details medication use.

Sexual dysfunction in allo-HSCT survivors was common. Although similar percentages of males and females resumed sexual activity post transplant (males 69.2%, females 68.5%), both genders reported high incidences of sexual difficulties. Two-thirds of females (66.4%) and half of males (51.5%) reported any sexual dysfunction. Being female increased the risk of post-transplant sexual dysfunction (OR 1.8, $P=0.01$), particularly for decreased pleasure (OR 4.3, $P<0.0001$), libido (OR 1.4, $P=0.002$) and dyspareunia (OR 26.1, $P<0.0001$). Erectile dysfunction was reported by 76.6% of males with sexual difficulties.

Specialist medical referrals were common (89%), and the median number of specialty services referred was three. The commonest were dermatology (60.3%), ophthalmology (43.6%), respiratory (28.2%) and endocrinology (23%). Allied healthcare referrals were fewer, with 41% reporting follow-up with at least one allied health specialty; most commonly physiotherapy (24%), dietetics (23%) and clinical psychology (18%). Three-quarters (74.4%) of survivors expressed a preference for long-term follow-up through their transplant centres or a facility linked with their transplant centre including a satellite clinic or telemedicine facility, while a quarter preferred their primary/local haematologist or general practitioner.

Four hundred and twenty-one respondents reported household income before and following allo-HSCT. The proportion of those in the lowest household income strata increased from 21% pre-transplant to 36% post transplant (McNemar $\chi^2=46.3$, $P<0.001$) (Figure 1a). Pre-transplant and post-transplant employment status

Table 1. Survivor demographics and transplant characteristics

Characteristic (number of respondents)	*Number (percent)*
Gender (*n* = 441)	*n* (%)
Male	250 (56.7%)
Female	191 (43.3%)
Age (n = *441)*	
Median	49
19–29	30 (6.8%)
30–39	49 (11.1%)
40–49	83 (18.8%)
50–59	130 (29.5%)
60–69	127 (28.8%)
> 70	22 (5.0%)
Ethnicity (n = *372)*	
Australian/European	323 (86.8%)
Indigenous Australian	2 (0.5%)
Asian	30 (8.1%)
Middle Eastern	7 (1.9%)
Other	10 (2.7%)
Residential location (n = *431)*	
Major City	311 (72.2%)
Inner Regional	85 (19.7%)
Outer Regional	31 (7.2%)
Remote	4 (0.9%)
Years since transplant (n = *441)*	
Median	5
< 2 years	58 (13.2%)
2 to < 6 years	204 (46.3%)
6 to < 10 years	117 (26.5%)
> = 10 < 15 years	62 (14.1%)
Numbers by transplant year (N = *441)*	
2000–2005	136 (30.8%)
2006–2012	305 (69.1%)
Transplant recipients by centre (N = *441)*	
Centre A (Westmead)	193 (43.8%)
Centre B (St Vincent's)	124 (28.1%)
Centre C (Royal North Shore)	72 (16.3%)
Centre D (Royal Prince Alfred)	52 (11.8%)
Underlying diagnosis (N = *423)*	
AML/ALL	169/57 = 226 (53.4%)
CML	21 (5.0%)
CLL	19 (4.5%)
SAA	16 (3.8%)
NHL	79 (18.7%)
HL	5 (1.2%)
MM	14 (3.3%)
MDS/myeloproliferative disorder	39 (9.2%)
Other (unspecified)	4 (0.9%)
Remission status (N = *405)*	
CR1/CR2	271 (66.9%)
> CR2	22 (5.4%)
Chronic phase	18 (4.4%)
Accelerated phase and blast crisis	3 (0.7 %)
Refractory	22 (5.4%)
PR	23 (5.7%)
Other	46 (11.4%)
Donor type (N = *441)*	
Sibling	250 (56.9%)
Haploidentical	10 (2.3%)
Matched unrelated	158 (36%)
Mismatched unrelated	21 (4.8%)
Stem cell source (N = *441)*	
Bone marrow	48 (10.9%)
PBSCT	381 (86.4%)
Cord	12 (2.7%)
Conditioning (N = *439)*	
Myeloablative	214 (48.7%)
TBI containing	101 (47.2%)
Bu/Cy	79 (36.9%)
Cy/TBI	99 (46.3%)
Bu/Flu	28 (13.1%)
Cy/ATGAM	5 (2.3%)
Cy/Flu/ATGAM	1 (0.5%)
Bu/Flu/Thymoglobulin/TBI	1 (0.5%)
Etop/TBI	1 (0.5%)
Reduced intensity	225 (51.3%)
TBI containing	26 (11.6%)
Flu/Cy	24 (10.7%)
Flu/Cy/TBI	14 (6.2%)
Flu/Mel	98 (43.6%)
FLAMSA	1 (0.4%)
Flu/BCNU/Mel/ATG	42 (18.7%)
Flu/TBI	12 (5.3%)
Other (unspecified)	34 (15.1%)
GVHD prophylaxis (N = *440)*	
CSA+MTX	157 (35.7%)
CSA+MTX+pred	166 (37.7%)
CSA+MMF+pred	4 (0.9%)
MTX+pred	10 (2.3%)
Tacro+MTX	0 (0.2%)
CSA+Tacro+MMF	9 (2.0%)
MMF+MTX	0
Other (unspecified)	94 (21.4%)
T-cell depletion (N = *426)*	
Yes	122 (28.6%)
ATGAM/ATG (Fresnius/Thymoglobulin)	113 (92.6%)
Alemtuzumab (Campath)	4 (3.2%)
No	304 (71.4%)
Not reported	5 (4.1%)

Abbreviations: ATGAM = anti-thymocyte globulin; equine; Bu = busulfan; cGVHD = chronic GVHD; CSA = cyclosporine; Cy = cyclophosphamide; Etop = etoposide; FLAMSA = fludarabine, cytarabine, amsacrine; Flu = fludarabine; HL = Hodgkin's Lymphoma; MDS = myelodysplastic syndrome; MM = multiple myeloma; MMF = mycophenolate mofotil; Mel = melphalan; MTX = methotrexate; NHL = non-Hodgkin's lymphoma; PBSCT = peripheral blood stem cell transplantation; Pred = prednisolone; SAA = severe aplastic anaemia; tacro = tacrolimus. This table summarizes characteristics of study participants.

was reported by 404 patients. Two hundred and sixty-one (65%) were in full-time employment pre-transplant, which fell to 130 (32.5%) following allo-HSCT (McNemar $\chi^2 = 106.6$, $P < 0.001$). Importantly, ill-health as a cause for being unable to work increased from 3.4% prior to allo-HSCT to 13.8% after (McNemar $\chi^2 = 33.0$, $P < 0.001$) (Figure 1b). Differences in pre-transplant and post-transplant occupational and income status remained significant when stratified by survival cohort (< 2 years, 2 to < 6 years, 6 to < 10 years, > = 10 years).

QoL measured by the FACT-BMT (Version 4) demonstrated high internal consistency, with Cronbach's alpha for the test scale of 0.83 (Table 5). The correlation between subscale and summary FACT-BMT test scores was highest for functional well-being (correlation coefficient = 0.89) and lowest for social well-being (correlation coefficient = 0.63). Across FACT-BMT domains, social well-being further demonstrated the lowest reliability, with

Table 2. Chronic GVHD

cGVHD characteristic (number of respondents)	*Number (percent)*
cGVHD (*n* = 434)	301 (69.3%)
Male (*n* = 246)	177 (72%)
Female (*n* = 188)	124 (66.0%)
*cGVHD by age group (*N = *434)*	
19–29 (*n* = 30)	19 (63.3%)
30–39 (*n* = 49)	31 (63.3%)
40–49 (*n* = 81)	58 (71.6%)
50–59 (*n* = 129)	89 (69%)
60–69 (*n* = 123)	85 (69.1%)
> = 70 (*n* = 22)	19 (86.4%)
*cGVHD organ involvement (*n = *434)*	
Skin	203 (46.7%)
Eyes	153 (35.2%)
Lungs	79 (18.2%)
Mouth	155 (35.7%)
Liver	99 (22.8%)
Stomach and intestines	61 (14.1%)
Nails	53 (12.2%)
Vagina (females)	41/188 (21.8%)
Penis (males)	13/246 (5.3%)
Muscle/joints	64 (14.5%)
Other organ (not specified)	18 (4.1%)
Not sure	10 (2.3%)
Lee GVHD scores (median, IQR, range)	
Skin score	10 (IQR: 0, 25; Range 0–100)
Eye score	33 (IQR: 8, 75; Range 0–100)
Mouth score	0 (IQR: 0, 25: Range 0–100)
Nutrition score	0 (IQR: 0, 5: Range 0–100)
Lung score	5 (IQR: 0, 15: Range 0–70)
Psych score	17 (IQR: 0, 33: Range 0–100)
Energy score	32 (IQR: 17, 50: Range 0–100)
Global score	19 (IQR 9, 30: Range 0–77)
Vulvovaginal symptoms (females)	45 (46.8%)
*GVHD patient global ratings of symptoms (*N = *111)*	
None	18 (16.2%)
Mild	57 (51.4%)
Moderate	31 (27.9%)
Severe	5 (4.5%)
Symptom severity at study compared with 1 month ago	
Very much better	40 (15.2%)
Moderately better	21 (7.9%)
A little better	34 (12.9%)
About the same	149 (56.5%)
A little worse	13 (4.9%)
Moderately worse	4 (1.5%)
Very much worse	13 (0.8%)

Abbreviations: cGVHD = chronic GVHD; IQR = interquartile range. This table summarizes the incidence, extent and severity of cGVHD in study participants. For the Lee cGVHD score, median and interquartile range are provided.

removal of this item increasing test scale reliability (from 0.83 to 0.85). Mean QoL scores showed no significant differences when stratified by years from transplant ($P = 0.12$). Lee cGVHD score showed a negative correlation with QoL measures (Pearson's correlation coefficient = − 0.63).

In total, 364 (86%) of 441 patients had an underlying cancer diagnosis at transplantation. Median fear of cancer recurrence score in those within 2 years of transplant was 15 (IQR 12, 19; range 5–24) as compared with 13 (IQR 10, 16; range: 5–25) for those who were late transplant survivors ($P < 0.001$).

Table 3. Chronic co-morbidities and secondary malignancies

Co-morbidity (number of respondents)	*Number affected (percentage)*
Chronic medical morbidities	
Hypothyroidism (*n* = 391)	16 (4.1%)
Hyperthyroidism (*n* = 390)	5 (1.3%)
Diabetes mellitus (*n* = 398)	57 (14.3%)
Any of the above (*n* = 395)	75 (19.0%)
Osteoporosis/osteopaenia (*n* = 399)	116 (29.1%)
Avascular necrosis (*n* = 389)	14 (3.6%)
Any spinal/hip fracture (*n* = 392)	17 (4.3%)
Hypertension (*n* = 409)	118 (28.9%)
Hypercholesterolaemia (*n* = 402)	96 (23.9%)
Cataracts (*n* = 409)	118 (28.9%)
Iron overload (*n* = 403)	131 (32.5%)
Recurrent upper respiratory tract infections (*n* = 402)	92 (22.9%)
Malignancies	
Skin cancer (*n* = 404)	93 (23%)
BCC	41 (44%)
SCC	14 (15%)
Melanoma	5 (6%)
Combined mixed	17 (18%)
BCC+SCC	14 (15%)
BCC+melanoma	2 (2%)
SCC+melanoma	1 (1%)
Unspecified/unknown	16 (17%)
Oral cancers (*n* = 392)	6 (1.5%)
Other malignancies (*n* = 370)	18 (4.9%)
Urological (prostate and/or bladder)	5 (27%)[a]
Breast	2 (11%)
Bowel	1 (6%)
Ovarian	1 (6%)
Head (unspecified)	1 (6%)
Myeloid sarcoma	1 (6%)
Haematological–relapsed disease[§§]	2 (11%)
Haematological–secondary malignancy[§]	5 (27%)
Depression and anxiety, self reported	
Self-reported depression (*N* = 407)	95 (23.3%)
Self-reported anxiety or depression (*N* = 403)	83 (20.6%)
Self-reported anxiety and/or depression (*N* = 409)	118 (28.8%)
Depression anxiety and stress scores (DASS21)	*Median (IQR; range)* n = *438*
Depression score	4 (2, 14; 0-40)
Normal (0–9)	287 (65.2%)
Mild (10–13)	41 (9.4%)
Moderate (14–20)	65 (14.8%)
Severe (21–27)	23 (5.2%)
Extremely severe (28+)	22 (5%)
Anxiety score median (IQR, range) *n* = 438	4 (2,10; 0-42)
Normal (0–7)	280 (63.7%)
Mild (8–9)	31 (7.1%)
Moderate (10–14)	58 (13.2%)
Severe (15–19)	23 (5.2%)
Very severe (20+)	46 (10.5%)
Stress score (median, IQR, range) *n* = 437	8 (2,16; 0-42)
Normal (0–14)	315 (72.1%)
Mild (15–18)	35 (8.0%)
Moderate (19–25)	40 (9.1%)
Severe (26–33)	34 (7.8%)
Very severe (34+)	13 (3.0%)
Total DASS21 score median (IQR, range) *n* = 437	20 (8, 40; 0-118)

Abbreviations: BCC = basal cell carcinoma; DASS = The Depression Anxiety Stress Scales, see reference 37; IQR = interquartile range; SCC = squamous cell carcinoma. [§]Two non-Hodgkin lymphomas (primary = AML, severe aplastic anaemia); two Hodgkin lymphomas (primary = NHL); one post transplant lymphoproliferative disease. [§§]One relapsed AML; one relapsed mantle cell lymphoma. This table summarizes the physiological (including malignant) and psychological chronic co-morbidities experienced by study participants, reported as a percentage of respondents. [a]3 prostate, 1 bladder, 1 bladder + prostate.

Table 4. Health checks, cancer screening and vaccination

Health screen/promotion (number of respondents)	*Uptake (percentage)*
Skin checks ($n = 436$)	228 (52.3%)
Colorectal carcinomal screening ($n = 432$)	140 (32.4%)
Cervical carcinoma screening ($n = 186$)	118 (63.4%)
Breast carcinoma screening ($n = 184$)	98 (53.3%)
Prostate checks ($n = 246$)	89 (36.2%)
Regular dental and oral reviews ($n = 436$)	288 (66.1%)
Vaccination uptake status[a] (n = *428)*	
Complete	31.80%
Partial	57.90%
No vaccine	7.20%
Uncertain	3%
Vaccination	
Diphtheria, tetanus, pertussis ($n = 419$)	303 (72.3%)
1 to < 2 years from allo-HSCT	36/56 (64.3%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	75/107 (70.1%)
$\geqslant 10$ years from allo-HSCT	40/57 (70.2%)
Polio ($n = 416$)	280 (67.3%)
1 to < 2 years from allo-HSCT	36/58 (62.1%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	65/106 (61.3%)
$\geqslant 10$ years from allo-HSCT	32/55 (58.2%)
Haemophilus influenza ($n = 405$)	229 (56.5%)
1 to < 2 years from allo-HSCT	30/53 (56.6%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	53/104 (51.0%)
$\geqslant 10$ years from allo-HSCT	17/52 (32.7%)
Hepatitis B ($n = 414$)	270 (65.2%)
1 to < 2 years from allo-HSCT	35/56 (62.5%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	62/105 (59.1%)
$\geqslant 10$ years from allo-HSCT	29/54 (53.7%)
Pneumococcal vaccine for *Streptococcus pneumoniae* ($n = 402$)	226 (56.2%)
1 to < 2 years from allo-HSCT	29/53 (54.7%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	51/106 (48.1%)
$\geqslant 10$ years from allo-HSCT	28/53 (52.8%)
Influenza ($n = 426$)	349 (81.9%)
1 to < 2 years from allo-HSCT	40/56 (71.4%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	95/113 (84.1%)
$\geqslant 10$ years from allo-HSCT	48/58 (82.8%)
Meningococcal vaccine for *Neisseria meningitidis* ($n = 407$)	201 (49.3%)
1 to < 2 years from allo-HSCT	31/54 (57.4%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	47/103 (45.6%)
$\geqslant 10$ years from allo-HSCT	16/55 (29.1%)
Measles, mumps, rubella ($n = 409$)	226 (55.3%)
1 to < 2 years from allo-HSCT	16/52 (30.8%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	66/106 (62.2%)
$\geqslant 10$ years from allo-HSCT	31/57 (54.4%)
Varicella ($n = 399$)	106 (26.6%)
1 to < 2 years from allo-HSCT	11/53 (20.7%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	28/100 (28%)
$\geqslant 10$ years from allo-HSCT	8/53 (15.1%)
Human papillomavirus (females, $n = 174$)	26 (14.9%)
1 to < 2 years from allo-HSCT	1/20 (5%)
2 to < 6 years from allo-HSCT	15/82 (18.3%)
6 to < 10 years from allo-HSCT	9/48 (18.7%)
$\geqslant 10$ years from allo-HSCT	1/24 (4.2%)

The number of patients who take up health checks, screening and vaccination, and as a percentage of respondents are provided. [a]influenza, diphtheria, tetanus pertussis (dTpa), poliovirus, hepatitis B, haemophilus influenza type b (Hib), pneumococcus and meningococcus.

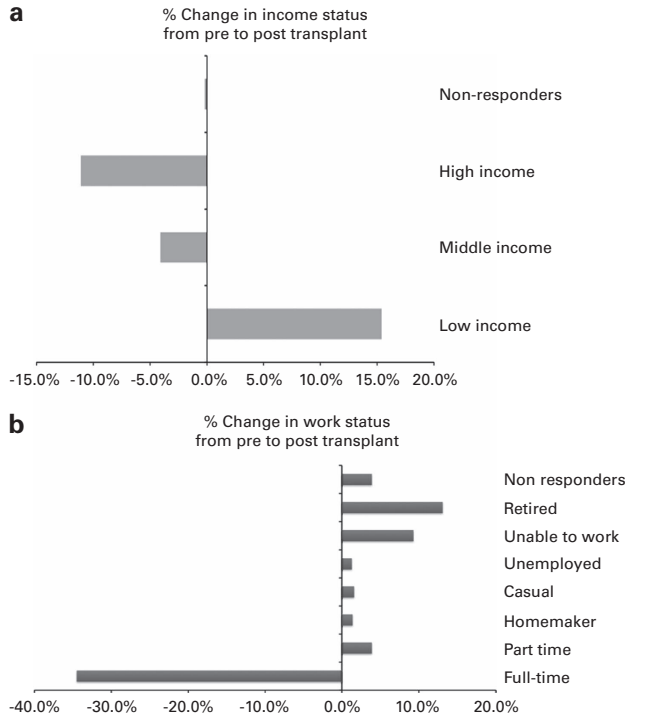

Figure 1. (**a**, **b**) Social changes following allo-HSCT; (**a**) income (**b**) work status. Change in income as a percentage following allo-HSCT is shown in **a**. Change in employment status as a percentage following allo-HSCT is shown in **b**. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

There were some differences between genders in personal growth following allo-HSCT measured by PTGI; females exhibited greater growth than males in relationship with others ($P < 0.001$), personal strength ($P < 0.001$) and spiritual growth ($P < 0.001$).

DISCUSSION

This study is the largest and most comprehensive assessment of allo-HSCT survivorship in a contemporary Australian cohort. The results reveal a high incidence and broad range of physiological and psychosocial complications that adversely affect the health and functional status of survivors.

The incidence of cGVHD was 69% for the studied group, which is within reported ranges in the literature despite an older cohort (median age 54), utilisation of unrelated and mismatched donors (43.1%) and PBSC (86.4%).[1,24,25]

Chronic physiological effects were common with 57% of the study group reporting two or more active medical co-morbidities. Importantly, cGVHD increased the odds of chronic medical and psychological sequelae, particularly osteoporosis/osteopenia, diabetes mellitus, cataracts, recurrent respiratory tract infections and anxiety.

After cGvHD, sexual dysfunction was the most adversely affected domain following allo-HSCT reported by allo-HSCT survivors in this study. Over 95% of study participants provided insight into resumption of sexual activity following allo-HSCT, which was similar between males and females (69%). Approximately 60% of respondents reported sexual difficulties post transplant (66.4% females, 51.5% males). As sexual dysfunction likely results from multiple chronic physical and psychological co-morbidities, our results suggest the need for a comprehensive multidisciplinary approach to prevention and management that includes education of allo-HSCT candidates and partners prior to transplantation, ongoing assessment and counselling post

Table 5. Quality of life, FACT–BMT

	ALL survivors		*< 2 years post allo-HSCT*		*2 to < 6 years post allo-HSCT*		*6 to < 10 years post allo-HSCT*		*⩾ 10–14 years post allo-HSCT*	
	Mean (s.d.)	*Cronbach alpha*	*Mean (s.d.)*	*Cronbach alpha*	*Mean (s.d.)*	*Cronbach alpha*	*Mean (s.d.)*	*Cronbach alpha*	*Mean (s.d.)*	*Cronbach alpha*
Physical well-being (PWB)	22.4 (5.4)	0.9	21.2 (5.9)	0.91	22.4 (5.4)	0.9	22.7 (5.1)	0.91	22.8 (5.2)	0.9
Social well-being (SWB)	20.0 (5.6)	0.91	20.1 (5.6)	0.92	20.5 (5.6)	0.91	19.9 (5.4)	0.91	19.5 (6.2)	0.91
Emotional well-being (EWB)	16.3 (3.6)	0.91	15.5 (3.6)	0.92	16.4 (3.4)	0.91	16.7 (3.5)	0.91	15.9 (4.8)	0.91
Functional well-being (FWB)	19.3 (6.5)	0.9	17.5 (6.8)	0.9	19.4 (6.3)	0.89	20.0 (6.6)	0.89	19.1 (6.1)	0.89
BMT score (BMTS)	27.8 (6.3)	0.9	25.7 (7.8)	0.9	27.6 (6.1)	9.9	28.5 (5.7)	0.9	28.9 (5.7)	0.9
FACTG (PWB+SWB+EWB+FWB)	78.3 (16.2)	0.87	74.4 (17.8)	0.87	78.7 (16.1)	0.87	79.8 (15.8)	0.87	77.8 (15.8)	0.86
FACT–BMT total score (FACTG+BMTS)	106.0 (21.5)	0.89	100.0 (24.8)	0.89	106.3 (21.1)	0.88	108.3 (20.6)	0.87	106.7 (20.1)	0.87
FACT–BMT Trial Outcome index (PWB+FWB+BMTS)	69.5 (16.1)	0.87	64.4 (18.8)	0.88	69.4 (15.9)	0.87	71.4 (15.3)	0.87	70.9 (14.9)	0.87

Results of the FACT–BMT are summarised. Mean, s.d. and Cronbach alpha for all respondents, and respondents classified into time periods post allo-HSCT are provided.

transplant and early specialist referral to prevent delayed diagnosis and treatment.

The psychosocial impact of allo-HSCT was profound, affected by loss of employment and reduced income. Social re-integration was modest, with significant underemployment, unemployment and non-return to work (most often as a consequence of chronic ill-health), and increase in the number of survivors in the lowest income bracket. Although strategies aimed at the prevention and treatment of chronic physical and psychological complications of allo-HSCT may improve social re-integration and minimise financial disenfranchisement, these are unlikely to completely ameliorate the psychosocial impacts of allo-HSCT. These results suggest potential transplant recipients should receive pre-transplant and post transplant counselling and be directed to seek appropriate assistance to reorganise their finances and assets. This study shows that 'financial toxicity' is an adverse effect of allo-HSCT that should be considered on par with other long-term effects. In addition, financial stress may contribute to non-adherence and lifestyle modifications that are detrimental to a survivor's QoL.[26] A graded, objective measure of financial toxicity is needed.[27,28]

Improvements in vaccination and uptake of screening following allo-HSCT are urgently needed. Less than a third of respondents had completed the recommended post-transplant vaccination schedule, and this is reflected by a high incidence of vaccine-preventable diseases (42%). These alarming statistics suggests that current systems are resulting in an unacceptably high 'miss' rate and arguably mandate a change in vaccination promotion and delivery. Furthermore, national immunisation guidelines for allo-HSCT and other transplant recipients have been available and published within the most recent editions of the national Australian Immunisation handbook that is easily accessible to the public and healthcare workers. In this regard, it is noteworthy that in multivariate analysis, demographic differences and the presence of cGVHD had no effect on vaccination uptake, whereas those who had an allo-HSCT for over 2 years were 12 times more likely to be vaccinated. The results suggest that there are barriers to vaccination during the first 2 years post transplant and that these are unrelated to the presence or severity of cGvHD or to baseline demographics. Of those who had received vaccinations (31% complete, 51% partial), three-quarters were administered by general practitioners—an important reminder both of the importance of primary/local healthcare providers in the long-term care of allo-HSCT recipients and of the need for ongoing communication with, and education of, health practitioners involved in the care of survivors.[29,30] That said, the fact that most allo-HSCT survivors receive post-transplant care through their transplant centre and express a preference for centrally coordinated care suggests that long-term follow-up clinics may need to provide post transplant vaccination service, at the very least for survivors who do not have a general practitioner.

Other health screenings assessed in the study were also suboptimal. Only 52% of respondents had routine skin checks, a disappointing response given the high incidence of skin malignancies following allo-HSCT and the high background incidence of both melanoma and non-melanoma cancers in Australia.[31,32] Likewise, only 63% and 53%, respectively, of female survivors of allo-HSCT had had recommended PAP smear cervical carcinoma screening and 53% screening mammography. Just two-thirds of survivors have regular dental/oral reviews; older age, higher income and residing in a metropolitan area were predictors of regular dental review. Non-attendance was reported to be due to finances by a third and due to thinking that dental reviews were unnecessary by another third. There is an urgent need for education about the long-term effects of oral health following allo-HSCT. These results may also evidence systemic failings as it is well recognised that there are a number of financial and structural barriers that prevent Australians accessing affordable dental care;

with a 2010 Australian Institute of Health and Research survey reporting that 30% of adults avoided dentists owing to costs (http://www.aihw.gov.au/dental/cost/). Although there are public dental services in New South Wales, and some transplant centres have access to hospital-based dental clinics, the waiting times are long and the location inconvenient for many survivors.

Summarily, these results suggest that survivors with cGVHD should receive additional psychological intervention, dedicated screening and aggressive prevention and treatment of osteoporosis/ostepenia and diabetes mellitus. Other groups identified in need of additional focus to reinforce and improve health screening are younger transplant recipients, those with less education, those in the 'early' post-transplant period and survivors residing in rural/regional Australia.

Although the large number of participating survivors, high response rate, multi-centre cohort and comprehensive assessment makes it likely that these results represent an accurate account of the experience of contemporary survivors of allo-HSCT in Australia, there are a number of factors that may limit the generalisability of these results to allo-HSCT survivors in other countries and settings.

First, despite the high response rate (76%), participation was incomplete resulting in possible participation bias. Second, the study was a cross-sectional study that included only those alive at study recruitment, thereby excluding those who may have died because of post-transplant complications, which may have been more rapidly progressive or highly lethal. Third, the use of a questionnaire as the research methodology has well-recognised inherent limitations, including recall and misclassification biases that, despite piloting, the use of validated instruments and simple English, could potentially limit self-reported response internal validity. Misclassification biases may go in either directions, thereby over-estimating or under-estimating effects. Fourth, the veracity of participants' responses was not compared with medical records, which may compromise factorial validity. Fifth, the questionnaire could not distinguish between the effects of cGVHD from complications of its treatment—a limitation that may be of no consequence to the study of chronic health, as most survivors with cGVHD require prolonged immunosuppression. Sixth, the respondents to this study were disproportionately white/Caucasians (86.9%), thus limiting the ability to generalise to other ethnic groups.

This study provides the largest and most comprehensive account of the incidence and range of late complications following allo-HSCT in a contemporary population of Australian survivors. For the most part, the incidence of cGVHD and chronic post transplant co-morbidities were similar to that reported in available literature.[6,24,25] Our results also reveal the extent to which allo-HSCT transforms the lives of survivors—causing psychological, social and sexual dysfunction, financial insecurity and occupational vulnerability in many survivors. Perhaps most worryingly, this study also suggests that the care of allo-HSCT recipients is deficient in many ways, with suboptimal health screening, dental care and vaccination uptake as areas of unmet need in Australian allo-HSCT survivors. Addressing these deficiencies will clearly require a multidisciplinary approach and may necessitate changes in the delivery of healthcare to Australian patients. Extrapolating from paediatric experiences[33–35] and overseas models (such as the Fred Hutchison Cancer Research Centre/Seattle Cancer Care Alliance or MD Anderson Cancer Centre in the United States),[30] centralized co-ordination through a long-term follow-up survivor's clinic may best address inadequacies of the current system. Such structures may avoid fragmentation of services and provides continuity of care, both of which are essential to address complex problems such as sexual dysfunction and adherence/compliance with health promotion. But the success of such a service cannot be assumed and would need to be the focus of ongoing research. Irrespective of what model of care proves to be most effective, the results of this study make clear that as allo-HSCT recipients live longer, the focus of care and resources must proportionately shift to improving their QoL and optimising their experience of survivorship.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)

5.5. Synopsis

This paper presents the most comprehensive account of the experience of survival in an Australian cohort of allogeneic BMT recipients. It provides detailed data on late effects of BMT which enable comparison with registry and single centre data from international transplant centres. In addition, these data provide the first account of a number of hitherto unknown aspects of BMT survivorship e.g. the financial and occupational impact of BMT, and so enables identification of areas of unmet need.

Other areas of unmet need revealed by these data include adherence with general population cancer screening guidelines, dental care, vaccination uptake and prevalent sexual dysfunction. The insights described here are important because each of them significantly adds to the burden of illness experienced by BMT survivors and may increase their morbidity and mortality. These issues are explored further in subsequent chapters of this thesis:

- Cancer screening in Chapter 8
- Dental care in Chapter 11
- Vaccination uptake in Chapter 12 (in press manuscript)
- Sexual dysfunction in Chapter 7
- Income and occupational changes in Chapter 10

Importantly, these data add significantly to what is known about BMT survival in Australia. While the ABMTRR follow BMT recipients for life, it only collects information on; date last seen, relapse, secondary cancers, cGVHD and death. The lack of comprehensive regular and uniform data collection on all aspects of BMT survivorship makes it difficult to determine the extent of the impact of long-term BMT survival, how morbidity may change over time and how long-term morbidity and mortality varies or compares to national and international outcomes. These data are critical for any subsequent efforts to improve long-term survivorship.

In this regard it is noteworthy that since publication of this manuscript the ABMTRR commenced a pilot project (ASTRO BMT LTFU Module) to include data fields addressed in this study including screening and preventative care tests and assessments. It is anticipated that potential future implementation of this LTFU Module nation-wide would greatly increase Australia and NZ's ability to improve LTFU outcomes and survivorship, to monitor progress and inform heath care delivery, patient and clinician education and informed consent requirements in real-time. Indeed, without collection of data on long-term outcomes, the types of long-term issues identified in this study will continue to compromise BMT survival and QoL.

The results of this study have important implications for BMT patients, BMT units, haematologists, GPs, APNs and others who are involved in the care of BMT survivors. These results are also relevant to state government policymakers, who have committed to keep people healthy and out of hospital(1).

While these results provide important metrics about BMT outcomes, they also raise important questions for future research and for those concerned with the design and delivery of health care services for BMT survivors. The challenge for policymakers and health care providers is two-fold: firstly to prove that screening and preventive care, and comprehensive LTFU can reduce the late effects of BMT and improve the experience of BMT survival, and secondly, to articulate the ways in which the unmet needs of BMT survivors can be addressed and the care that they are provided with be improved.

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Chapter 6: What they want: inclusion of blood and marrow transplantation survivor preference in the development of models of care for long-term health in Sydney, Australia

6.1. Chapter overview

This chapter reports on BMT survivors preferred MOC for the delivery of LTFU. It consists of a published manuscript entitled, 'What They Want: Inclusion of Blood and Marrow Transplantation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia'. The manuscript reports on the demographic, socioeconomic, transplant factors, and complication of BMT associated with different preferences for follow-up. Specifically, BMT survivors were asked about preferred location (transplant centre and/or local health care setting including satellite clinic and telemedicine options), provider (transplantation team and/or local/referring haematologist and/or general practitioner) and model (specialised LTFU care provided at one site only, or shared care).

Overwhelmingly, the results showed that BMT survivors want their transplant team involved (in some form) in their long-term care. This is particularly true for BMT survivors who experience cGVHD. This has major resource implications for BMT centres as they need to ensure provision of equitable and high quality long-term care, accommodate the care preferences of BMT survivors and ensure the sustainability of inpatient and outpatient care in the context of finite health resources. Just as importantly however, our results emphasise the importance of other health care providers in the long-term care of BMT survivors including subspecialist, referring haematologists, local medical practitioners advanced practice nurses and other allied health care staff. This suggests that further work will be required to ensure optimal communication and collaboration within the health sector, particularly as BMT survivors move between different health providers and different health care contexts during the course of their illness and recovery.

6.2. Publication details

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6.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

6.4. Manuscript

The published version of the manuscript follows.

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Clinical Research: Analysis

What They Want: Inclusion of Blood and Marrow Transplanation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia

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A B S T R A C T

Four hundred forty-one adult allogeneic blood and marrow transplantation (BMT) survivors participated in a cross-sectional survey to assess long-term follow-up (LTFU) model of care preference. Survey instruments included the Sydney Post BMT Survey, Functional Assessment of Cancer Therapy-BMT, Depression Anxiety Stress Scales 21, the Chronic GVHD Activity Assessment—Patient Self Report (Form B), the Lee Chronic GVHD Symptom Scale and the Post-Traumatic Growth Inventory. We found most BMT survivors (74%) would prefer LTFU with their transplantation physicians alone or in combination with transplantation center–linked services (satellite clinics or telemedicine) Over one-quarter indicated a preference for receiving comprehensive post-transplantation care in a "satellite" clinic staffed by their BMT team situated closer to their place of residence, with higher income, higher educational level, and sexual morbidity being significant social factors influencing this preference. Regular exercise was reported less often in those who preferred telemedicine, which may reflect reduced mobility. The factor most strongly associated with a preference for transplantation center follow-up was the severity of chronic graft-versus-host disease. Full- and part-time work were negatively associated with transplantation center follow-up, possibly implying decreased dependency on the center and some return to normalcy. This study is the first to explore the preferences of BMT survivors for long-term post-transplantation care. These data provides the basis for LTFU model of care development and health service reform consistent with the preferences of BMT survivors.

INTRODUCTION

Advances in transplantation technologies, better patient and donor selection, and improved supportive care over the past 2 decades have significantly improved outcomes of bone marrow transplantation (BMT) such that 70% to 80% of those who are alive at 2 years can expect to live long term [1,2]. Unfortunately, many of these survivors experience significant late morbidity and mortality. A collective effect of underlying disease and comorbidities, prior treatment, toxicity of conditioning therapies and immunosuppression, and effects of graft-versus-host disease (GVHD) [3-5] results in a 59% cumulative incidence of developing a chronic health condition by 10 years after transplantation [6], a 3.5-fold increased risk of developing a severe or life-threatening condition compared with siblings [7], and a 30% lower life expectancy in adult BMT survivors [8]. Each of these

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long-term and late effects are even more profound in adult survivors of childhood BMT [9-11]. Life-long follow-up is, therefore, essential to optimize the benefit and minimize the prevalence and impact of the adverse late effects of BMT [12].

Consensus guidelines for screening and preventative practices for long-term survivors of BMT have been available for almost a decade [13,14]. These guidelines, agreed to by 7 international BMT organizations, outline the surveillance tests, clinical assessments, and preventative care that BMT survivors require at regular intervals—for life—to monitor for recurrent and secondary malignancies; chronic GVHD; infections; respiratory, cardiovascular, renal, musculoskeletal, ocular, oral, gastrointestinal, dermatological, and endocrine dysfunction; and psychosocial issues, among others. Given the range of morbidities experienced by BMT survivors, it is unsurprising that a BMT survivor receiving follow-up care according to these guidelines would require up to 34 assessments annually; including health history, clinical examinations, laboratory analysis, diagnostic imaging, psychosocial assessments, health counseling and education; and involve at least 6 clinical specialties [14]. This demand is likely to increase in coming years as the indications for BMT expand, more recipients of BMT survive [15], knowledge of late effects increases, and the BMT physician workforce plateaus [16,17]. Although there is broad agreement about the necessity for comprehensive follow-up of BMT survivors, the demand for long-term follow-up (LTFU) is placing an overwhelming demand on the capacity of transplantation centers (TC) that have historically been responsible for such care. Given the diverse needs of transplantation survivors and the variable capacity of TCs to provide LTFU [18], different models for delivery of long-term health care for BMT survivors have been developed. Drawing on experience in both cancer survivorship and chronic care, these models of care include variations of specialized LTFU clinics at BMT centers, referral back to local hematologists and/or primary care providers, shared care models, telemedicine, and videoconferencing [12,19-25].

Patterns of BMT activity, BMT survival, and issues with BMT LTFU in Australia mimic international trends [26]. BMTs are only performed in selected major urban tertiary centers that have the necessary expertise, training, resources, and accreditation. BMT recipients who live in rural and regional areas must relocate to metropolitan areas for the pre, peri-, and acute post-transplantation period. Returning to their homes, many BMT survivors experience difficulties with access to and cost of specialist services, fragmentation of care, and poor communication in a complex health care system, which includes public and private services, and are easily lost to follow-up, particularly as time from transplantation increases. This has meant large variations in care and long-term outcomes, particularly for BMT units that perform fewer than 50 allogeneic transplantations per year. Establishing an effective model of long-term care is essential to reduce late effects and prevent premature mortality [12]. We report the results of a cross-sectional study of long-term survivors of BMT in New South Wales (NSW), Australia to identify their preferences for long-term care; to examine the demographic, socioeconomic, and transplantation factors and sequelae associated with different preferences for follow-up; to identify gaps in service provision provided to this vulnerable and high-risk patient group; and to support clinical and health policy decision-making around long-term care.

METHODS

Background to NSW BMT Service

NSW is Australia's most populous state, with a population of ~ 7.5 million, and covers an area of 800,628 km [2]. Over one third of the residents live outside the greater Sydney area [27]. At the time of study commencement, there were 4 adult allogeneic centers in NSW, all based in Sydney and collectively performing approximately 175 BMTs annually [26]. A survey of BMT survivors was undertaken to explore survivors' health status, demographics, service utilization, and follow-up preferences.

Patients and Procedures

Potential participants were identified from allogeneic transplantation databases from all adult allogeneic TCs in NSW. Participants were eligible if they were ≥18 years of age (at the time of survey) and had undergone an allogeneic BMT at an adult BMT center between January 1, 2000 and December 31, 2012, were ≥17 years at the time of transplantation, could read and write English, and could provide consent. Names and phone numbers were provided to the research team. Consenting participants were given the option to self-complete the questionnaire or complete it via a phone interview with 1 of the researchers. A second round of telephone calls was made to 178 participants who had not returned the survey within 1 month. All authors had access to primary clinical trial data. The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Instruments

The Sydney Post-BMT Study Survey was developed by the research team from a review of the literature and discussion with patients attending BMT LTFU clinics. The survey comprised 402 questions grouped into 20 domains and included questions relating to specialist referrals and LTFU preferences with respect to location and provider. Other relevant domains included demographics, medical complications, tests and assessments, medications and therapies, infections, vaccinations, complementary therapy use, cancer screening, relationship status income, and lifestyle factors after allogeneic BMT. The questionnaire used tick-box responses, short-answer questions, and 5-step Likert scales measuring attitudes and other factors and took approximately 1 hour to complete. The questionnaire was piloted with 6 BMT survivors in clinic and phone interviews to assess face and content validity and to check for comprehension. For each consenting participant, data were collected on dates of diagnosis and transplantation, stage/remission status at transplantation, transplantation conditioning, GVHD prophylaxis, stem cell source, and donor type.

Preference for LTFU for specialist care and health service utilization were analyzed according to a range of demographic, transplantation, psychosocial, and lifestyle variables assessed using the Functional Assessment of Cancer Therapy—Bone Marrow Transplant (FACT-BMT Version 4) [28,29], anxiety stress and depression (the DASS 21) [30-32], chronic GVHD (Chronic GVHD Activity Assessment—Patient Self Report [Form B] [33] and the Lee Chronic GVHD Symptom Scale) [34], and the Post-Traumatic Growth Inventory score [35,36]. For ease of completion, all instruments were combined into 1 booklet.

Statistical Analysis

Categorical responses were summarized using frequencies and percentages. Parametric continuous variables were summarized using means and standard deviations, and nonparametric variables using medians, interquartile ranges, or ranges. Odds ratios (OR) and 95% confidence limits (CI), Pearson chi-square test, or Fishers exact tests were used for comparative analysis of dichotomous categorical variables. Adjusted OR (AOR) to account for potential confounding effects were determined using multivariable logistic regression analysis. Two sample comparisons of parametric and nonparametric data were determined using the independent *t*-test, and Wilcoxon rank-sum tests, respectively; greater than 2 sample comparisons were determined using 1-way analysis of variance and Kruskal Wallis tests. A 2-tailed P value $< .05$ was used as the level of statistical significance.

Statistical analysis was performed using STATA version 12.1 statistical package (StataCorp, College Station, TX).

RESULTS

A total of 1475 allogeneic BMT were performed in the study period. Of the 667 recipients known to be alive at study sampling, 581 (87%) were contactable and were sent study packs. Four hundred forty-one (66% of total eligible, 76% of those contacted) returned the completed survey. Three percent declined participation.

Of those completing the survey, 250 (57%) were male and 191 (43%) were female. The median age of survey respondents was 54 years (range, 19 to 79). The median age at time of transplantation procedure was 49 years (range, 17 to 71). (Table 1)

LTFU Provider Preferences

One or more preferences for medical follow-up were indicated by those surveyed (Figure 1). Overall, 275 (62.3%) preferred a single provider for their primary transplantation follow-up (ie, general practitioner [GP] alone, local hematologist [LH] alone, or transplantation physician [TP] alone). An additional 149 (33.8%) preferred a combination of providers and 17 (3.8%) indicated no preference.

The majority (44.9%) of those surveyed indicated a preference for their TP alone to be primarily responsible for their LTFU care. The second preferred option included a combination of TP and LH (14.2%), followed by LH alone (13.1%), GP and LH and TP (7.7%), GP and TP (7.7%), GP alone (4.3%), or GP and LH (4.1%) (Figure 1).

Of the 441 patients surveyed, 329 (74.6%) indicated a follow-up preference that included a TP, 173 (39.2%) included a LH, and 105 (23.8%) included a GP.

Table 1
Demographic, Social, and Clinical Characteristics of Transplantation Survivors Responding to Survey (n = 441)

Characteristic	Distribution
Sociodemographic	
Gender (male) n/total (%)	250 of 441 (57)
Age, median (range), yr	54 (19-79)
Postcode location	
City/inner regional n/total (%)	396 of 431 (92)
Income status (AUD) n/total responses (%)	
Low income $20,000-$39,999	155 of 423 (37)
Middle income $40,000-$79,999	123 of 423 (29)
High income ≥ $80,000	145 of 423 (34)
Educational status n/total responses (%)	
Some high school	53 of 333 (16)
Completed high school	79 of 333 (24)
Trade qualifications/diploma	47 of 333 (14)
Some university	24 of 333 (7)
Completed university	130 of 333 (39%)
Transplantation factors	
Time since transplantation, median (range), yr	5 (1-14)
Underlying diagnosis n/total responses (%)	
Acute leukemia	226 of 423 (53)
Other*	197 of 423 (47)
Donor type n/total responses (%)	
Sibling related	250 of 439 (57)
Matched unrelated	158 of 439 (36)
Haploidentical/mismatched	31 of 439 (7)
Conditioning n/total responses (%)	
Myeloablative	214 of 439 (49)
Reduced intensity	225 of 439 (51)
Post-transplantation morbidity and quality of life	
cGVHD	
Total reported cGVHD since transplantation n/total responses (%)	301 of 434 (69)
Total LEE GVHD score, median (range)	19 (0-77)
Chronic diseases/psychological morbidity n/total responses (%)	
Bone disease (osteopenia, spinal fractures, or avascular necrosis)	126 of 400 (32)
Cardiovascular risk factors (diabetes, hypertension, or elevated cholesterol)	180 of 414 (43)
Cancer (mouth, skin, or other)	108 of 389 (28)
Anxiety	83 of 403 (21)
Depression	95 of 407 (23)
DASS21, median score (range)	20 (0-118)
Lifestyle n/total responses (%)	
Smoke	33 of 438 (7)
Drink alcohol	282 of 441 (64)
Exercise/play sport	300 of 436 (69)
Always use sun protection (sunscreen, hat, clothing sunglasses)	333 of 431 (77)
BMI, median (range) for males	25 (17-63)
BMI, median (range) for females	24 (16-53)
Total FACT BMT, median (range)	110 (32-144)

AUD indicates Australian dollars; DASS, depression anxiety stress scales; BMI, body mass index; FACT, functional assessment of cancer therapy.

* Other includes chronic myeloid leukemia, chronic lymphocytic leukemia, severe aplastic anemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, myelodysplastic disorder/myeloproliferative disease, and other (unspecified).

Setting or Location for LTFU Care

Of the locations for delivery of LTFU care, 234 (53%) survey respondents indicated a single site as their preferred option, and 185 (42%) indicated a preference for a combination of locations. Overall, 22 (5%) indicated no preference for LTFU location. Figure 2

TC

Overall, 328 of 441 (74%) BMT survivors reported a preference for follow-up at TC alone or in combination with other provider locations, such as satellite clinics linked with a TC or telemedicine services administered by the primary TC. Of the entire cohort, TC alone was the preferred option by 121 (27.4%) and LH practice alone was preferred by 57 (12.9%). Twenty-one (5%) indicated a preference for follow-up with GP practice alone, 18 (4.1%) for telemedicine alone, and 17 (3.8%) for satellite clinic alone (Figure 2). Four of 7 patients with post-transplantation hematological malignancies (2 relapse, 5 unspecified) nominated a LTFU preference with LH alone. Appendix 1

On univariate analysis, variables associated with an increased preference for TC or TC-linked follow-up included being in a married/de facto relationship (OR, 1.67; $P = .04$) and sexual dysfunction (OR, 2.15; $P = .006$). Those in full-time or part-time employment indicated a decreased though nonsignificant preference for follow-up with TC or TC-linked services (OR, .67; $P = .08$). On multivariable analysis, no variables showed a significant association with a preference for TC or TC-linked follow-up. Those reporting increased severity of GVHD symptoms showed a trend towards increased preference for TC or TC-linked follow-up (AOR, 1.16; 95% CI, .99 to 1.36; $P = .06$) and those in full- or part-time employment showed a trend towards decreased preference for TC or TC-linked follow-up (AOR, .44; 95% CI, .19 to 1.03; $P = .06$).

No significant differences in nontransplantation-related chronic disease, cancer, or psychological morbidity were observed in those who preferred LTFU in a TC or TC-linked service.

No significant difference in cancer screening was observed between survivors preferring LTFU with TC or TC-linked service, with the exception of Pap smear uptake in females. Females preferring follow-up through TC or TC-linked services were less likely to report having had a post-transplantation Pap smear (OR, .50; 95% CI, .22 to 1.06: $P = .05$). After adjusting for potential confounders including age, educational status, residential location, marital status, GVHD severity, and sexual dysfunction, no significant difference was observed (AOR, .19; 95% CI, .03 to 1.25; $P = .08$).

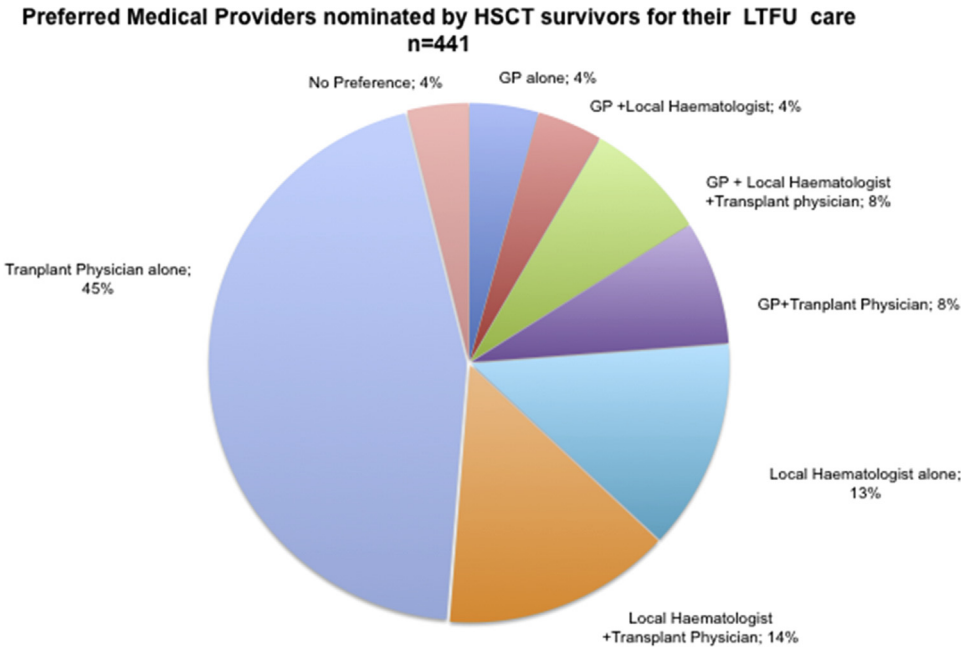

Figure 1. Distribution of preferred medical providers nominated by HCST survivors for their LTFU care.

Satellite Clinic

Overall, 119 of 441 (27.0%) BMT survivors indicated a preference for LTFU that included a satellite clinic attended by a TP from the center where they had received their allograft. Of these, 17 (14.3%) indicated a preference for satellite clinic follow-up alone, with the remainder indicating a preference for satellite clinic in combination with other LTFU options. Appendix 2

Those preferring LTFU in satellite clinic settings were more likely to be from a middle/high income group (OR, 1.98; 95% CI, 1.20 to 3.33; $P = .005$) and to have a higher educational status (OR, 2.07; 95% CI, 1.23 to 3.49; $P = .003$), defined as partial or complete attainment of a university qualification.

The rates of chronic GVHD (cGVHD) did not differ significantly between groups expressing a positive or negative preference for satellite clinic follow-up. However, the self-reported cGVHD symptoms described as moderate/severe were significantly lower in those preferring follow-up in a satellite clinic setting (OR, .55; 95% CI, .29 to 1.0; $P = .04$), and median self-reported current GVHD severity scores were significantly lower ($P = .05$).

Sexual dysfunction was significantly higher in those expressing a preference for satellite clinic follow-up (OR, 2.61; 95% CI, 1.46 to 4.74; $P < .001$).

After adjusting for potential confounders, those factors that retained a significant association with a preference for satellite clinic care included higher income status (AOR, 4.67;

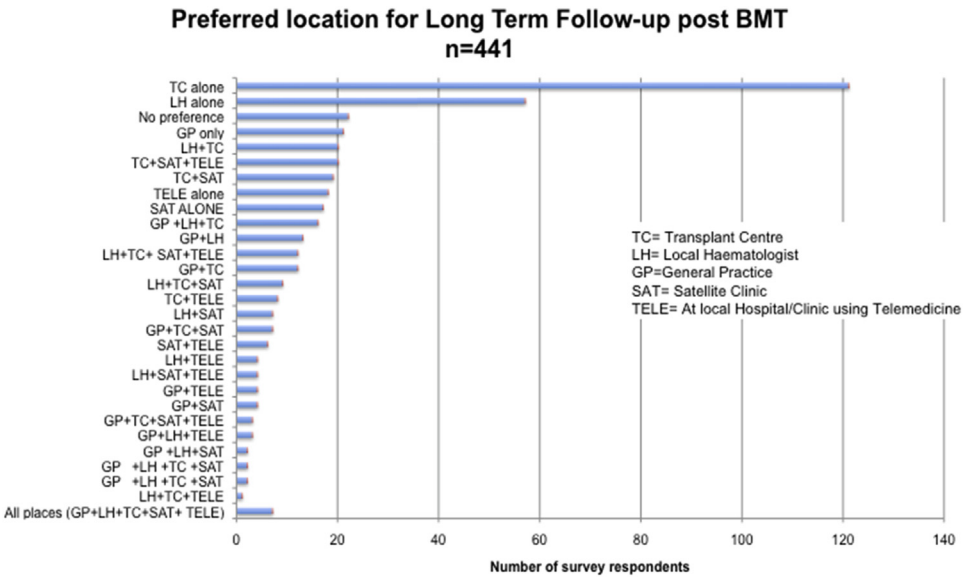

Figure 2. Location preference for LTFU.

95% CI, 1.22 to 17.8; $P = .02$), educational status (AOR, 3.26; 95% CI, 1.28 to 8.30; $P = .01$), and sexual dysfunction (AOR, 3.27; 95% CI, 1.21 to 8.78; $P = .02$).

Telemedicine Location for LTFU

Overall, 92 of 441 (20.9%) BMT survivors reported a preference for follow-up that included a telehealth facility. Of these, few (18, 19.6%) indicated a preference for LTFU using telehealth alone, with the majority indicating a preference for telehealth in combination with LH practice, TC, satellite clinic, or GP practice.

Patients preferring the use of telehealth in LTFU compared with those who did not tended to be younger (median, 52 versus 55 years; $P = .07$), to have significantly higher educational status ($P = .004$), and to have been conditioned using a myeloablative regimen ($P = .06$). Appendix 3

Higher psychological morbidity in those preferring telemedicine was reflected in higher median DASS21 scores (22 versus 18; $P = .03$) and a trend towards higher self-reported anxiety and/depression ($P = .06$). Sexual dysfunction was more commonly reported in those expressing a preference for telemedicine (OR, 3.96; 95% CI, 1.20 to 16.8; $P = .06$). After adjustment for potential confounders using multivariable logistic regression, those factors that retained significance included educational status (AOR, 5.10; 95% CI, 1.72 to 15.1; $P = .003$) and sexual dysfunction (AOR, 3.25; 95% CI, 1.02 to 10.3; $P = .05$).

A reduced odds of regular exercise (OR, .6; 95% CI, .4 to 1.0; $P = .04$) was reported in those patients reporting a preference for telemedicine. After adjusting for age, gender, chronic diseases, and GVHD severity, exercise remained independently and significantly associated with reduced telemedicine preference (AOR, .46; 95% CI, .24 to .87; $P = .02$).

No significant differences were reported for cGVHD, self-reported severity of GVHD symptoms, and Lee GVHD scores in those preferring telehealth compared with those preferring non–telehealth-based locations for LTFU.

Specialist and Allied Health Referrals

The median number of specialist medical referrals was 3 (interquartile range, 1 to 4; range, 0 to 11) with the most common referral being to ophthalmologists (60.1%), dermatologists (43.7%), and, in women, gynecologists (51.6%). Forty-eight percent had been referred to 1 or more allied health professionals (range, 0 to 6), including physiotherapists (24.3%), dietitians (23.8%), and psychologists (19.0%) (Figure 3).

One third (19 of 57, 33.3%) of those who were within 2 years of transplantation were attending a hospital or medical/practice facility at least once per month, and of these, 9 of 19 (47%) were being seen at least weekly. Of those who were 2 or more years since transplantation, medical practice or hospital attendances were reported at least monthly in 98 of 376 (26%) and of these, 76 of 98 (77%) were attending a medical facility at least weekly. A requirement to stay overnight and close to the hospital/medical facility was reported by 52 of 439 (11.8%) of survey respondents. The variety of accommodation arrangements for those who are required to stay overnight included hospital accommodation (16 of 52, 30.8%) other subsidized accommodation (from charitable organizations/foundations (10 of 52, 19.2%), lodging with friends or family (23 of 52, 44.2%), and paid accommodations (20 of 52, 38.5%)).

DISCUSSION

There is now broad agreement that LTFU is necessary to reduce the mortality and morbidity associated with BMT [12,14]. How this care should be delivered, however, remains uncertain and contested [20,21]. This study is the first to explore the preference of BMT survivors for long-term post-transplantation care.

The results of this study confirm what is known about post-BMT survival that health care utilization by long-term BMT survivors is high [37], that cGVHD is a major determinant of quality of life [38], and that medical issues, fatigue,

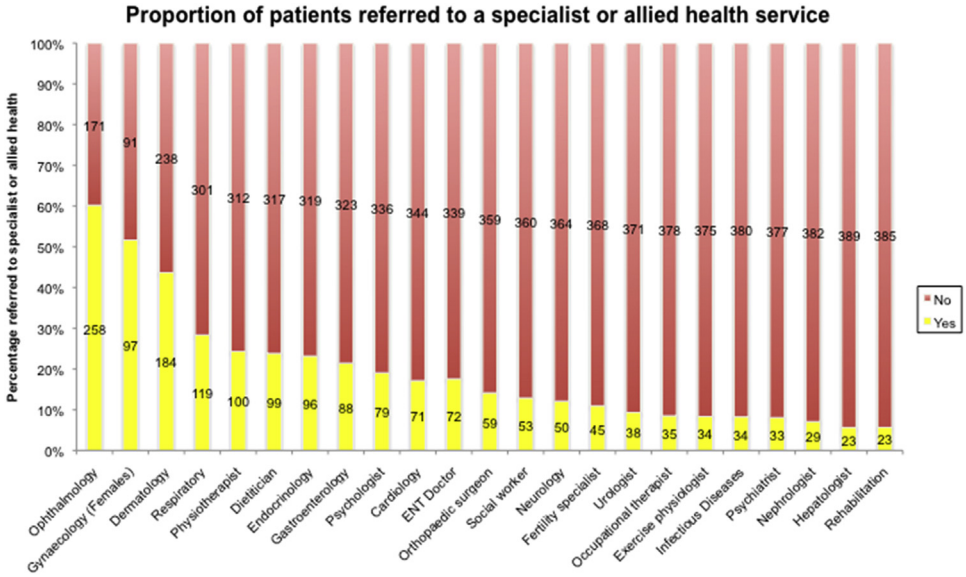

Figure 3. Referral patterns. Additional referrals: oncologist-breast cancer (1), cataract surgeon (1), chiropractor (3), counselor (2), dentist (6), diabetes educator (1), dietitian (1), drug trial (1), endocrine clinic (1), gastrointestinal endoscopist (1), hematology (2), head/neck surgeon (1), lung transplant team (1), multiple (1), maxillofacial surgeon (1), oral clinic (1), osteopath (1), palliative medicine (1), pelvic physiotherapy (1), podiatrist (2), rheumatologist (7), skin cancer specialist (1), upper gastrointestinal surgeon (1), hormone replacement review (testosterone) (1), trichologist (1), urogynecologist (1), vascular surgeon (1), and unspecified (1).

depression, and emotional distress are high compared with those of other cancer survivor populations [3,4,39-41]. A model of care for LTFU must, therefore, address the increased health care needs of this population in ways that are sustainable, cost-effective, and consistent with the preferences of BMT survivors.

This study demonstrated that the majority of BMT survivors would prefer LTFU with their TP and that 74% preferred follow-up at a TC or through a satellite clinic or telemedicine service linked with or administered by that TC. One-quarter indicated a preference for receiving comprehensive post-transplantation care in a satellite clinic staffed by their BMT team situated closer to their place of residence. A number of social factors, including higher income, educational status, and sexual morbidity, were significantly associated with a preference for satellite care. Fewer patients expressed interest in telemedicine/web-based care, with those interested in these options having higher educational status and sexual morbidity. The observation that exercise was reported less often in those who preferred telemedicine may reflect reduced mobility. The factor that showed the greatest trend towards preference for transplantation center follow-up was the severity of cGVHD symptoms. In contrast, those in full-time or part-time work showed a trend towards decreased preference for TC or TC-linked follow-up, which may reflect a declining dependency on TC-based care as patients' lives return to normal.

These are important findings, particularly for countries like Australia where TCs are concentrated in major urban centers, as they provide support for the development of models of care that are responsive to different medical and sociodemographic needs of BMT survivors. But devolved models of post-transplantation care that integrate facilities, specialties, and models of care beyond the TC are only likely to work where they are sufficiently organized and resourced [42]. In this regard, it is noteworthy that recent studies suggest that the survival of BMT patients from rural/regional areas is not inferior if LTFU is carefully and rigorously structured and if there is good communication between referring specialists and GPs [43-45]. Likewise, it is reassuring that recent data in a range of patient populations, including solid organ transplant recipients and patients with cancer, suggest that satellite clinics staffed by personnel from tertiary hospitals have shown similar patient outcomes, subjective health status, and clinical efficiency when compared with outcomes from tertiary clinics [46-48] and that telemedicine can be successfully used to deliver preventive health care, including for sexual and relationship counseling, weight management, advice regarding nutrition and exercise, and mental health care [49-53].

Although the sample size and high response rate (76%) make it likely that these results represent an accurate account of BMT survivor's preferences for long-term care, there are a number of limitations to our study that may limit the generalizability of these results to BMT survivors in other countries and other settings. These limitations are principally a function of our study population and include Australia's geographical size, predominantly urban population, concentration, climate, and health system, which includes both universal publicly funded and private health care. Additionally, we did not specifically ask participants if they had private health insurance or relied upon public health care (in large measure as these are not generally regarded as influencing the standard post-BMT care in Australia) and so are not sure of the impact this has on preferences for follow-up. Also, we did not ask about preferences for nurse-led services, which are commonly used in international BMT centers and cancer care but less a feature of BMT care in Australia [54,55]. It is also possible that the account of patient preferences for post-BMT care is compromised by the use of quantitative instruments incorporate dichotomous variables; however, each of the instruments used in the study have been validated in the target population and so provide the basis for further qualitative study.

This study has provided important insights into BMT survivor preferences for long-term care in an Australian cohort. Given the number of survivors who prefer LTFU at and/or coordinated by their TC, it is clear that TC need to standardize their follow-up, clearly define referral pathways for ancillary and specialist medical services, and ensure LTFU guidelines are disseminated to all relevant health providers and communicated effectively with the range of primary and tertiary care providers involved in post-BMT care [56]. Should other models of care be integrated into the long-term care of BMT survivors, including satellite clinics and telehealth, attention should be paid to the likely adopters of these services and their needs, particularly if these modes of care are chosen for delivery of psychosexual health care and health education. As the success of any model of care is likely to reflect the specific context of its application, further work will be required to establish if this care does indeed decrease morbidity and mortality of long-term BMT survivors.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2015.12.019.

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Appendix 1

Sociodemographic Factors, Transplantation Factors, and Post-Transplantation Complications associated with a Preference for LTFU When There is TC Involvement (TC, Satellite Clinic, or Telemedicine)

Factors	LTFU with TC, Satellite Clinic, or Telemedicine (n = 328)	LTFU that Excludes TC or TC-Linked Care (LH, GP, or No Follow-Up Preference) (n = 113)	OR (95% CI)	*P* Value	AOR (95% CI) *P* Value
Gender					
Male	188 (57.3%)	62 (54.9%)	1.1 (.70-1.74)	.65	1.36 (.60-3.05)
Female	140 (42.7%)	51 (45.1%)			*P* = .46
Age, median (IQR, range), yr	54 (45-62, 19-79)	53 (43-62, 21-74)	1.00 (.99-1.02)	.52	1.00 (.97-1.03) *P* = .92
Postcode					
RA1/2 (major city/inner regional)	298 (93.1%)	98 (88.3%)	1.79 (.80-3.89)	.12	1.62 (.51-7.22)
RA3/4 (outer regional/remote)	22 (6.9%)	13 (11.7%)			*P* = .41
Relationship status					
Married/de facto	265 (81.5%)	79 (72.5%)	1.67 (.97-2.85)	.04	1.15 (.39-3.39)
Single, divorced, separated	60 (18.5%)	30 (27.5%)			*P* = .78
Income status (AUD)					
Middle/high income (>$40,000)	205 (64.9%)	63 (58.9%)	1.29 (.80-2.07)	.27	
Low income ($20,000-$39,999)	111 (35.1%)	44 (41.1%)			
Education status					
Some/completed university	117 (48.0%)	37 (41.6%)	1.29 (.77-2.18)	.30	
Other (diploma, trade, secondary)	127 (52.0%)	52 (58.4%)			
Occupational status					
Full-time/part-time	149 (48.2%)	60 (58.2%)	.67 (.41-1.07)	.08	.44 (.19-1.03)
Other (home duties, casual, retired unable to work, retired)	160 (51.8%)	43 (41.8%)			*P* = .06
Age at transplantation, yr					
Median (IQR; range)	49 (39-57; 17-71)	46 (36-55; 17-70)		.35	
Time since transplantation, yr					
Median (IQR; range)	5 (3-8; 1-14)	5 (3-9; 1-14)		.44	
Underlying disease					
Acute leukemia	172 (54.3%)	54 (50.9%)	1.14 (.72-1.82)	.55	
Other[*,‡]	145 (45.7%)	52 (49.1%)			
Stage of disease at transplantation					
CR 1/2	200 (61.0%)	71 (62.8%)	.92 (.58-1.47)	.73	
Other[†]	128 (39.0%)	42 (37.2%)			
Conditioning					
Myeloablative	158 (48.5%)	56 (49.6%)	.96 (.61-1.50)	.84	
RIC	168 (51.5%)	57 (50.4%)			
Donor type					
Matched (sibling, unrelated)	304 (93.2%)	104 (92.0%)	1.19 (.47-2.81)	.67	
Haploidentical/mismatched	22 (6.8%)	9 (8.0%)			
cGVHD					
Yes	227 (70.7%)	74 (65.5%)	1.27 (.78-2.05)	.30	
No	94 (29.3%)	39 (34.5%)			
Patient global ratings GVHD					
Moderate/severe	74 (37.2%)	22 (32.3%)	1.24 (.67-2.34)	.47	
None/mild	125 (62.8%)	46 (67.7%)			
Severity score, median (IQR), 0-10	3 (1-6)	3 (1-5)	1.06 (.96-1.17)	.24	1.16 (.99-1.36) *P* = .06
Reporting GVHD worse than 1 month ago	17 (8.5%)	2 (3.2%)	2.83 (.64-25.9)	.26	
	183 (91.5%)	61 (96.8%)			
LEE cGVHD symptom score, median (IQR)					
Skin	10 (0-25)	7 (0-25)		.14	
Eye	33 (8-75)	25 (0-67)		.12	
Mouth	0 (0-25)	0 (0-38)		.12	
Lung	5 (0-19)	3 (0-15)		.39	
Nutrition	0 (0-5)	0 (0-5)		.46	
Muscle/joint	2 (0,6)	2 (0-6)		.41	
Energy	32 (17-50)	32 (18-46)		.70	
Mental emotional	17 (0-42)	8 (0-25)		.01	
Total	20 (9-31)	17 (10-26)		.40	
Chronic diseases					
Any chronic disease[‡]	231 of 317 (72.9.5%)	76 of 105 (72.4%)		.92	
Any cancer[§]	80 of 287 (27.9%)	27 of 101 (26.7%)		.82	
Psychological and sexual morbidity					
Anxiety	65 of 300 (21.7%)	18 of 103 (17.5%)	1.30 (.71-2.48)	.36	
Depression	72 of 303 (23.8%)	23 of 104 (22.1%)	1.10 (.63-1.96)	.73	
Anxiety and/or depression	92 of 304 (30.3%)	26 of 105 (24.8%)	1.32 (.78-2.28)	.28	
Total DASS21 score, median (IQR)	20 (10-40)	18 (6-38)		.27	
Sexual dysfunction	138 of 222 (62.2%)	29 of 67 (43.3%)	2.15 (1.19-3.90)	.006	1.61 (.73-3.55) *P* = .24

(*Continued on next page*)

Appendix 1
(*continued*)

Factors	LTFU with TC, Satellite Clinic, or Telemedicine (n = 328)	LTFU that Excludes TC or TC-Linked Care (LH, GP, or No Follow-Up Preference) (n = 113)	OR (95% CI)	*P* Value	AOR (95% CI) *P* Value
Cancer screening					
Skin check	172 of 324 (53.1%)	56 of 112 (50%)	1.13 (.72-1.78)	.57	
Bowel check	106 of 321 (33.0%)	34 of 111 (30.6%)	1.11 (.68-1.84)	.64	
Pap smear (F)‖	80 of 135 (59.3%)	38 of 51 (74.5%)	.50 (.22-1.06)	.05	.19 (.03-1.25) $P = .08$
Mammogram (F)	73 of 133 (54.9%)	25 of 51 (49.0%)	1.26 (.63-2.54)	.47	
Prostate (M)	64 of 184 (34.8%)	25 of 62 (40.3%)	.79 (.42-1.50)	.43	
Lifestyle					
Smoking	21 of 326 (6.4%)	12 of 112 (10.7%)			
Alcohol	205 of 328 (62.5%)	77 of 113 (68.1%)			
Exercise/sport	220 of 326 (67.5%)	80 of 110 (72.7%)			
Sun protection	252 of 319 (67.3%)	81 of 112 (72.3%)			
BMI, median (IQR)	25 (22-28)	25 (22-28)		.79	
Total FACT BMT	110 (94-121)	109 (92-127)		.47	
Post-transplantation growth inventory score	58 (43-72)	59 (33-68)		.20	

IQR indicates interquartile range; CR, complete remission; RIC, reduced-intensity conditioning; F, female; M, male.
Adjusted odds derived from multivariable logistic regression fitting the following potential confounders: age, gender, occupational status, marital status, residential location (metro/inner regional), GVHD severity, sexual dysfunction.

* Other includes chronic myeloid leukemia, chronic lymphocytic leukemia, severe aplastic anemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, myelodysplastic disorder/myeloproliferative disease, and other (unspecified).

† Includes > 2 complete remissions, refractory, chronic phase, accelerated phase, blast crisis, partial remission, other (unspecified).

‡ Any chronic disease includes hypertension, hypercholesterolemia, diabetes, bone disease (osteoporosis, osteopenia, spinal/hip fractures, or avascular necrosis), iron overload, thyroid disease.

§ Any cancer includes skin, mouth or other specified.

‖ Adjusted odds derived from multivariable logistic regression fitting the following potential confounders: age, educational status, marital status, residential location, sexual dysfunction, and GVHD severity.

Appendix 2
Sociodemographic, Transplantation Factors, and Post-transplantation Complications associated with a Preference for LTFU that Includes a Satellite Clinic

Factor	LTFU with Satellite Clinic ± Other Option (n = 119)	Options that Exclude Satellite Clinic (n = 322)	OR (95% CI)	*P* Value	AOR (95% CI) *P* Value
Gender					
Male	70 (58.8%)	180 (55.9%)	1.13 (.72,1.77)	.58	1.20 (.49-3.00)
Female	49 (41.2%)	142 (44.1%)			*P* = .68
Age, median (IQR; range), yr	54 (45-61; 22-75)	54 (44-62; 19-79)	1.0 (.98-1.02)	.77	1.03 (.99-1.08)
					P = .09
Postcode					
RA1/2 (Major city/inner regional)	106 (91.3%)	290 (92.0%)	.91 (.41-2.21)	.82	.70 (.12-4.08)
RA3/4 (Outer regional/remote)	10 (8.7%)	25 (7.8%)			*P* = .70
Relationship status					
Married/de facto	96 (81.4%)	248 (78.5%)	1.20 (.68-2.15)	.51	
Single, divorced, separated	22 (18.6%)	68 (21.5%)			
Income status (AUD)					
Middle/high income (>$40,000)	84 (74.3%)	184 (59.3%)	1.98 (1.20,3.33)	.004	4.67 (1.22-17.8)
Low income ($20,000-$39,999)	29 (25.7%)	126 (40.7%)			*P* = .02
Education status					
Some/completed university	54 (59.3%)	100 (41.3%)	2.07 (1.23-3.49)	.003	3.26 (1.28-8.30)
Other (diploma, trade, secondary)	37 (40.7%)	142 (58.7%)			*P* = .01
Occupational status					
Full-time/part-time	55 (49.5%)	154 (51.2%)	.94 (.59-1.48)	.77	.71 (.25-2.03)
Other (home duties, casual, retired unable to work)	56 (50.4%)	147 (48.8%)			*P* = .53
Age at transplantation, yr					
Median (IQR; range)	49 (39-55)	49 (37-56)		.95	
Time since transplantation, yr					
Median (IQR; range)	5 (3-8)	5 (3-8)		.49	
Underlying disease					
Acute leukemia	60 (53.6%)	166 (53.4%)	1.01 (.64-1.59)	.97	
Other*	52 (46.4%)	145 (46.6%)			
Stage of disease at transplantation					
CR 1/2	73 (61.3%)	198 (61.5%)	1.00 (.64-1.59)	.98	
Other†	46 (38.7%)	124 (38.5%)			
Conditioning					
Myeloablative	59 (49.6%)	155 (48.4%)	1.05 (.67-1.63)	.83	
RIC	60 (50.4%)	165 (51.6%)			
Donor type					
Matched (sibling, unrelated)	113 (95.8%)	295 (91.9%)	1.99 (.73-6.80)	.21	
Haploidentical/mismatched	5 (4.2%)	26 (8.1%)			
cGVHD					
Yes	86 (74.1%)	215 (67.6%)	1.37 (.83-2.30)	.19	
No	30 (25.9%)	103 (32.4%)			
Patient global ratings GVHD					
Moderate/severe	21 (26.6%)	75 (39.9%)	.55 (.29-1.00)	.04	
None/mild	58 (73.4%)	113 (60.1%)			
Severity score, median (IQR), 0-10	2 (1-4)	3 (1-6)		.05	.99 (.83-1.18)
					P = .94
Reporting GVHD worse than 1 month ago	2 (2.6%)	17 (9.1%)			
	75 (97.4%)	169 (90.9%)	.26 (.03-1.17)	.07	
LEE cGVHD symptom score, median (IQR)					
Skin	15 (5-30)	10 (0-25)		.03	
Eye	25 (17-67)	33 (8-75)		.94	
Mouth	0 (0-12)	0 (0-37)		.006	
Lung	5 (0-10)	5 (0-20)		.16	
Nutrition	0 (0-5)	0 (0-5)		.17	
Muscle/joint	2 (0-5)	2 (0-6)		.56	
Energy	29 (17-43)	32 (17-50)		.42	
Mental emotional	17 (0-33)	17 (0-33)		.90	
Total	17 (8-28)	20 (10-32)		.23	
Chronic diseases					
Any chronic disease‡	84 of 114 (73.7%)	223 of 308 (72.4%)	1.07 (.64-1.80)	.79	
Any cancer§	30 of 109 (27.5%)	77 of 279 (27.6%)	.99 (.58-1.67)	.99	
Psychological and sexual morbidity					
Anxiety	20 of 114 (17.5%)	63 of 289 (21.8%)	.76 (.41-1.36)	.34	
Depression	26 of 116 (22.4%)	69 of 291 (23.7%)	.93 (.53-1.59)	.78	
Anxiety and/or depression	33 of 116 (28.4%)	85 of 293 (29.0%)	.97 (.58-1.60)	.91	
Total DASS21 score, median (IQR)	18 (10-34)	20 (8-40)		.65	
Sexual dysfunction	63 of 86 (73.3%)	104 of 203 (51.2%)	2.61 (1.46-4.74)	<.001	3.27 (1.21-8.78)
					P = .02
Cancer screening					
Skin check	68 of 118 (57.6%)	160 of 318 (50.3%)		.17	
Bowel check	38 of 116 (32.3%)	102 of 316 (32.3%)		.92	
Pap smear (F)‖	27 of 46 (58.7%)	91 of 140 (65%)		.44	
Mammogram (F)	30 of 46 (65.2%)	68 of 138 (49.3%)		.06	
Prostate (M)	26 of 69 (37.7%)	63 of 177 (35.6%)		.76	

(*Continued on next page*)

Appendix 2
(*continued*)

Factor	LTFU with Satellite Clinic ± Other Option (n = 119)	Options that Exclude Satellite Clinic (n = 322)	OR (95% CI)	*P* Value	AOR (95% CI) *P* Value
Lifestyle					
Smoking	8 of 118 (6.8%)	25 of 320 (7.8%)		.72	
Alcohol	83 of 119 (69.7%)	199 of 322 (61.8%)		.12	
Exercise/sport	76 of 118 (64.4%)	224 of 318 (70.4%)		0.22	
Sun protection	92 of 118 (78.0%)	241 of 313 (77.0%)		.83	
BMI, median (IQR)	25 (22-28)	25 (22-28)		.50	
Total FACT BMT	110 (94-120)	109 (93-125)		.70	
Post-transplantation growth inventory score	57 (44-71)	59 (38-70)		.77	

Adjusted odds derived from multivariable logistic regression fitting the following potential confounders: age, gender, occupational status, income, educational status, residential location (metro/inner regional compared to outer regional/remote), GVHD severity, sexual dysfunction.

* Other includes chronic myeloid leukemia, chronic lymphocytic leukemia, severe aplastic anemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, myelodysplastic disorder/myeloproliferative disease, and other (unspecified).

† Includes > 2 complete remissions, refractory, chronic phase, accelerated phase, blast crisis, partial remission, other (unspecified).

‡ Any chronic disease includes hypertension, hypercholesterolemia, diabetes, bone disease (osteoporosis, osteopenia, spinal/hip fractures, or avascular necrosis), iron overload, thyroid disease.

§ Any cancer includes skin, mouth or other specified.

‖ Adjusted odds derived from multivariable logistic regression fitting the following potential confounders: age, educational status, marital status, residential location, sexual dysfunction, and GVHD severity.

Appendix 3
Sociodemographic Factors, Transplantation Factors, and Post-transplantation Complications associated with a Preference for LTFU that Includes Telemedicine

Factor	LTFU with Telemedicine ± Other Option (n = 92)	LTFU Options that Exclude Telemedicine (n = 349)	OR (95% CI)	*P* Value	AOR (95% CI) *P* Value
Gender					
Male	55 (59.8%)	195 (55.9%)	1.17 (.72-1.93)	.51	1.02 (.38-2.74)
Female	37 (40.2%)	154 (44.1%)			*P* = .97
Age, median (IQR; range), yr	52 (43,58; 24-70)	55 (44,63; 19-79)	.99 (.97-1.01)	.07	1.02 (.98-1.07)
					P = .33
Postcode					
RA1/2 (Major city/inner regional)	81 (91%)	315 (92%)	.87 (.36-2.29)	.74	.46 (.08-2.60)
RA3/4 (Outer regional/remote)	8 (9%)	27 (8%)			*P* = .38
Relationship status					
Married/de facto	74 (82.2%)	270 (78.5%)	1.26 (.68-2.47)	.43	
Single, divorced, separated	16 (17.8%)	74 (21.5%)			
Income status (AUD)					
Middle/high income (>$40,000)	56 (62.9%)	212 (63.5%)	1.02 (.61-1.70)	.92	
Low income ($20,000-$39,999)	33 (37.1%)	122 (36.5%)			
Education status					
Some/completed university	42 (61.8%)	112 (42.3%)	2.20 (1.23-3.98)	.004	5.10 (1.72-15.1)
Other (diploma, trade, secondary)	26 (38.2%)	153 (57.7%)			*P* = .003
Occupational status					
Full-time/part-time	35 (42.2%)	174 (52.9%)	.65 (.39-1.08)	.08	.77 (.26-2.28)
Other (home duties, casual, retired unable to work)	48 (57.8%)	155 (47.1%)			*P* = .64
Age at transplantation, median (IQR; range), yr	47 (37-52)	50 (38-57)		.06	
Time since transplantation, median (IQR; range), yr	5 (3-8)	5 (3-8)		.56	
Underlying disease					
Acute leukemia	48 (53.3%)	178 (53.4%)	1.00 (.61-1.63)	.98	
Other*	42 (46.7%)	155 (46.5%)			
Stage of disease at transplantation					
CR 1/2	58 (63.0%)	213 (61.0%)	1.09 (.66-1.81)	.72	
Other†	34 (37.0%)	136 (39.0%)			
Conditioning					
Myeloablative	53 (57.6%)	161 (46.4%)	1.57 (.96-2.57)	.06	1.80 (.62-5.22)
RIC	39 (42.4%)	186 (53.3%)			*P* = .28
Donor type					
Matched (sibling, unrelated)	88 (96.7%)	320 (91.9%)	2.57 (.76-13.47)	.16	
Haploidentical/mismatched	3 (3.3%)	28 (8.1%)			
cGVHD					
Yes	64 (70.3%)	237 (69.1%)	1.06 (.62-1.83)	.82	
No	27 (29.8%)	106 (30.9%)			
Patient global ratings GVHD					
Moderate/severe	21 (37.5%)	136 (64.4%)	1.08 (.56-2.08)	.79	
None/mild	35 (62.5%)	75 (35.6%)			
Severity score, median (IQR), 0-10	3 (1-5)	3 (1-6)		.79	.95 (.79-1.16)
					P = .63
Reporting GVHD worse than 1 month ago	6 (10.9%)	13 (6.3%)	1.84 (.54-5.49)	.24	
	49 (89.1%)	195 (93.7%)			
LEE cGVHD symptom score, median (IQR)					
Skin	10 (0-31)	10 (0-25)		.38	
Eye	33 (17-75)	33 (8,75)		.52	
Mouth	0 (0-25)	0 (0-25)		.49	
Lung	5 (0-20)	5 (0-15)		.69	
Nutrition	0 (0-5)	0 (0-5)		.78	
Muscle/joint	3 (0-7)	2 (0-6)		.20	
Energy	36 (21-54)	32 (14-50)		.10	
Mental emotional	21 (8-42)	17 (0-33)		.18	
Total	19 (9-36)	18 (9-29)		.44	
Chronic diseases					
Any chronic disease‡	66 of 89 (74.2%)	239 of 331 (72.2%)	1.10 (.63-1.97)	.71	
Any cancer§	19 of 94 (22.6%)	87 of 303 (28.7%)			
Psychological and sexual morbidity					
Anxiety	21 of 84 (25.0%)	62 of 319 (19.4%)	1.38 (.74-2.50)	.26	
Depression	27 of 87 (31.0%)	68 of 320 (21.2%)	1.67 (.94-2.90)	.06	
Anxiety and/or depression	32 of 87 (36.8%)	86 of 322 (26.7%)	1.60 (.93-2.70)	.06	1.34 (.44-4.02)
					P = .60
Total DASS21 score, median (IQR)	22 (10-46)	18 (8-38)		.03	
Sexual dysfunction	48 of 62 (77.4%)	119 of 227 (52.4%)	3.96 (1.20-16.8)	<.001	3.25 (1.02-10.35)
					P = .05
Cancer screening					
Skin check	43 of 91 (47.2%)	185 of 345 (53.6%)	.77 (.47,1.26)	.28	
Bowel check	26 of 91 (28.6%)	113 of 340 (33.2%)	.8 (.46-1.37)	.40	
Pap smear (F)	20 of 35 (57.1%)	98 of 151 (64.9%)	.7 (.3,1.6)	.39	
Mammogram (F)	23 of 36 (63.9%)	75 of 148 (50.7%)	1.7 (.8-4.0)	.15	
Prostate (M)	15 of 54 (27.8%)	74 of 192 (38.5%)	.61 (.29,1.23)	.14	

(*Continued on next page*)

Appendix 3
(*continued*)

Factor	LTFU with Telemedicine ± Other Option (n = 92)	LTFU Options that Exclude Telemedicine (n = 349)	OR (95% CI)	*P* Value	AOR (95% CI) *P* Value
Lifestyle					
Smoking	5 of 92 (5.4%)	28 of 346 (8.0%)		.39	
Alcohol	63 of 92 (68.5%)	219 of 349 (62.7%)		.30	
Exercise/sport‖	55 of 92 (59.8%)	245 of 346 (70.8%)		.04	.46 (.24-.87) *P* = .02
Sun protection	73 of 91 (80.2%)	260 of 340 (76.5%)		.45	
BMI, median (IQR)	25 (22, 28)	25 (22, 28)		.86	
Total FACT BMT	108 (94-119)	110 (93-125)		.30	
Post-transplantation growth inventory score	53 (41-71)	59 (40-71)		.66	

Adjusted odds derived from multivariable logistic regression fitting the following potential confounders: age, gender, occupational status, educational status, residential location (metro/inner regional compared to outer regional/remote), anxiety/depression, GVHD severity, conditioning at transplantation, and sexual dysfunction.

* Other includes chronic myeloid leukemia, chronic lymphocytic leukemia, severe aplastic anemia, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, myelodysplastic disorder/myeloproliferative disease, and other (unspecified).

† Includes > 2 complete remissions, refractory, chronic phase, accelerated phase, blast crisis, partial remission, other (unspecified).

‡ Any chronic disease includes hypertension, hypercholesterolemia, diabetes, bone disease (osteoporosis, osteopenia, spinal/hip fractures, or avascular necrosis), iron overload, thyroid disease.

§ Any cancer includes skin, mouth or other specified.

‖ Adjusted odds for exercise derived from multivariable logistic regression fitting the following potential confounders: age, gender, GVHD severity, any chronic disease.

6.5. Synopsis

This manuscript provides the only national or international data on BMT survivors preference for long term care including the association of care preferences with demographics, co-morbidities and QoL. For the first time, therefore, we have empirical data to support the development of MOCs tailored to the specific needs of BMT survivors, including those with severe cGVHD, those who have returned to work, those living in rural areas, those transitioning from hospital-based to community care and those who are less mobile.

These insights are important because hitherto limited attention has been paid to outpatient and community care of BMT survivors and BMT LTFU is a relatively new area of practice and not universally well established. For the most part, acute and early post-BMT care is provided exclusively by the transplant team in the BMT centre. It is well co-ordinated and managed - generally by a small team of BMT specialist doctors and APNs. LTFU in contrast, is less well established and more complex, more open-ended and involves multiple subspecialists and allied health professionals, is provided in tertiary and primary care settings and in the public and private sector, and often relies upon the survivor navigating this fragmented care themselves. (As the manuscript shows, even at two years post BMT, when the highest risk of relapse has passed, over a quarter of survivors are continuing to attend for medical care at least monthly and the range of non-BMT specialists involved in survivor care is 0-11).

In this regard it is noteworthy that since study commencement the NSW Agency for Clinical Innovation (ACI), BMT Network has been working on the development of a state-wide BMT LTFU MOC. This work has been prompted by publication of the results of an informal review of BMT LTFU services at each of the allogenic centres in NSW which showed that there was no consistent, robust LTFU process in place to accommodate the care needs of BMT survivors (detailed in Chapter 3; Table 3.1). Just as worryingly, every BMT centre reported a proportion of survivors who were lost to follow-up and no centre was able to show full compliance with clinical guidelines for BMT LTFU(1). It is anticipated that development (and implementation of) a MOC to inform the required care and pathway of both adult and adult survivors of childhood BMT will greatly increase NSW's ability to improve LTFU outcomes and survivorship. While only in the early stages of development however, it appears that no single MOC suits all types of BMT survivors, a finding supported by the results of this manuscript and by recent international literature(2-5). (This is explored further in the discussion section (Chapter 16) of this thesis).

It is increasingly clear that BMT centres need to establish a MOC for LTFU processes specific to their needs (centre, patient, clinician) in order to harmonise data collection, optimise data reporting, and

reduce variation in care in order to improve long-term outcomes. Establishing and adopting a MOC which aligns centre BMT LTFU goals, service capacity and configuration, and survivor and clinician preference will ensure that BMT survivors are able to access services, expertise and resources that are consistent with their needs and values.

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Chapter 7: A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia.

7.1. Chapter overview

This chapter reports on the reproductive and sexual health of our long-term BMT survivors. It consists of a published manuscript entitled, 'A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia'. The manuscript reports on sexual function and fertility issues analysed according to demographics, transplant factors, co-morbidities and QoL scores.

The results of the manuscript demonstrate that while most BMT survivors resume sexual activity post BMT, sexual dysfunction is prevalent in both sexes, but it occurs significantly more often in women (66% vs 51%). It was also found that genital cGVHD occurs disproportionately more often in women than in men (22.1% vs 5%). And while a small proportion of our survivors had successful live births in the years following BMT, it is noteworthy that women of childbearing age were more likely not to be offered fertility preservation treatments prior to BMT. The findings have implications for sexual health and fertility education and support both pre and post-BMT and highlight the importance of quality gynaecological care and review in the longer-term post-transplant.

7.2. Publication details

Dyer G, Gilroy N, Bradford J, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. "A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia." *Br J Haematol* 2016;172(4):592-601.

7.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

7.4. Manuscript

The published version of the manuscript follows.

bjh research paper

A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia

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Summary

Four hundred and twenty-one adult allogeneic haematopoietic stem cell transplant (HSCT) survivors participated in a cross-sectional study to assess sexual dysfunction and infertility post-transplant. Survey instruments included the Sydney Post-Blood and Marrow Transplant (BMT) Survey, Functional Assessment of Cancer Treatment (FACT) – BMT, the Depression, Anxiety, Stress Scales (DASS 21), the Chronic Graft-versus-Host Disease (cGVHD) Activity Assessment- Patient Self Report (Form B), the Lee cGVHD Symptom Scale and The Post-Traumatic Growth Inventory. Most HSCT survivors reported sexual difficulties (51% of males; 66% of females). Men reported erectile dysfunction (79%) and decreased libido (61·6%) and women reported loss of libido (83%), painful intercourse (73%) and less enjoyment of sex (68%). Women also commonly reported vaginal dryness (73%), vaginal narrowing (34%) and vaginal irritation (26%). Woman had much higher rates of genital cGvHD than men (22% vs. 5%). Age and cGVHD were significantly associated with sexual dysfunction. Few survivors had children following transplant (3·3%). However, for those of reproductive age at HSCT, 22% reported trying to conceive, with 10·3% reporting success. This study is the largest to date exploring sexual function in survivors of allo-HSCT. This data provides the basis for health service reform to better meet the needs of HSCT survivors, including evidence to support counselling and education both pre- and post-transplant.

Keywords: allogeneic HSCT, sexual dysfunction, infertility, survivors, survey, Australia.

Allogeneic haematopoietic stem cell transplantation (HSCT) is an established treatment for malignant and non-malignant diseases affecting both adults and children. Advances in patient and donor selection, management of acute toxicities and supportive care have significantly improved outcomes following transplant with 1-year survival rates now 80% or more for some conditions (Mohty & Mohty, 2011; Pasquini & Zhu, 2014). Unfortunately, many HSCT survivors experience significant morbidity following HSCT with late effects reducing the quality and duration of their life (Savani *et al*, 2011). Sexual dysfunction and infertility are among the most prevalent long-term sequelae (Mosher *et al*, 2009).

Sexual dysfunction and infertility occurs primarily because of the adverse effect of high dose chemo-radiotherapy, resulting in interruption of the sexual response cycle, decreased libido, erectile and ejaculatory dysfunction, vaginal alterations (dryness, narrowing, fibrosis), dyspareunia and infertility or sub-fertility due to primary ovarian failure and impaired spermatogenesis (Carter *et al*, 2006; Humphreys *et al*, 2007). In general, women tend to experience more

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sexual dysfunction than men (78% at 1 year compared to 50%), are more likely to experience long-term sexual dysfunction and are more likely to be infertile following HSCT (Marks *et al*, 1997; Humphreys *et al*, 2007; Thygesen *et al*, 2012). While successful pregnancies have occurred in survivors of HSCT, they are rare, 0·6% in the largest report on over 37 000 HSCT survivors (both allogeneic and autologous) (Salooja *et al*, 2001). With the exception of a limited number of registry studies, there is limited data on sexual dysfunction and infertility post-HSCT with most studies reporting small populations from single centres. There is no data describing the late effects in an Australian cohort of HSCT survivors. The aims of this cross-sectional study were to present data on the range and frequency of sexual dysfunction and infertility in survivors of HSCT, to address gaps in service provision and to provide better information to those undergoing HSCT, their families/carers and health care professionals.

Methods

Patients and procedures

Potential participants were identified from allogeneic transplant databases of all adult allogeneic transplant centres in New South Wales [NSW; Australia's most populous state – ~7·5 million in 2013 (Australian Bureau of Statistics, 2014)]. Participants were eligible if they were ≥18 years of age and had undergone an allogeneic HSCT between 1 January 2000 and 31 December 2012, could read and write English and could provide consent. Names and phone numbers were provided to the research team. Consenting participants were given the option to self-complete the questionnaire or complete it via a phone interview with one of the researchers. A second round of telephone calls were made to participants who had not returned the survey within a month. All authors had access to primary clinical trial data. The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Instruments

The Sydney Post-BMT Study Survey (SPBS) (Appendix S1) was developed by the research team. Item construction was informed by a review of the literature and discussions with patients attending HSCT long-term follow-up clinics. It consisted of 402 questions grouped into 20 domains, including questions relating to fertility and sexual function. Other relevant domains included demographics, medical complications, specialist referrals, tests and assessments, medications and therapies, infections, vaccinations, complementary therapy use, cancer screening, close personal contacts, lifestyle, diet nutrition, occupational and relationship status following stem cell transplantation. The questionnaire used tick box responses, short answer questions and 5-step Likert scales measuring attitudes and other factors and took approximately 1 h to complete. The questionnaire was piloted in clinic and phone interviews to assess face and content validity and comprehension.

Associations between sexual function and fertility were explored against demographics, medical complications, post-transplant medical therapies, treatments and complementary therapies, relationship status and social determinants, including income and occupational status. The relationships between sexual function and fertility were further explored against a range of validated survey instruments that measured quality of life [Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4; Cella *et al*, 1993; McQuellon *et al*, 1997)], anxiety stress and depression [The DASS (Depression Anxiety Stress Scales) 21] (Lovibond & Lovibond, 1996; Crawford & Henry, 2003; Dahm *et al*, 2013), chronic graft-versus-host disease (GVHD) [The Chronic GVHD Activity Assessment – Patient Self Report (Form B) (Pavletic *et al*, 2006) and The Lee Chronic GVHD Symptom Scale (Lee *et al*, 2002b)] and an assessment of life changes in response to traumatic events (The Post-Traumatic Growth Inventory score) (Tedeschi & Calhoun, 1996; Morris *et al*, 2013). For ease of completion all instruments were combined into one booklet.

For each participant, data was collected on dates of diagnosis and transplant, stage/remission status at transplant, conditioning, GVHD prophylaxis, stem cell source and donor type, which was completed by the research team. This information was used to compare HSCT clinical variables and the impact on sexual function and fertility in survivors.

Statistical analysis

Categorical responses were summarized using frequencies and percentages. Parametric continuous variables were summarized using means and standard deviations, and non-parametric variables using medians and interquartile ranges. The Pearson χ^2 test or Fishers Exact tests were used for comparative analysis of dichotomous categorical variables. Two sample comparisons of means and medians were determined using the independent *t*-test and Wilcoxon Rank Sum tests respectively; greater than two sample comparisons of means and medians were determined using one way analysis of variance (ANOVA) and Kruskal–Wallis tests, respectively. A two-tailed $P < 0{\cdot}05$ was used as the level of statistical significance.

Statistical analysis was performed using the STATA version 12.1 statistical package (StataCorp, College Station, TX, USA).

Results

A total of 1475 allogeneic HSCT were performed in the study period. Of the 669 survivors known to be alive at study sam-

pling, 583 were contactable and were sent study packs. Four hundred and forty-one (66% of total eligible, 76% of those contacted) returned the completed survey. Three per cent declined participation (Fig 1).

Patient characteristics

Of those who completed the survey, 250 (57%) were male and 191 (43%) female. The median age of survey respondents was 54 years (range: 19–79). The median age at time of transplant was 49 years (range: 17–71). Forty per cent of survey respondents were 6 or more years post-transplant. The majority of patients resided in a major city (72%), were of middle/high income status (53%) and were in a married or defacto relationship (79%). The main indication for transplantation was acute leukaemia (62%). Matched siblings accounted for 57% of donors and a myeloablative conditioning regimen was used in 49% of transplant procedures (Table I).

Resumption of sexual activity post-HSCT

A total of 421 respondents provided information about sexuality, fertility and sexual activity post-HSCT; 241 (96·4%) of 250 males and 178 (93·2%) of 191 females.

One hundred and sixty-seven (69·2%) males and 122 (68·5%) females reported resumption of sexual activity post-transplant; 30 (12·4%) of males and 21 (11·8%) of females had not yet resumed sexual activity post-HSCT. The remaining 44 (18·3%) of males and 35 (19·7%) females reported being sexually inactive pre and post-transplant.

Males who had resumed sexual activity had a median age of 52 years, compared to 58 years for those who had not yet resumed sexual activity post-transplant ($P = 0{\cdot}04$). The median years since transplantation in males who had returned to sexual activity was 5 years, and was not significant from males who had not yet returned to sexual activity. Males who had resumed sexual activity showed no significant differences in relationship status, donor type, diagnosis, conditioning, remission status or distribution of comorbidities when compared to males who had not resumed sexual activity. Morbidity from cGVHD was significantly higher in males who had not resumed sexual activity post-transplant. These males reported significantly higher rates of moderate and severe cGVHD symptoms ($P = 0{\cdot}03$), significantly higher Lee Chronic GVHD scores ($P = 0{\cdot}01$) and had significantly higher rates of immunosuppression ($P = 0{\cdot}01$) and anti-infective drug use ($P = 0{\cdot}007$). Males who had not returned to sexual activity post-transplant had significantly lower scores on physical ($P = 0{\cdot}01$), functional ($P = 0{\cdot}009$) and HSCT FACT subscales ($P = 0{\cdot}003$), and had significantly lower scores on composite FACT scores ($P = 0{\cdot}01$). No significant difference was observed in the Post-Traumatic Growth Inventory scores for males who had resumed sexual activity (Tables II and III).

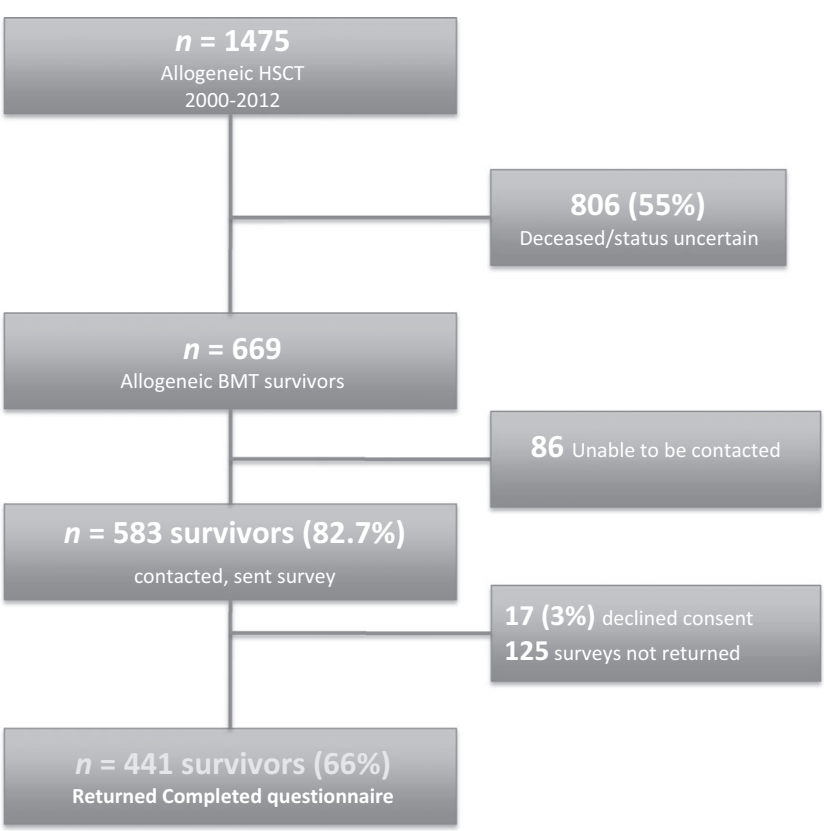

Fig 1. Post-haematopoietic stem cell transplantation (HSCT) survey study flowchart.

Table I. Participant characteristics.

Socio-demographic	
Gender (n = 441)	
Male	250 (56·7)
Female	191 (43·3)
Age (years) at survey (n = 441)	
Median (IQR; range)	54 (44, 62; 19–79)
Age (years) at transplant (n = 441)	
Median (IQR; range)	49 (37, 56; 17–71)
Ethnicity (n = 372)	
Caucasian, European	323 (86·8)
Other*	49 (13·2)
Educational status (n = 335)	
University (some/completed)	154 (46·2)
Other	179 (53·8)
Post transplant income status (n = 423)	
Low income $20 000–$39 999	155 (36·6)
Middle income $40 000–$79 999	123 (29·1)
High income ≥$80 000	145 (34·3)
Residence (n = 431)	
Major city	311 (72·2)
Other (inner regional, outer regional, remote)	120 (27·8)
Relationship status (n = 436)	
Married/defacto	344 (79·3)
Other (separated, single, divorced)	90 (20·7)
Transplant-related	
Years since transplant (n = 443)	
<2	58 (13·1)
2 to <6	204 (46·3)
6 to <10	117 (26·5)
≥10	62 (14·1)
Underlying diagnosis (n = 425)	
Acute leukaemia (AML/ALL)	226 (53·4)
Other†	197 (46·6)
Remission status (n = 405)	
First/second complete remission	271 (66·9)
Other‡	134 (33·1)
Donor type (n = 439)	
Sibling	250 (56·9)
Matched unrelated	158 (36·0)
Haploidentical	10 (2·3)
Mismatched unrelated	21 (4·8)
Stem cell source (n = 441)	
Bone marrow	48 (10·9)
Peripheral blood	381 (86·4)
Cord blood	12 (2·7)
Conditioning chemotherapy (n = 439)	
Myeloablative	214 (48·7)
Reduced intensity	225 (51·2)

Values are expressed as n (%) unless otherwise stated. IQR, interquartile range.

*Other education-secondary school (some or complete); trade or diploma.

†Other diagnoses: chronic myeloid leukaemia; chronic lymphocytic leukaemia (non-Hodgkin lymphoma; Hodgkin lymphoma; multiple myeloma; myelodysplastic syndrome/myeloproliferative disorder; Other (unspecified)

‡Other remission status; more than second complete remission; Refractory; chronic Phase; Accelerated Phase; Blast crisis; Partial Remission; other (unspecified).

Females who had resumed sexual activity had a median age of 49 years compared to 57 years for those who had not resumed sexual activity (P = 0·06) and were more likely to be further out from their date of transplant than those who had not resumed sexual activity with a median duration of 6 years since transplantation, compared to 3 years (P = 0·0009). Females returning to sexual activity were more likely to be in a married/defacto relationship, though this was not statistically significant (P = 0·09). In contrast to male survivors of HSCT, the self-reported severity of GVHD symptoms and Lee GVHD scores were not significantly different in women who had, or had not resumed sexual activity. Females who had returned to sexual activity had significantly higher FACT BMT subscale scores, but did not have any significant differences across other FACT domains or in the post-transplant Growth Inventory scores. Females who had resumed sexual activity reported significantly higher rates of anxiety and/or depression (P = 0·05). The use of psychotropic medications (antidepressants, anxiolytics and/or sedatives) was not significantly different between the two groups. The underlying haematological diagnosis, conditioning regimen, donor type, medical comorbidity profile and medication use was not significantly different in females who had resumed sexual activity (Tables II and III).

Sexual dysfunction

Fifty-one per cent of males who had resumed sexual activity since their HSCT reported difficulties with sexual function since transplant (Table IV). The majority (77%) of sexual difficulties in males related to erectile dysfunction, and decreased libido was the second most common reported problem (62%). Pain with intercourse accounted for 9% of sexual difficulties. Of the 122 females who had resumed sexual activity since their HSCT, 81 (66%) reported having difficulties with sexual function since transplant (Table IV). Specific issues in those who had resumed sexual activity post-transplant were compared across genders. Females had significantly less enjoyment of sex [odds ratio (OR) 4·3 95% confidence interval (CI) 2·2, 8·8 P < 0·0001], less sexual desire (OR 3·0 95% CI 1·4, 6·6 P = 0·002) and more pain with intercourse (OR 26 95% CI 10·2, 71·3 P < 0·0001) when compared to their male counterparts. Sexual problems arising from partner issues were similar between the two genders.

Genital pathology

The only genital pathology reported in men was penile cGVHD, which occurred in 13 (5%) of 250 respondents.

Genital problems reported by sexually active females included vaginal dryness (73%), vaginal narrowing (34.%), vaginal irritation and soreness (26.%), thrush (8.%), cystitis (17%) and lower back pain (27%). Vaginal dryness was the only symptom that was statistically significantly different between women who were sexually active and those who were not (OR 5·2 95% CI 2·5, 11; P < 0·0001).

Table II. Demographic, social and clinical variables and their association with resumption of sexual activity post-transplant, by gender.

	Males			Females		
	Resumed sexual activity post-HSCT (n = 167)	Not resumed sexual activity post-HSCT (n = 30)	P value	Resumed sexual activity post-HSCT (n = 122)	Not resumed sexual activity post-HSCT (n = 21)	P value
Socio-demographic factors						
Age (years) at survey, median (range)	52 (21–79)	58 (21–73)	**0·04**	49 (21–75)	57 (34–69)	0·06
Years since transplant, median (range)	5 (1–14)	5 (1–14)	0·32	6 (1–14)	3 (1–8)	**0·0009**
Relationship status						
Married/defacto	137/166 (82·5%)	22/30 (73·3%)	0·31	106/119 (89%)	15/20 (75%)	0·09
Single, divorced, separated	29/168 (17·5%)	8/30 (26·7%)		13/119 (11%)	5/20 (25%)	
Transplant factors						
Diagnosis						
Acute leukaemia	75/140 (53·6%)	14/25 (56·0%)	0·82	76/102 (65·5%)	14/18 (73·7%)	0·60
Other diagnoses	65/140 (53·6%)	11/25 (44·0%)		40/102 (35·5%)	4/18 (26·3%)	
Donor type						
Sibling	89/166 (53·6%)	16 (53·3%)	0·55	74 (60·7%)	12 (57·1%)	0·93
Haploidentical	4/166 (2·4%)	1 (3·3%)		3 (2·5%)	1 (4·8%)	
Unrelated (matched)	63/166 (38·0%)	13 (43·3%)		38 (31·5%)	7 (33·3%)	
Unrelated (mismatched)	10/166 (6·0%)	0		7 (5·7%)	1 (4·8%)	
Conditioning						
Myeloablative	84 (50·9%)	11 (36·7%)	0·15	77 (63·1%)	10 (47·6%)	0·18
Reduced Intensity	81 (49·1%)	19 (63·3%)		45 (36·9%)	11 (52·4%)	
Remission status						
CR1/CR2	95 (56·9%)	14 (46·7%)	0·30	87 (71·3%)	17 (81·0%)	0·36
Other	72 (43·1%)	16 (53·3%)		35 (28·7%)	4 (19·0%)	
Post-transplant factors						
Comorbidity						
Cardiovascular risk factors	69 (43·7%)	16 (53·3%)	0·13	45 (36·9%)	6 (28·6%)	0·62
Bone disease	39 (24·3%)	11 (36·7%)	0·15	41 (33·6%)	5 (23·8%)	0·45
Anxiety/depression	48 (28·7%)	8 (26·7%)	0·82	32 (26·2%)	1 (4·8%)	**0·05**
Thyroid disease	5 (3·4%)	2 (7·1%)	0·31	7 (5·7%)	2 (9·5%)	0·62
Iron overload	53 (35·6%)	6 (23·1%)	0·26	34 (27·9%)	6 (28·6%)	1·0
Medical therapy						
Immunosuppression	65 (38·9%)	19 (63·3%)	**0·01**	26 (21·3%)	5 (23·8%)	0·78
Anti-infective	67 (40·1%)	20 (66·7%)	**0·007**	39 (32·0%)	10 (47·6%)	0·16
Psychotropic medication	37 (22·2%)	5 (16·7%)	0·63	22 (18·0%)	3 (14·3%)	1·00
Hormone replacement	12 (7·2%)	0	0·22	41 (33·6%)	5 (23·8%)	0·45
Chronic GVHD						
Self-reported severity						
None	20/105 (19·1%)	1/19 (5·3%)	**0·03**	15/77 (19·5%)	1/12 (8·3%)	0·66
Mild	55/105 (52·4%)	6/19 (31·6%)		41/77 (53·2%)	6/12 (50·0%)	
Moderate	18/105 (17·1%)	7/19 (36·8%)		18/77 (23·4%)	4/12 (33·3%)	
Severe	12/105 (11·4%)	5/19 (26·3%)		3/77 (3·9%)	1/12 (8·3%)	
Lee chronic GVHD score						
Median (range)	16 (0–77)	30 (5–54)	**0·01**	15 (0–61)	20 (6–47)	0·40

HSCT, haematopoietic stem cell transplantation; CR1/CR2, first/second complete remission; GVHD, graft-versus-host disease.
Numbers in bold indicate statistically significant.

Menstrual irregularities

Seventy-nine (44%) of 178 females reported having menstrual cycles prior to HSCT. Fourteen (18%) reported a return of menstrual function post-transplant, of which seven experienced a temporary cessation of up to 2 years following the transplant procedure.

Fertility post-HSCT

Three hundred and ninety-three participants provided a response to questions regarding post-transplant conception. Thirty-five of 395 respondents indicated that they had tried to conceive post-HSCT: 21 (10%) males and 14 (8%) females. Of these 35 participants, 15 (43%) were successful

Table III. Quality of life measures (FACT-BMT), post-traumatic growth inventory measures and resumption of sexual activity post-transplant, by gender.

	Males			Females		
	Resumed sexual activity post-HSCT	Not resumed sexual activity post-HSCT	*P* value	Resumed sexual activity post-HSCT	Not resumed sexual activity post-HSCT	*P* value
FACT scores, median (range)						
FACT-physical	24 (0–28)	19 (5–28)	**0·01**	25 (0–28)	24 (12–28)	0·34
FACT-social	21 (4–28)	22 (1–27)	0·92	22 (7–28)	21 (14–28)	0·70
FACT-emotional	17 (1–24)	17 (7–20)	0·66	16 (0–20)	17 (0–20)	0·77
FACT-functional	21 (4–28)	16 (0–28)	**0·009**	21 (5–28)	19 (8–28)	0·21
FACT-HSCT subscale	30 (9–40)	26 (7–38)	**0·003**	29 (11–40)	26 (18–32)	0·02
FACT-G	82 (22–104)	70 (40–95)	**0·03**	83 (36–104)	81 (61–103)	0·58
FACT BMT Total	113 (32–144)	94 (52–129)	**0·01**	111 (49–141)	109 (80–134)	0·23
Post-Traumatic Growth Inventory, median (range)	54 (0–96)	54 (16–79)	0·74	63 (12–103)	53 (18–93)	0·35

HSCT, haematopoietic stem cell transplantation; FACT, Functional Assessment of Cancer Treatment; BMT, Bone Marrow Transplantation. Numbers in bold indicate statistically significant.

Table IV. Sexual dysfunction reported by males and females who had resumed sexual activity post-transplant.

Type of sexual dysfunction	Sexual dysfunction following resumption sexual activity (females) (*n* = 81)	Sexual dysfunction following resumption sexual activity (males) (*n* = 86)	Odds ratio (95% confidence interval)	*P* value
Decreased enjoyment of sex	55/81 (67·9%)	28/86 (32·6%)	4·3 (2·2, 8·8)	<0·0001
Pain with intercourse	59/81 (72·8%)	8/86 (9·3%)	26·1 (10·2, 71·3)	<0·0001
Decreased sexual desire	67/81 (82·7%)	53/86 (61·6%)	3·0 (1·4, 6·6)	0·002
Difficulties with arousal	47/81 (58%)	N/A	Not comparable to males	–
Difficulties with erection	N/A	66/86 (76·7%)	Not comparable to females	–
Difficulties with partner regarding issue of sex	27/81 (33·3%)	28/86 (32·6%)	1·03 (0·5, 2·1)	0·91
Other	Other difficulties described by females included vaginal bleeding/ dryness/graft-versus-host disease (11) mobility/flexibility issues (1) post-gynaecological surgery problems (1) body confidence (1) low libido (1) partner issues (1)	Other difficulties described by males included recurrent hospitalizations (1), neurological damage to penis following episode of shingles (1), reduced muscular strength & joint pains and breathing difficulties (3)		

(11 males; 4 females). Females who successfully conceived were all aged less than 30 years and males less than 41 years at the time of transplantation ($P = 0{\cdot}08$).

Of the 15 successful pregnancies, 6 (40%) were the result of natural conception (two females; four males) and two were the result of natural conception that followed prior attempts at *in vitro* fertilization (IVF), including IVF in one male and his partner and IVF followed by implantation of a donor egg in one female. A total of seven successful pregnancies were the result of IVF; six (all males) with IVF alone and one IVF and donor egg (female). No association was found between the use of reproductive technologies by HSCT survivors with residential location (major city *versus* inner or outer regional) and household income.

Fertility preservation pre HSCT

Forty-seven (20%) of 233 males reported banking sperm pre-HSCT with a median age (at transplant) of 31 years [inter-quartile range (IQR) 24–40; range 18–51]. There were no statistically significant socio-demographic differences (income, residence) between males who did and did not bank sperm Donor type did have a significant effect on banking sperm with those who had a haplo/MUD or mismatched transplant being 2·6 times more likely to bank than those who had a matched sibling transplant (95% CI 1·28, 5·44; $P = 0{\cdot}004$). Males who had a myeloablative HSCT had a threefold higher rate of banking sperm than those who had reduced intensity conditioning (95% CI 1·67, 6·58; $P =$

0·0004) though this was not significant when adjusting for the effect of younger age for those receiving myeloablative conditioning [adjusted odds ratio (AOR) 0·82; 95% CI 0·32, 2·08; $P = 0·67$).

Three hundred and sixty-one participants responded to the question of embryo banking after a cycle of IVF. A total of 6 (2%) reported using this technology (two males and four females). Three hundred and twenty-nine participants reported whether or not they had donated ovarian tissue and frozen eggs for storage. Overall, 7 (2%) had used this procedure (six females and one male HSCT recipient with his female partner).

The most common reasons for young women (aged 18–29) to have not pursued fertility preservation pre-HSCT were they had already completed a family or were too sick to have done so. For females in the 30–39 years age group, 40% declined the procedure but in a significant proportion (23%) the reproductive intervention was not offered. In females aged 40–49, the majority declined the procedure, though 15% reported that it had not been offered. Of male HSCT survivors who did not store sperm this was generally because they declined to do so (79%) or were too unwell to undergo the procedure (8%). Only 8 (5%) men, 2 of whom were under 40 years of age, were not offered sperm storage (Tables V and VI).

Discussion

While sexual dysfunction has previously been documented in HSCT survivors, most reports are from single centres and/or comprise small sample sizes. This study is the largest to date exploring sexual activity in survivors of allogeneic HSCT and the largest and most comprehensive study of fertility and sexuality in an Australian context. While the high response rate (76%) and use of validated instruments makes it likely that these results represent an accurate account of the experience of survivors of HSCT, the heterogeneity and restricted ethnic diversity in our population may limit the generalizability of these results to HSCT survivors in other countries and settings. The results from this research are also limited by the fact that it relied upon self-report and because no data is available about non-responders. Further, the instruments used in this study were ones that are widely used in HSCT settings to assess quality of life, physical and psychosocial function in HSCT survivors and were not specifically targeted at sexual function.

This study demonstrates that the majority of HSCT survivors experience a wide range of sexual difficulties in the years following transplantation. Although most had resumed sexual activity, a significant proportion reported sexual difficulties (51% of males; 66% of females). Common to both genders were loss of libido and less enjoyment of sexual activity while 72% of women experienced pain with intercourse. These results are broadly consistent with other reports of sexual dysfunction after HSCT (Marks *et al*, 1997; Lee *et al*, 2002a; Tierney *et al*, 2007). As with other studies, age and cGVHD were significantly associated with sexual dysfunction post-HSCT (Heinonen *et al*, 2001; Lara *et al*, 2010; Mueller *et al*, 2013; Wong *et al*, 2013).

While most patients generally resumed sexual activity post-HSCT, consistent with other research, we found that this occurs most frequently and earlier in men than in women, and in younger HSCT survivors (Watson *et al*, 1999; Shanis *et al*, 2012). The association between cGVHD and the lack of return to sexual activity appeared to be more evident in males than females, with males who had not resumed sexual activity following transplant reporting higher rates of immunosuppression, higher anti-infective drug use and higher self-reported cGVHD symptoms which is in keeping with previous studies (Lee *et al*, 2002a; Humphreys *et al*, 2007; Lara *et al*, 2010). Quality of life measures, especially those reflecting physical and functional well-being, were lower in males

Table V. Reasons given by females who did not use medically assisted reproductive methods pre-transplant by age.

Age range (years)	18–29 ($n = 19$)	30–39 ($n = 30$)	40–49 ($n = 26$)	50–59 ($n = 47$)	60–69 ($n = 21$)	≥70 ($n = 1$)	All ($N = 144$)
Not offered ($n = 19$)	1 (5·3%)	7 (23%)	4 (15·4%)	2 (4·3%)	0	0	14/144 (9·7%)
Declined	1 (5·3%)	12 (40%)	18 (69·2%)	44 (93·6%)	20	0	95/144 (66%)
Too sick or other health problems	5 (26·3%)	2 (6·7%)	3 (11·5%)	1 (2·1%)	0	0	11/144 (7·6%)
Completed family	12 (63·1%)	9 (30%)	1 (3·8%)	0	1	1	24/144 (16%)

Table VI. Reasons given by males who did not use medically assisted reproductive methods pre-transplant by age.

Age range (years)	18–29 ($n = 7$)	30–39 ($n = 16$)	40–49 ($n = 43$)	50–59 ($n = 63$)	60–69 ($n = 28$)	≥70 ($n = 1$)	All ($N = 156$)
Not offered ($n = 19$)	1	1	2	3	1	0	8/156 (5·1%)
Declined	0	8	34	54	27	1	124/156 (79·5%)
Too sick or other health problems	1	4	5	2	0	0	12/156 (7·7%)
Completed family	3	3	2	4	0	0	12/156 (7·7%)

who had not returned to normal sexual activity and Lee cGVHD scores were significantly higher in these survivors.

Female HSCT survivors commonly report a range of genitourinary symptoms with significant vulvo-vaginal cGVHD occurring in 22·1% of women who develop cGVHD post-transplant. Genitourinary symptoms are more often reported in women who have resumed sexual activity however it is unclear if sexual activity exacerbated the problem, or if sexual activity allowed women to identify these problems (Spinelli *et al*, 2003; Zantomio *et al*, 2006; Stratton *et al*, 2007).

As has been reported elsewhere, HSCT is invariably associated with premature ovarian failure and azoospermia; however, small numbers of survivors, particularly those aged under 30 years at the time of HSCT, may recover ovarian function/spermatogenesis and fertility (Sanders *et al*, 1988; Wang *et al*, 1998; Grigg *et al*, 2000; Salooja *et al*, 2001; Rovo *et al*, 2006; Jadoul *et al*, 2011; Wu *et al*, 2012). The majority of HSCT survivors are rendered infertile, however because the mean age at HSCT is 49 years this may not constitute a significant concern for many HSCT survivors. While few HSCT survivors attempt to conceive post-transplant, many will be successful (43%), often with assisted reproductive technologies (Lipton *et al*, 1997; Demeestere *et al*, 2006; Donnez *et al*, 2011). Unfortunately such technologies are expensive and are located primarily in metropolitan areas – raising questions about equity of access. The challenges involved in conception post-HSCT underlie the importance of utilizing pre-HSCT fertility preservation measures, including sperm storage, ovarian tissue and/or oocyte or embryo storage (Lee *et al*, 2006; Wallace, 2011; Joshi *et al*, 2014). In this regard it was noteworthy that, in our population, a significant number of women rather than men (23% vs. 5% respectively) were not offered reproductive interventions. While this probably reflects practical difficulties associated with fertility preservation methods in women, it also highlights continuing uncertainty regarding the availability and efficacy of techniques for females.

This study provides important insights into sexual dysfunction and infertility in an Australian cohort of HSCT survivors. Given the high prevalence of continued sexual dysfunction in the post-HSCT period (>66% for females, >50% for males), it is clear that pre-HSCT counselling and post-HSCT care needs to include full disclosure and assessment of the effects of transplant on sexual health and fertility, both for men and women, with greater attention paid to vaginal cGVHD than currently occurs. Consensus guidelines have recently been released with recommendations for regular, integrated gynaecological review both pre- and post-HSCT (Frey Tirri *et al*, 2015; Stratton, 2015). While such practice change seems undeniable, further work is required to establish whether other pre- and post-HSCT interventions, including education, counselling and early treatment, improves sexual function and quality of life outcomes for survivors.

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Author contibutions

GD, NG, LB and IK designed the study. All authors contributed to study recruitment, data analysis, drafting of the publication and approval of the final version.

Conflicts of interest

The authors declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. The Sydney post-BMT study.

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7.5. Synopsis

This manuscript provides the largest and most comprehensive account of sexual function and fertility post allogeneic BMT in Australia. The results indicate that sexual dysfunction is common post-BMT, that sexual dysfunction is complex and multifactorial, and the data clearly showed that women are disproportionately affected by symptoms of sexual dysfunction and are often not given the option to preserve fertility prior to transplantation.

The results presented in this paper have implications for pre and post-BMT discussions and education regarding these 'hidden' and often under-reported adverse effects of BMT, as these have a profound impact on survivors' QoL. Educating and consenting BMT recipients and their partners about the likely impact that BMT may have on their relationship, sexuality and fertility, and establishing systems and practices that enable the early recognition of sexual dysfunction, may facilitate clinical and psychological care and improve both sexual function and QoL outcomes for both men and women.

In this regard it is noteworthy that there appears to be general lack of training for physicians and allied health professionals to adequately address such issues with patients and their partners(1-3).Thus, education and training of health care professionals involved in the care of long term survivors in how to initiate these conversations is also pivotal.

While fertility preservation is often not possible for BMT recipients, either because the kinetics or phenotype of their disease make it impossible, or because treatment prior to BMT has already rendered patients infertile, it seems increasingly likely that considerations regarding fertility may need to be more explicitly included in the care of BMT recipients. Ovarian cryopreservation in particular is becoming a more established option for women of reproductive age who are likely to become infertile because of their treatment. While fertility is not a concern for most adult BMT recipients, progress in reproductive sciences and the increase in maternal age at first pregnancy, suggest that BMT services will need to be more prepared to explicitly address these issues pre and post-transplant.

Likewise, while BMT services have been focussed simply on ensuring survival, improvements in BMT outcomes and survivorship demand that more attention is focused on QoL. This is particularly the case for those domains of QoL that have been ignored within hospitals and health services and that have not been a part of routine history taking and care, such as sexuality. Attending to the sexual health of BMT recipients will require cultural, educational and systemic reform of BMT services and is an area where the involvement of APNs may have a profound impact. This is also an area where research is desperately needed in order to more clearly identify the barriers to addressing issues of fertility, sexuality and identity pre-BMT and to improving the medical and behavioural interventions

that definitively improve both sexual function and fertility preservation and treatment in this vulnerable and high-risk group.

7.6. Chapter references

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Chapter 8: Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)

8.1. Chapter overview

This chapter reports on the incidence of secondary cancers in long-term survivors of BMT and their subsequent adherence with Australian cancer screening guidelines. It consists of a published manuscript entitled, 'Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)'. The manuscript reports on demographics, socioeconomics, transplant factors, co-morbidities and QoL scores associated with compliance with cancer screening. Specifically, survivors were asked about compliance with recommended general population screening for bowel, cervical and breast cancer and also skin cancer screening due to the high incidence of skin cancer in Australian populations(1) and because allogenic BMT survivors, particularly those with skin cGVHD who receive prolonged IST and azole antifungal agents are at significantly increased risk of skin cancer(2).

The results of this study demonstrate that secondary cancers post BMT are common (24%) and that despite an increased risk of cancer, our BMT survivors were not fully compliant with either general population cancer screening guidelines, or cancer screening and preventative care guidelines specific for BMT survivors(3). Disturbingly, many survivors noted that they did not adhere to cancer screening guidelines because they did not believe it was necessary or because they had not been advised to do so by their treating team. The findings have profound implications for education and counselling of both BMT recipients and health care professionals involved in their long-term care. At the same time, however, our results place onus upon researchers to demonstrate proof of efficacy for cancer screening in this population.

8.2. Publication details

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8.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

8.4. Manuscript

The published version of the manuscript follows.

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ORIGINAL RESEARCH

Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)

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Abstract

Allogeneic Blood and Marrow Transplant (BMT) survivors are at high risk of secondary cancers. Although current guidelines endorse survivors following Country-specific general population screening recommendations to mitigate this risk, little is known about cancer screening adherence in Australian BMT survivors. We conducted a cross-sectional survey of 441 BMT survivors who were >1 year post transplant, to explore rates of screening for secondary cancers and to identify barriers to cancer screening recommendations. Survey instruments included the Sydney Post-BMT Survey, FACT-BMT, DASS 21, The Chronic Graft versus Host Disease (GVHD) Activity Assessment–Patient Self-Report (Form B), the Lee Chronic GVHD Symptom Scale, Fear of Cancer Recurrence Scale, and The Post Traumatic Growth Inventory. Fifty-seven percent of respondents were male, median age 54 years, and 40% were ≥6 years post-BMT. Rates of cancer screening adherence were as follows: cervical 63.4%, breast 53.3%, skin 52.4%, and bowel 32.3%. Older BMT survivors and those >2 years post transplant were more likely to undergo cancer screening. Improved quality of life was associated with screening for skin, breast, and cervical cancer. Fear of cancer recurrence negatively impacted on cervical screening. For those who had not undergone screening, the majority reported not being advised to do so by their treatment team. This study is the largest and most comprehensive to date exploring cancer screening adherence in BMT survivors in Australia. These data provide the basis for health service reform to better meet the needs of BMT survivors and provide evidence to support counseling and education of both patients and professionals.

Introduction

Survivors of allogeneic Blood and Marrow Transplant (BMT) are at a significant risk of developing many long-term and adverse late effects in the years following transplantation [1]. Of these late effects, secondary malignancies are a particular concern. Cumulative incidence rates of up to 12% at 15 years post-BMT have been reported, and no plateau has been identified [2, 3]. All cancers have been found to occur in survivors of BMT

with skin, thyroid, oral cavity, esophagus, breast, liver, brain/nervous system, bone, and connective tissue cancers, all more frequently diagnosed in BMT survivors than the general population [4–6]. Risk factors for higher rates of secondary cancers include younger age at BMT, total body irradiation (TBI), prolonged immunosuppression, chronic graft-versus-host disease (cGVHD), and smoking prior to allogeneic BMT [5–8].

For almost a decade international consensus guidelines for the care of long-term survivors of BMT have been available [9, 10]. These guidelines include recommendations for cancer screening, preventive health care and health promotion, noting that survivors follow general population screening recommendations in their country for breast, cervical, skin, genital, and bowel cancer, and avoid high-risk behaviors (smoking, excess drinking, overweight and obesity, inactivity, and unprotected skin UV exposure). These guidelines also make clear that in patients with chronic GVHD, additional attention needs to be paid to surveillance for oral, pharyngeal, and early skin cancer. While some controversy exists regarding the commencement, frequency, and modality for breast cancer screening, it is generally suggested that for woman who received TBI and/or chest irradiation, mammography screening should be commenced at age 25 or 8 years after radiation exposure, whichever occurs later, but no later than age 40 years [8, 10, 11].

In Australia, the Commonwealth Government funds three national screening programs to reduce the burden of cancer nationwide; Breast Screen Australia, the National Cervical Screening Program, and the National Bowel Cancer Screening Program. These programs offer free screening to the Australian public at specific age and interval time points (Table 1) [12, 13]. Cancer Australia (the lead national cancer control agency) also advocates known healthy lifestyle behaviors such as quitting smoking, being 'sun smart', being active, maintaining a healthy diet, and limiting alcohol intake for the entire population. Participation in these programs and health promotion behaviors in Australian BMT survivors is largely unknown.

Despite the availability of long-term follow-up guidelines [9, 10], and the excess burden of secondary cancers post allogeneic BMT [14], international studies have shown that cancer screening uptake and health behaviors in BMT survivors are similar, if not worse than people who have had cancer but not had an allogeneic BMT, and people who have never had cancer [15, 16]. In this study we aimed to explore rates of screening for secondary malignancies in an Australian cohort of allogeneic BMT survivors and identify barriers to adherence with cancer screening recommendations.

Methods

A cross-sectional survey of BMT survivors was undertaken to explore late effects of BMT and the quality of survival post transplant. This survey of BMT survivors in New South Wales (NSW) Australia included questions regarding rates of secondary cancers, adherence to cancer screening, and modifiable healthy lifestyle behavior, together with demographic and social characteristic associated with barriers to uptake of cancer screening recommendations.

NSW is Australia's most populous state with a population of ~7.5 million and covers an area of 800,628 km^2. Over a third of residents live outside the greater Sydney area [17]. At the time of study commencement there were four adult allogeneic transplant centers in NSW, all

Table 1. Australia's National Cancer Screening Programs with recommendations for the general population [13].

Cancer Screening Program [13]	Recommendations [13]
BreastScreen Australia	BreastScreen Australia invites women aged 50–74 to have free 2 yearly mammogram. Women aged 40–49 and 75 and over are eligible to receive free mammograms, but do not receive an invitation to attend.
National Bowel Cancer Screening Program (NBCSP)	The NBCSP invites men and women turning 50, 55, 60, 64, 65, 70, 72, and 74 to screen for bowel cancer. Participants are sent a free, easy to use screening kit that can be completed at home. Between 2015 and 2020, more age groups will be added to the screening program: • 2017—68, 58, and 54 year olds. • 2018—62 and 66 year olds. • 2019 and 2020—52 and 56 year olds.
National Cervical Screening Program (NCSP)	The NCSP invites all women aged between 18 and 70 who have ever been sexually active to have 2 yearly Pap tests. Cervical screening is provided through general practice, community or women's health centers, family planning clinics, sexual health clinics, or Aboriginal Medical Services. From 1 May 2017, the NCSP will be changed to inviting women aged 25–74 years (both HPV vaccinated and unvaccinated) to undertake an HPV test every 5 years.

based in Sydney and collectively performing approximately 175 BMTs annually [18].

Potential participants were identified from allogeneic transplant databases from all adult allogeneic transplant centers in NSW. Participants were eligible if they were ≥18 years of age and had undergone an allogeneic BMT between 1 January 2000 and 31 December 2012, could read and write English, and could provide consent. Names and phone numbers were provided to the research team. Consenting participants were given the option to self-complete the questionnaire or complete it via a phone interview with one of the researchers. A second round of telephone calls was made to 187 participants who had not returned the survey within a month. All authors had access to primary clinical trial data. The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Instruments

Participants were asked to complete seven instruments.

The Sydney Post BMT Study Survey (SPBS) was developed by the research team from a review of the literature and discussion with patients attending BMT long-term follow-up clinics. The survey comprised 402 questions grouped into 20 domains and included questions relating to secondary cancer diagnosis, cancer screening adherence, and lifestyle behavior choices. Other relevant domains included demographics, medical complications, tests and assessments, medications and therapies, infections, vaccinations, complementary therapy use, relationship status, income (Australian Dollars, AUD), and lifestyle factors, following allogeneic BMT. The questionnaire used tick box responses, short answer questions, and five-step Likert scales measuring attitudes and other factors and took approximately 1 h to complete. The questionnaire was piloted with six BMT survivors in clinic and phone interviews to assess face and content validity and to check for comprehension. For each consenting participant, data were collected on dates of diagnosis and transplant, stage/remission status at transplant, transplant conditioning, GVHD prophylaxis, stem cell source, and donor type.

Cancer screening adherence and health behavior choices were analyzed according to a range of demographic, transplant, psychosocial, and lifestyle variables assessed using the *Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4)* [19, 20], anxiety stress and depression (*The DASS 21)* [21–23], chronic GVHD (*The Chronic GVHD Activity Assessment – Patient Self Report (Form B)* [24], *The Lee Chronic GVHD Symptom Scale)* [25], the *Fear of Cancer Recurrence (FoCR) Scale* [26], and *The Post Traumatic Growth Inventory (PTGI)* score [27, 28]. For ease of completion all instruments were combined into one booklet.

Statistical analysis

Categorical responses were summarized using frequencies and percentages. Parametric continuous variables were summarized using means and standard deviations, and nonparametric variables using medians, interquartile ranges (IQR), or ranges. Odds ratios and 95% confidence limits, Pearson χ^2 test, or Fishers Exact tests were used for comparative analysis of dichotomous categorical variables and multivariable logistic regression to adjust for relevant confounders. Two sample comparisons of parametric and nonparametric data were determined using the independent *t*-test, and Wilcoxon rank sum tests, respectively; greater than two-sample comparisons were determined using one-way Analysis of Variance (ANOVA) and Kruskal–Wallis tests, respectively. A two-tailed *P*-value <0.05 was used as the level of statistical significance.

Statistical analysis was performed using STATA version 12.1 statistical package (StataCorp, College Station, TX).

Results

A total of 1475 Allogeneic BMT were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable and were sent study packs. Four hundred and forty one (66% of total eligible, 76% of those contacted) returned the completed survey. Three percent (17) declined participation.

Of those completing the survey, 250 (57%) were male and 191 (43%) female. The median age of survey respondents was 54 years (Range: 19–79). The median age at time of transplant was 49 years (Range: 17–71) (Table 2).

Secondary cancer diagnosis

One hundred and six (24.0%) reported a diagnosis of at least one cancer following BMT of which 104 were non-relapse malignancies. Skin cancers accounted for the largest number of secondary cancers (Table 3).

Cancer screening

Skin cancer screening

A total of 436 (98.9%) participants provided a response to whether or not they had had undergone skin cancer screening since transplant. Two hundred and twenty eight (52.3%) reported having had a skin check and 208 (47.7%) reported never having had a skin check since BMT. Of those who reported having had a skin check, 75% had

Table 2. Participant characteristics.

Sociodemographic	
Gender (*n* = 441)	
Male *n* (%)	250 (56.7%)
Female *n* (%)	191 (43.3%)
Age (years) at survey (*n* = 441)	
Median (IQR; range)	54 (44,62; 19–79)
Age (years) at transplant (*n* = 441)	
Median (IQR; range)	49 (38, 56; 17–71)
Ethnicity (*n* = 372)	
Caucasian, European *n* (%)	323 (86.8%)
Other *n* (%)	49 (13.2%
Educational status (*n* = 333)	
University (some/completed) *n* (%)	154 (46.2%)
Other[1] *n* (%)	179 (53.8%)
Post transplant income status (AUD[4]) (*n* = 423)	
Low income $20,000–$39,999 *n* (%)	155 (36.6%)
Middle income $40,000–$79,999 *n* (%)	123(29.1%)
High income ≥ $80,000 *n* (%)	145 (34.3%)
Residence (*n* = 431)	
Major city *n* (%)	311 (72.2%)
Other (inner regional, outer regional, remote) *n* (%)	120 (27.8%)
Relationship status (*n* = 434)	
Married–Defacto *n* (%)	344 (79.3%)
Other (separated, single, divorced) *n* (%)	90 (21.8%)
Transplant –related	
Years since transplant (*n* = 441)	
<2 years *n* (%)	58 (13.1%)
=2 to <6 years *n* (%)	204 (46.3%)
=6 to <10 years *n* (%)	117 (26.5%)
≥10 years *n* (%)	62(14.1%)
Underlying diagnosis (*n* = 423)	
Acute leukemia (AML/ALL) *n* (%)	226 (53.4%)
Other[2] *n* (%)	197 (46.6%)
Remission status (*n* = 405)	
First/second complete remission	271 (66.9%)
Other[3]	134 (33.1%)
Donor type (*n* = 441)	
Sibling *n* (%)	250 (59.9%)
Matched unrelated *n* (%)	158 (36.0%)
Haploidentical *n* (%)	10 (2.3%)
Mismatched unrelated *n* (%)	21 (4.8%)
Stem cell source(*n* = 441)	
Bone marrow *n* (%)	48 (10.9%)
Peripheral blood *n* (%)	381 (86.4%)
Cord blood *n* (%)	12 (2.7%)
Conditioning chemotherapy (*n* = 439)	
Myeloablative	214 (48.7%)
Reduced intensity	225 (51.3%)

[1]Other Education—secondary school (some or complete); trade or diploma.

[2]Other diagnoses: CML, Chronic Myeloid Leukemia; CLL, Chronic Lymphocytic Leukemia; NHL, Non-Hodgkin Lymphoma; HL, Hodgkin Lymphoma; MM, Multiple Myeloma; Myelodysplastic Syndrome/ Myeloproliferative disorder; Other (unspecified).

[3]Other remission status; more than second complete remission; Refractory; Chronic Phase; Accelerated Phase; Blast Crisis; Partial Remission; other (unspecified).

[4]AUD—Australian Dollars; IRQ, interquartile ranges.

Table 3. Secondary cancer diagnosis post blood and marrow transplant (BMT).

Cancer types (*N* = Number of Responses)	*n* (% reporting cancer type of total responses)
Skin cancer (*n* = 404)	93(23.0%)
Skin cancer type	% of all skin cancers
Basal cell carcinoma (BCC)	41 (44%)
Squamous cell carcinoma (SCC)	14 (15%)
Melanoma	5 (6%)
Mixed	17 (18%)
BCC + SCC	14(15%)
BCC + Melanoma	2 (2%)
SCC + Melanoma	1(1%)
Unspecified/don't know	16(17%)
Mouth cancers (*n* = 392)	6 (1.5%)
Other (*n* = 370)	18 (4.9%)
	n (% of all other cancers)
Urological (prostate and/or bladder)	5/18 (27%)[1]
Breast	2(11%)
Bowel	1(6%)
Ovarian	1(6%)
Myeloid sarcoma	1(6%)
Head (unspecified)	1(6%)
Hematological (nonrelapse)	5 (27%)[2]
Hematological (relapse)	2(11%)[3]

[1]3 prostate, 1 bladder, 1 bladder + prostate.

[2]1 NHL (primary = AML); 1 NHL (Primary = SAA); 2 Hodgkin Lymphoma (Primary = NHL); 1 post transplant lymphoproliferative disease.

[3]1 Relapse AML; 1 relapse Mantle Cell Lymphoma; AUD, Australian Dollars

done so in the preceding 18 months (range 1 month to 9 years). One hundred and sixty six of the 228 (72.8%) reported attending for skin checks at least once a year.

Demographic, social, transplant-related, treatment-related, and behavioral factors were assessed for their association with having skin checks as part of cancer screening post transplant. Of note, skin checks were not significantly associated with skin GVHD, receipt of azole antifungals, or outdoor occupations (gardening, construction, or agriculture). Univariate analysis demonstrated a significantly increased odds of skin checks with older age, higher education status, being in a married or defacto relationship, and a high compliance with "sun smart" behaviors including the routine use of sunscreen, hats, sun protective attire, sunglasses, and sun avoidance during the daily periods for peak exposure. Factors associated with a reduced odds of skin checks on univariate analysis included an acute leukemia diagnosis, receipt of a myeloablative conditioning regimen, and being within 2 years of transplant. After adjusting for potential confounders, those factors that demonstrated an independent and significant association with having skin checks post transplant included older age (Adjusted 1.03 95% CI: 1.0, 1.05; $P = 0.03$), higher educational status (Adjusted Odds Ratio

[AOR]: 1.87 95% CI: 1.11, 3.15; $P = 0.02$), and "Sun smart" behavior (AOR: 1.89 95% CI: 1.06, 3.37; $P = 0.03$).

Compliance with skin cancer screening was further assessed against measures including quality of life (FACT-BMT and subscales) and psychological morbidity (DASS21 and subscales), Lee GVHD scores, self-reported GVHD symptom severity, and Fear of Cancer recurrence and Post Transplant Growth Inventory scores. Survivors who had skin checks had significantly higher scores on FACT emotional subscale ($P = 0.03$), BMT subscale ($P = 0.007$), and overall FACT-BMT scores ($P = 0.03$), and significantly lower scores on depression subscales ($P = 0.02$), with no significant difference observed on other subscale or composite DASS21 measures (Appendix A1).

Reasons cited for not undergoing skin cancer screening in 208 patients included lack of time in 13 (6.2%), cost in five (2.5%), and belief that screening was not necessary in 54 (26.0%). One hundred and forty nine patients (71.6%) indicated that they had not been advised by their treating team to undergo skin cancer screening. Twenty nine (13.9%) of those who had never undertaken skin cancer screening were receiving azole antifungal therapy.

Bowel cancer screening

A total of 432 participants provided a response to whether or not they had undergone bowel cancer screening (either colonoscopy or stool hemoccult testing) since transplant. One hundred and forty (32.4%) reported having had a bowel cancer check and 292 (67.6%) reported not having had a bowel cancer check since BMT. Of those who reported having had a bowel cancer check, 75% had done so in the preceding 2 years (range <1 month to 11 years). Forty-seven of 140 (33.8%) reported having bowel checks at least every 2 years.

On univariate analysis, older BMT survivors and those in a married or defacto relationship showed a significantly increased odds of undergoing bowel cancer screening. Transplant-related factors including an underlying diagnosis of acute leukemia and receiving myeloablative conditioning were associated with significantly decreased odds of bowel cancer screening. On multivariable analysis, the only variable with an independent and significant increased association with bowel cancer screening was older age (AOR: 1.06; 95% CI: 1.03, 1.08; $P < 0.0001$).

No significant differences were evident in DASS21 and FACT-BMT scores and subscales, Lee GVHD or other psychosocial metrics in those who reported bowel screening and those who did not (Appendix A2).

Of the 292 patients who did not have bowel screening, 8 (2.7%) cited time, 2 (0.7%) cost, and 75 (25.7%) feeling that screening was not necessary as the main reasons for not attending to a bowel check since transplant. Two hundred and twenty five patients (77% of those not having a bowel cancer check) reported that they had not been advised to undergo bowel cancer screening by their treating team.

Cervical cancer screening

A total of 186 of female participants provided a response to whether or not they had had a Paapaniolou (pap) smear since transplant. One hundred and eighteen (63.4%) females reported having had a pap smear and sixty eight (36.6%) reported not having had a pap smear since BMT. Of those who reported having had a pap smear, 75% had done so in the preceding 2 years (range: 1 month to 5 years).

Younger age was significantly associated with having had a pap smear ($P = 0.04$) and women who were less likely to have had a pap smear if within 2 years of the transplant procedure. Following multivariable analysis, a trend for a reduced odds with older age was observed (AOR: 0.97; 95% CI: 0.94, 1.0: $P = 0.09$) and a significantly reduced odds of pap screening for women less than 2 years post transplant (AOR: 0.30; 95% CI: 0.11, 0.85: $P = 0.02$).

Those reporting cervical cancer screening post transplant showed no overall differences in DASS 21 scores, although on a trend toward lower Anxiety scores was observed in females who had undergone pap screening ($P = 0.06$). Patients undergoing pap screening reported a trend toward higher emotional subscale scores ($P = 0.054$) and significantly higher functional well-being ($P = 0.008$) and overall scores on FACT-BMT ($P = 0.02$). This would suggest a positive association between improved quality of life in women who had pap screening. Lower uptake of cervical screening was associated with a significantly increased fear of cancer recurrence (FoCR) score ($P = 0.003$). (Appendix A3).

Barriers to undergoing cervical cancer screening included lack of time in 8 (11.8%), cost in 2 (2.9%), and a belief that Pap screening was not necessary in 20 (29.4%). A total of 31 women (45.6%) reported that they had not been advised to have a Pap smear by their treating team.

Breast cancer screening

A total of 184 female participants provided a response to whether or not they had had a mammogram for breast cancer screening since transplant. Ninety-eight (53.3%) females reported having had a mammogram and 86 (46.7%) reported not having had a mammogram since BMT. Seventy-five percent reporting having a mammogram in the preceding 2 years (range 2.5 month to 4 years). The

age of first mammogram was reported by 68 women; in their 20s (8), 30s (12), 40s (31), 50s (16), and 60s (1). Older age (AOR: 1.11; 95% CI: 1.07, 1.16; $P < 0.001$) and residing in a city/inner-regional center (AOR: 5.33; 95% CI: 1.37, 20.8; $P = 0.03$) were the only variables associated with a significantly increased odds of screening mammography on multivariable analysis. Total Body Irradiation (TBI) as part of the conditioning regimen showed a trend toward increased mammography uptake (AOR: 2.35; 95% CI: 0.99, 5.58; $P = 0.052$) and being less than 2 years post transplant a trend toward decreased mammography uptake (AOR: 0.31; 95% CI: 0.09, 1.05; $P = 0.06$).

For those reporting mammography screening post transplant, there were no overall differences in DASS 21 scores, although lower depression subscales were associated with mammography uptake ($P = 0.04$). Patients undergoing mammography reported significantly higher emotional ($P < 0.001$) and BMT subscale scores on FACT-BMT ($P = 0.02$). This would suggest a positive association between improved quality of life in women who had mammography. Mammography screening was associated with significantly lower median Lee GVHD severity scores ($P = 0.02$), although no significant differences were observed using the alternative metric for GVHD severity (cGVHD activity assessment Form B) (Appendix A4).

For those not having mammography, 5 (5.8%) reported lack of time, 2 (2.3%) had an issue with cost, 23 (26.7%) felt it was not necessary, and 57 (66.3%) reported not being advised by their treating team to undergo breast cancer screening.

Discussion

The results of this study confirm that secondary cancers occur commonly after allogeneic transplantation [7, 29, 30] and that cancer screening is not being performed according to recommended BMT long-term follow-up guidelines [10, 15] or with recommendations for cancer screening in the general Australian population [12]. Our cohort had lower rates of screening for bowel cancer (32.3%), cervical cancer (63.4%), and breast cancer (53.3%) than previous studies in BMT survivor populations [31]. These rates are, however, similar to adherence rates among the general Australian population who participate in Breast Screen Australia (55%), the National Cervical Screening Program (58%), and the National Bowel Cancer Screening Program (33%) [12]. Only half of the cohort had had a skin cancer check (52.4%) following transplant. This is significant because although there is currently insufficient evidence to support population-based screening for non-melanocytic and melanoma skin cancer [32], and skin cancer screening not recommended by major public health bodies [12, 32], Australians experience a melanoma incidence rate 11 times that of the average world rate [12] and BMT recipients are at markedly higher risk of developing all forms of skin cancer as a consequence of cutaneous graft-versus-host disease (GVHD), long-term use of immunosuppressive drugs, and azole antifungal agents [29].

In this study the major determinant of cancer screening, with the exception of cervical screening, was older age. In contrast to other studies, which have shown that being further out from BMT decreased adherence to preventive care practices [31], we observed a trend toward increased screening for skin, bowel, and breast cancers in late compared to early transplant survivors. A significant association with cervical screening was observed in females beyond the first 2 years of their transplant procedure. It is difficult, however, to know the significance of this finding as there are no data regarding whether the age time points for general population cancer screening apply to BMT survivors, many of whom experience an increased risk from a younger age of secondary cancer, particularly breast and skin cancers. For this reason alone the 'benchmarking' of cancer screening adherence against general population recommendations raise real questions regarding best practice and the possibility of both over- and underdiagnosis [33]. In this regard it is noteworthy that rates of cancer screening in our study population were not only inconsistent with recommendations for general population screening but also with recommendations for BMT recipients and for high-risk cancer survivors. The finding that women exposed to TBI were no more likely to have mammography or to commence mammography at an earlier age is of enormous concern given the recognized association between radiation exposure and breast cancer [34].

Interestingly, our study found a significant association between participation in skin, cervical, and breast cancer screening and higher quality of life. Although this is reassuring to those involved in post transplant care, it runs counter to recent literature that suggests that cancer screening can increase anxiety and overdiagnosis [33, 35]. There are at least two possible explanations for this finding—firstly, that those who report higher quality of life may be more motivated to maintain good health, or conversely, participating in cancer prevention may confer quality of life and survival benefits.

We were unable to identify a significant association between social factors such as being in a married/defacto relationship with increased screening uptake, a finding that is otherwise well-described in other cancer screening studies [36–39].

Fear of cancer recurrence (FoCR) in those with an underlying hematological malignancy at transplantation

was investigated for its associations with screening uptake. FoCR was negatively associated with cervical screening uptake, but had no association with other screening procedures. Positive measures of personal growth assessed using the PGTI was not associated with adherence to cancer screening. The severity of GVHD symptoms was further explored for any potential association with screening uptake. We hypothesized that more symptomatic GVHD may result in patients being under closer medical surveillance and, therefore, more likely to be screened for cancers. Lee GVHD scores were observed to in fact be lower in females who did undergo post transplant breast screening, which may also attest to the better quality of life that such patients have.

Perhaps most importantly, the results of our study provide clues as why BMT survivors may not participate in cancer screening programs. Over a quarter of our respondents reported that they did not feel that screening was necessary—suggesting failures in the education and/or counseling of transplant recipients—a finding reported in previous studies [14]. In addition, of those who reported that they had not undergone any cancer screening, the vast majority gave the reason that the screening test/s had not been recommended by their treating team. While we did not verify this report for individual patients, it is consistent with the findings of studies conducted in general populations [40] and may likely be true in this population given the inadequate resourcing of post transplant care in many BMT centers. Cost was reported to be a barrier to uptake for very few survivors in our study; however, financial difficulties (low income) have been shown to impact cancer screening rates in other populations [38]. This may be a function of Australia's aforementioned free national cancer screening programs. The barrier of cost was reported for younger survivors who do not meet age criteria (e.g., annual mammograms for those age 25 years if they had TBI). These explanations for the low rates of adherence with cancer screening recommendations are also consistent with the literature that suggests that many factors may act as barriers to optimal preventive care including: lack of knowledge regarding the importance of cancer screening in both patients and providers, deficiencies in the organization of preventive health-care services [31], and skepticism regarding the value of screening [33, 41].

This study is important because it is one of the largest studies describing adherence with cancer screening guidelines in a BMT population and the first to explore cancer risk behavior and adherence to cancer screening guidelines in an Australian cohort of BMT survivors. Although the sample size and high response rate (76%) make it likely that these results represent an accurate account of BMT survivor's health behaviors, there are a number of limitations to our study which may limit the generalizability of these results to BMT survivors in other countries and other settings. These limitations are principally a function of our study population and include Australia's geographical size, population pattern, climate and health system (which includes both universal publicly funded and private health care), and funded national cancer screening programs. The fact that the study relied upon self-reporting and did not capture data on nonresponders also limits our findings. Another area which may have been of interest is that relating to digital rectal examination (DRE) and/or prostate-specific antigen (PSA) for prostate cancer screening in BMT survivors, however, due to the controversy regarding these modalities [42–45], and that general population prostate cancer screening is not recommended in Australia, we did not ask participants about this. Additionally, it should be noted that as only two of the respondents had a recurrence of the malignancy for which they were transplanted, our findings only apply to survivors who remain disease free following BMT. Also, as we did not ask respondents about adherence to cancer screening guidelines pre-BMT, we are not able to make any correlation between pre- and post-BMT practices.

What this study makes clear is that recommendations for cancer screening and for preventive health-care post-BMT are, in many situations, not being followed by health-care services and/or adopted by the target population. Although the exact reasons for this require further qualitative study, it seems likely that this is a result of both systems failures and inadequate or unsuccessful patient education. It is also possible, but entirely speculative, that this may result from awareness that there is currently limited data to support cancer screening in BMT patients—including those most at risk. Absence of good quality long-term data does not, however, create an argument for therapeutic nihilism or for failures to deliver comprehensive care post-BMT. Rather, data from studies such as this one should be used to drive the development and implementation of models of chronic care post-BMT that address gaps in health promotion, behavior modification, and cancer screening in order to prevent morbidity and mortality in long-term BMT survivors and increase awareness in health professionals and patients alike of the increased risk of secondary cancers in survivors of BMT.

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data. GD is an MPhil candidate at the University of Sydney and this work will be submitted in partial fulfillment of the requirement for the MPhil.

Conflict of Interest

None declared.

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Appendix A1. Demographic, social determinants, transplant factors, and instrument measures (QoL, psychological morbidity, GVHD, FoCR, PTGI), and their associations with having skin cancer screening.

	Skin check *N* = 228	No skin check *N* = 208	OR (95% CI)	Adjusted OR(95% CI)[1] *P*-value
Gender				
Male	127/228 (55.7%)	121/208 (58.2%)	0.90 (0.61, 1.34)	
Female	101/228 (44.3%)	87/208 (41.8%)	0.61	
Age (median, IQR)	58 (48, 64)	51 (42, 59)	1.03 (1.02, 1.05)	1.03 (1.0, 1.05)
			<0.0001	*P* = 0.03
Residence				
City/inner regional	209/223 (93.7%)	182/203 (89.7%)	1.72 (0.81, 3.77)	
Outer regional/remote	14/223 (6.3%)	21/203 (10.3%)	0.13	
Education				
Some/completed university	91/173 (52.6%)	60/156 (38.5%)	1.77 (1.12, 2.82)	1.87 (1.11, 3.15)
Trade/some or complete secondary school	82/173 (47.4%)	96/156 (61.5%)	0.03	*P* = 0.02
Household income (AUD)				
Low income $20,000–$39,999	71 (32.7%)	83 (41.3%)	0.69 (0.45, 1.05)	0.73 (0.42, 1.27)
Middle/high income ≥ $40,000	146 (67.3%)	118 (58.7%)	0.07	*P* = 0.27
Marital status				
Married/Defacto	188/225 (83.6%)	152/205 (74.1%)	1.77 (1.08, 2.92)	0.80(0.42, 1.51)
Single/divorced/separated	37/225 (17.3%)	53/205 (25.8%)	0.02	*P* = 0.48
Occupation				
Gardener	11/210 (5.2%)	1/187 (0.5%)		
Building/construction	17/211 (8.1%)	13/189 (6.9%)		
Agriculture/Farm worker	9/209 (4.3%)	7/189 (3.7%)	1.44 (0.77, 2.79)	
			0.22	
Any outdoor occupation				
Yes (Gardener, Builder, Ag worker)	31/215 (14.4%)	20/192 (10.4%)		
No	184/215 (85.6%)	172/192 (89.6%)		
Years since transplant				
<2 years	20/228 (8.8%)	37/208 (17.8%)	0.44 (0.23, 0.82)	0.69 (0.32, 1.48)
≥2 years	208/228 (91.2%)	171/208 (82.2%)	0.005	*P* = 0.34
Underlying diagnosis	100/215 (46.5%)	123/203 (60.6%)	0.56 (0.38, 0.85)	
Acute leukemia	115/215 (53.5%)	80/123 (39.4%)	0.004	0.70 (0.42, 1.16)
Other				*P* = 0.17
Donor type				
Matched (sibling/unrelated)	213/226 (94.2%)	190/208 (91.3%)	1.55 (0.70, 3.54)	
Mismatched (haploidentical, unrelated)	13/226 (5.8%)	18/208 (8.7%)	0.24	
Conditioning				
Myeloablative	98/226 (43.4%)	115/208 (55.3%)	0.62 (0.42, 0.92)	0.85 (0.49, 1.48)
Reduced Intensity	128/226 (56.6%)	93/208 (44.7%)	0.01	*P* = 0.57
Self-reported skin GVHD				
Yes	113/228 (49.5%)	89/208 (42.8%)	1.31 (0.88, 1.95)	
No	115/228 (50.4%)	119/208 (57.2%)	0.16	
Medications				
Immunosuppression				
Yes	73/228 (32.0%)	82/208 (39.4%)	0.72 (0.48, 1.09)	
No	155/228 (68.0%)	126/208 (60.6%)	0.11	
Azole antifungals				
Yes	24/228 (10.5%)	29/208 (13.9%)	0.73 (0.39, 1.34)	
No	204/228 (89.5%)	179/208 (86.1%)	0.27	
Routine use of sun protection				
Yes	183/223 (82.1%)	147/203 (72.4%)	1.74 (1.07, 2.84)	**1.89 (1.06, 3.37)**
No	40/223 (17.9%)	56/203 (27.6%)	0.02	***P* = 0.03**
DASS 21 score (median, IQR)	18 (8, 38)	20 (10,42)		*P* = 0.2
Depression subscale	4 (0,12)	6 (2,14)		***P* = 0.03**
Anxiety subscale	4 (2,10)	4 (2,12)		*P* = 0.53
Stress subscale	8 (2,16)	8 (4,16)		*P* = 0.69

Appendix A1. Continued.

	Skin check *N* = 228	No skin check *N* = 208	OR (95% CI)	Adjusted OR(95% CI)[1] *P*-value
FACT-BMT score (median, IQR)	112 (96, 125)	106 (88,119)		***P* = 0.01**
Physical well-being subscale	24 (20, 27)	24 (19,26)		*P* = 0.09
Social well-being subscale	22 (17,25)	20 (15, 24)		*P* = 0.11
Emotional well-being subscale	17 (15, 19)	16 (14,19)		***P* = 0.03**
Functional well-being subscale	21 (16,24)	19 (14,24)		*P* = 0.08
BMT well-being subscale	29 (25,33)	27 (23,32)		***P* = 0.007**
LEE GVHD score (Median, IQR)	21 (9,32)	19 (10, 29)		*P* = 0.51
Global severity GVHD symptoms (%)				
None	23 (16.1%)	16 (13.3%)		*P* = 0.64
Mild	65 (45.5%)	64 (53.3%)		
Moderate	39 (27.3%)	29 (24.2%)		
Severe	16 (11.2%)	11 (9.2%)		
Fear of cancer recurrence (median, IQR)	13 (10,16)	14 (11, 17)		*P* = 0.22
Post transplant growth inventory score	57 (37, 70)	60 (44,70)		*P* = 0.42

AUD, Australian Dollars; IRQ, interquartile ranges; PTGI, The Post Traumatic Growth Inventory.
[1]Variables included in multivariable logistic regression model to adjust for confounding: age, education, income and marital status, time from transplant (<2 years compared to later), underlying diagnosis (acute leukemia compared to other), conditioning regimen (myeloablative compared to reduced intensity), and "sun smart" practices.
Bold text indicates statistically significant figures.

Appendix A2. Demographic, social determinants, transplant factors, and instrument measures (QoL, psychological morbidity, GVHD, FoCR, PTGI), and their associations with having bowel cancer screening.

	Bowel Ca screen	No Bowel Ca Screen	OR (95% CI)	Adjusted OR (95% CI)
	N = 140	*N* = 292	*P*-value	*P*-value[1]
Gender				
Male	79/140 (56.4%)	168/292(57.5%)	0.95(0.62, 1.47)	
Female	61/140 (43.6%)	124/292 (42.5%)	0.83	
Age (Median, IQR)	59(53, 64)	50(40, 60)	1.06(1.03, 1.08) <0.0001	**1.06 (1.03,1.08)** ***P* < 0.0001**
Residence				
City/inner regional	128/137(93.4%)	262/285(91.9%)	1.25(0.54, 3.15)	
Outer regional/remote	9/137(6.6%)	23/285(8.1%)	0.69	
Education				
Some/completed University	50/105(47.6%)	101/222(45.5%)	1.09(0.66,.78)	
Trade/some or complete secondary school	55/105(52.4%)	121/222(54.5%)	0.72	
Household income (AUD)				
Low income $20,000–$39,999	56/136(41.2%)	95/280(33.9%)	1.36(0.87, 2.12)	
Middle/High income ≥ $40,000	80/136 (58.8%)	185/280(66.1%)	0.15	
Marital status				
Married/Defacto	116/136(85.3%)	222/289(76.8%)	1.75(0.99, 3.20)	1.14(0.63, 2.07)
Single/Divorced/separated	20/136(14.7%)	67/289(23.2%)	0.04	*P* = 0.65
Years since transplant				
<2 years	13/140(9.3%)	44/292(15.1%)	0.58(0.27, 1.14)	0.61(0.30, 1.21)
≥2 years	127/140(90.7%)	248/292(84.9%)	0.13	*P* = 0.16
Underlying diagnosis				
Acute Leukemia	60/135 (44.4%)	158/279(56.6%)	0.61(0.39, 0.95)	0.75(0.48, 1.19)
Other	75/135(55.6%)	121/279 (43.4%)	0.02	*P* = 0.23
Donor type				
Matched (sibling/unrelated)	126/138(91.3%)	274/292(93.8%)	0.69(0.30, 1.62)	
Mismatched (haploidentical, unrelated)	12/138	18/292(6.2%)	0.42	
Conditioning				
Myeloablative	57/138(41.3%)	155/292(53.1%)	0.62(0.40, 0.95)	1.20(0.72,2.00)
Reduced Intensity	81/138(58.7%)	137/292(46.9%)	0.02	*P* = 0.49

Appendix A2. Continued.

	Bowel Ca screen	No Bowel Ca Screen	OR (95% CI)	Adjusted OR (95% CI)
	N = 140	*N* = 292	*P*-value	*P*-value[1]
GVHD				
Yes	98/135(72.6%)	196/290(67.6%)	1.27(0.79, 2.06)	
No	37/135(27.4%)	94/290(32.4%)	0.3	
Self-reported GUT GVHD				
Yes	26/140 (18.6%)	34/292 (11.6%)	1.73(0.95, 3.12)	1.66(0.90, 3.05
No	114/140(81.4%)	258/292(88.4%)	0.05	*P* = 0.10
Medications				
Immunosuppression				
Yes	49/140(35.0%)	103/292 (35.3%)	0.98(0.63, 1.54)	
No	91/140(65.0%)	189/292(64.7%)	0.95	
DASS 21 score (Median, IQR)	19(10,38)	20(9,40)		*P* = 0.97
Depression subscale	4(2,14)	6(2,14)		*P* = 0.79
Anxiety subscale	4(2,8)	6(2,10)		*P* = 0.43
Stress subscale	10(4,18)	8(2,16)		*P* = 0.43
FACT-BMT score(Median, IQR)	112(93, 122)	108(92,122)		*P* = 0.39
Physical well-being subscale	24(20, 26)	24(19,26)		*P* = 0.46
Social well-being subscale	22(17,25)	21(16, 24)		*P* = 0.14
Emotional well-being subscale	17(14, 19)	17(14,19)		*P* = 0.79
Functional well-being subscale	20(15,24)	20(15,25)		*P* = 0.83
BMT subscale	29(24,33)	28(23,32)		*P* = 0.51
LEE GVHD score (median, IQR)	16(8, 28)	21(10,32)		*P* = 0.06
Global severity GVHD symptoms (%)				
Mild	15(16.5%)	26 (15.0%)		*P* = 0.76
Moderate	47(51.6%)	81 (46.8%)		
Severe	20(22.0%)	48 (27.7%)		
Very Severe	9(9.9%)	18(10.4%)		
Fear of cancer recurrence (Median, IQR)	**13(10, 15)**	**14(10,17)**		***P* = 0.3**
Post transplant growth inventory Score	58(42, 70)	58(38, 71)		*P* = 0.81

AUD, Australian Dollars; IRQ, interquartile ranges; PTGI, The Post Traumatic Growth Inventory

[1]Variables included in multivariable logistic regression model to adjust for confounding: age, marital status, time from transplant (<2 years compared to later), underlying diagnosis (acute leukemia compared to other), conditioning regimen (myeloablative compared to reduced intensity), and gut GVHD.

Bold text indicates statistically significant figures.

Appendix A3. Demographic, social determinants, transplant factors, and instrument measures (QoL, psychological morbidity, GVHD, FoCR, PTGI), and their associations with cervical cancer screening

	Cervical screen *N* = 118	No cervical screen *N* = 68	OR (95% CI)	Adjusted OR (95% CI)[1]
				P-value
Age (Median, IQR)	50(42, 58)	56 (42, 63)	0.04	0.97(0.94, 1.00) *P* = 0.09
Residence				
City/inner regional	109/117(93.2%)	58/65(89.2%)	1.64(0.48, 5.47)	
Outer regional/remote	8/117(6.8%)	7/65(10.8%)	0.4	
Education				
Some/completed University	41/93 (44.1%)	19/54 (35.2%)	1.45(0.69, 3.09)	
Trade/some or complete secondary school	52/93(55.9%)	35/54 (64.8%)	0.3	
Household income (AUD)				
Low income $20,000–$39,999	45/113 (39.8%)	25/66(37.9%)	1.81(0.86, 3.93)	1.13(0.58,2.19)
Middle/High income ≥ $40,000	68/113(60.2%)	41/66(62.1%)	0.09	*P* = 0.71
Marital status				
Married/Defacto	92/113 (81.4%)	52/87 (77.6%)	1.26(0.55, 2.82)	
Single/Divorced/separated	21/113 (18.6%)	15/67(22.4%)	0.54	

Appendix A3. Continued.

	Cervical screen *N* = 118	No cervical screen *N* = 68	OR (95% CI)	Adjusted OR (95% CI)[1] *P*-value
Years since transplant				
<2 years	8/118 (6.8%)	14/68 (20.6%)	0.28(0.09, 0.77)	**0.30(0.11, 0.85)**
≥2 years	110/118 (93.2%)	54/68(79.4%)	0.008	***P* = 0.02**
Underlying diagnosis				
Acute Leukemia	71/111(64.0%)	39/66(59.1%)	1.22(0.62, 2.40)	
Other	40/111(36.0%)	27/66(40.9%)	0.52	
Donor type				
Matched (sibling/unrelated)	108/118(91.5%)	64/68(94.1%)	0.67(0.15, 2.47)	
Mismatched (haploidentical, unrelated)	10/118(8.5%)	4/68(5.9%)	0.58	
Conditioning				
Myeloablative	70/118(59.3%)	33/68(48.5%)	1.55(0.81, 2.95)	0.98(0.47, 2.03)
Reduced Intensity	48/118(40.7%)	35/68(51.5%)	0.15	*P* = 0.97
GVHD				
Yes	78/117(66.7%)	44/66(66.7%)	1.0(0.50, 1.98)	
No	39/117(33.3%)	22/66(33.3%)	1	
Self-reported vaginal GVHD				
Yes	25/118(21.2%)	16/68(25.5%)	0.87(0.40, 1.92)	
No	93/118(78.8%)	52/68(76.5%)	0.71	
Medications				
Immunosuppression				
Yes	25/118 (21.2%)	21/68(30.9%)	0.60(0.30, 1.26)	0.78(0.38, 1.61)
No	93/118 (78.8%)	47/68(69.1%)	0.14	*P* = 0.50
DASS 21 score (Median, IQR)	18(8,34)	20(10,40)		*P* = 0.21
Depression subscale	4(1,9)	4(0,12)		*P* = 0.28
Anxiety subscale	4(1,8)	6(2, 10)		*P* = 0.06
Stress subscale	8(2,14)	10(4,16)		*P* = 0.63
FACT-BMT score (Median, IQR)	111(99, 123)	104(91, 119)		*P* = 0.02
Physical well-being subscale	25(22,27)	24(18,26)		*P* = 0.12
Social well-being subscale	22(17,26)	21(18,26)		*P* = 0.89
Emotional well-being subscale	17(15,19)	16(14, 18)		*P* = 0.054
Functional well-being subscale	21(18,26)	19(16,23)		***P* = 0.008**
BMT well-being subscale	28(25,32)	27(22, 32)		*P* = 0.07
LEE GVHD score (Median, IQR)	14 (8, 28)	19(9, 28)		*P* = 0.25
Global severity GVHD symptoms (%)				
Mild	12(16.0%)	6(17.1%)		
Moderate	41(54.5%)	15(42.9%)		*P* = 0.68
Severe	19(25.3%)	12(34.3%)		
Very Severe	3(4.0%)	2(5.7%)		
Fear of cancer Recurrence (Median, IQR)	12(9,15)	15(10,18)		***P* = 0.003**
Post transplant Growth Inventory Score	59(44,71)	68(49, 82)		*P* = 0.1

PTGI, The Post Traumatic Growth Inventory.

[1]Potential confounders included in multivariable logistic regression: age, income status (low compared to middle/high income), early post transplant (within 2 years), conditioning regimen (myeloablative compared to reduced intensity), and taking immunosuppression (tacrolimus, cyclosporine, mycophenolate, or prednisolone). IRQ, interquartile ranges.

Bold text indicates statistically significant figures.

Appendix A4. Demographic, social determinants, transplant factors, and instrument measures (QoL, psychological morbidity, GVHD, FoCR, and PTGI), and their associations with breast cancer screening.

	Mammogram *N* = 98	No Mammogram *N* = 86	OR (95% CI) *P*-value	Adjusted[1] OR (95% CI) *P*-value
Age (median, IQR)	57(50, 63)	43(32, 54)	1.09 (1.06, 1.13) <0.0001	**1.12(1.08, 1.17)** ***P* < 0.0001**
Residence				
City/inner regional	92/96 (95.8%)	73/84(86.9%)	3.46(0.97, 15.4)	**4.81(1.16, 19.9)**
Outer regional/remote	4/96 (4.2%)	11/84 (13.1%)	0.06	***P* = 0.03**
Education				
Some/completed University	35/83(42.2%)	23/63(36.5%)	1.27(0.61, 2.63)	
Trade/some or complete secondary school	48/83(57.8%)	40/63(63.5%)	0.49	
Household income (AUD)				
Low income $20,000–$39,999	39/96 (40.6%)	30/82(36.6%)	1.18(0.62, 2.28)	
Middle/High income ≥ $40,000	57/96 (59.4%)	52/82(63.4%)	0.58	
Marital status				
Married/Defacto	80/94(85.1%)	62/84(73.8%)	2.03(0.90, 4.64)	1.13(0.42, 3.07)
Single/divorced/separated	62/94 (73.8%)	22/84(26.2%)	0.06	*P* = 0.63
Years since transplant				
<2 years	6/98 (6.1%)	14/86 (16.3%)	0.33(0.10, 0.99)	0.31(0.09, 1.05)
≥2 years	92/98 (93.9%)	72/86(83.7%)	0.03	*P* = 0.06
Underlying diagnosis				
Acute Leukemia	57/96(59.4%)	53/81(65.4%)	0.77(0.40, 1.50)	
Other	39/96 (40.6%)	28/81(34.6%)	0.41	
Donor type				
Matched (sibling/unrelated)	90/98(91.8%)	79/86 (92.9%)	0.99(0.29, 3.30)	
Mismatched (haploidentical, unrelated)	8/98(8.2%)	7/86(7.1%)	1	
Conditioning				
Myeloablative	49/98(50%)	56/86(65.1%)	0.53(0.28, 1.01)	0.98(0.41, 2.37)
Reduced intensity	49/98(50%)	30/86(34.9%)	0.04	*P* = 0.98
Total body irradiation				
Yes	34/98 (34.7%)	28/86(32.6%)	1.1 (0.57, 2.13)	**2.35(0.99, 5.58)**
No	64/98(65.3%	58/86(67.4%)	0.76	***P* = 0.052**
GVHD				
Yes	61/96(63.5%)	60/85(70.6%)	0.73(0.37, 1.42)	
No	35/96(36.5%)	25/85(29.4%)	0.31	
Medications				
Immunosuppression				
Yes	22/98 (22.5%)	24/86(27.9%)	0.75(0.36, 1.54)	
No	76/98(77.5%)	62/86(72.1%)	0.39	
DASS 21 score (median, IQR)	19(8,30)	20(8,40)		*P* = 0.36
Depression subscale	4(0,8)	6(2,12)		***P* = 0.04**
Anxiety subscale	4(2,8)	4(2,10)		*P* = 0.3
Stress subscale	10(3,14)	8(2,16)		*P* = 0.99
FACT-BMT score (Median, IQR)	114(101, 126)	107(93, 119)		***P* = 0.02**
Physical well-being subscale	25(21,27)	24(20,27)		*P* = 0.24
Social well-being subscale	22(17,26)	20(17,25)		*P* = 0.18
Emotional well-being subscale	18(16,19)	16(13,18)		***P* < 0.001**
Functional well-being subscale	21(17,26)	20(16, 23)		*P* = 0.15
BMT well-being subscale	29(25,32)	27(23,31)		*P* = 0.049

Appendix A4. Continued.

	Mammogram *N* = 98	No Mammogram *N* = 86	OR (95% CI) *P*-value	Adjusted[1] OR (95% CI) *P*-value
LEE GVHD score (Median, IQR)	12(7, 24)	19(11, 29)		*P* = 0.02
Global severity GVHD symptoms (%)				
Mild	12(16.0%)	6 (17.1%)		*P* = 0.68
Moderate	41 (54.7%)	15 (42.9%)		
Severe	19 (25.3%)	12 (34.3%)		
Very Severe	3(4.0%)	2(5.7%)		
Fear of cancer recurrence (Median, IQR)	13(9, 15)	14(9, 17)		*P* = 0.48
Post transplant growth inventory score	61(51, 75)	59(42, 72)		*P* = 0.26

AUD, Australian Dollars; BMT, Bone marrow transplantation; IRQ, interquartile ranges; PTGI, The Post Traumatic Growth Inventory
[1]Potential confounders included in multivariable logistic regression: age, residential status, marital status, early post transplant (within 2 years), conditioning regimen (myeloablative compared to reduced intensity), and whether total body irradiation was used (Yes, No).
Bold text indicates statistically significant figures.

8.5. Synopsis

This manuscript provides the largest and most comprehensive account of cancer screening adherence in Australian allogeneic BMT survivors. The results indicate that secondary cancers post-BMT are common and that urgent attention is required to improve both knowledge of and compliance with cancer screening guidelines post BMT.

While rates of cancer screening adherence in our BMT survivors were comparable to that of the Australian general population (bowel 32.4% vs 39%, cervical 63.4% vs 56%, breast 53.3% vs 55%), this is deeply problematic as rates of cancer are higher (OR for some cancers in survivors of BMT are up to fifteen times the general population(4)). These data along with the fact that more than 25% of respondents did not feel that cancer screening was necessary and more than 75% had not been advised to undergo cancer screening by their treatment team - has significant implications for BMT survivors, health care professionals involved in their long term care and public health authorities who provide cancer screening services and health promotion. While widely recognised as an issue in oncology care and in BMT, these results suggest that more needs to be done to educate BMT survivors of the prolonged and increasing risk (to date no plateau in incidence has been identified(5)) of secondary cancer post-BMT. This is particularly important for survivors who experience cGVHD and are on prolonged IST. This will not only improve the validity and rigor of consent but also enable early identification and treatment of secondary cancers.

In this regard it is noteworthy that there is limited data about the efficacy of cancer screening in BMT survivors. In particular, we do not know if general population cancer screening, or BMT specific cancer screening will prevent or decrease morbidity and mortality in long-term survivors. This is a major lacunae as without this data it may be difficult to convince clinicians and health services to change their practice and add focus on health promotion in BMT survivor care.

Interestingly, we found that survivors with a better QoL were more motivated to follow screening and preventative care recommendations for their long-term care. This suggest that better, more comprehensive post-BMT care that engage patients more fully in their care and is cognizant of their lived experience and social world may both improve survivor QoL and improve cancer screening uptake in this vulnerable and high-risk group.

8.6. Chapter references

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Chapter 9: Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia

9.1. Chapter overview

This chapter reports on BMT survivors' engagement in high-risk health behaviours known to contribute to chronic non-communicable conditions. It consists of a published manuscript entitled, 'Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia'. The manuscript correlates demographics, socioeconomics, transplant factors, co-morbidities and QoL scores with high-risk lifestyle and health behaviour choices of BMT survivors and with survivors' adherence with preventive health measures advocated by leading health promotion and cancer control agencies (Cancer Australia, the Cancer Institute NSW etc.) and international and national BMT LTFU guidelines. Specifically, BMT survivors were asked about smoking, drinking >2 standard drinks per day, weight/BMI, physical activity levels and compliance with 'sun smart' behaviours (defined as always/routinely wearing sunscreen, hat, sunglasses, collared long sleeve shirts and avoiding sun exposure between 11-3pm).

The results of this study demonstrate that BMT survivors may engage in high risk health behaviours following transplant, despite the increased risks to their long-term health. The is significant because it is likely to result in an excess of many preventable chronic health conditions such as CVD and respiratory disease, DM, osteoporosis, anxiety and depression, and secondary cancers. The findings have implications for education and support both pre and post-BMT and highlight the importance of both health promotion advocacy and health promotion programs in Australia.

9.2. Publication details

Dyer G, Larsen SR, Gilroy N, Brice L, Kabir M, Hogg M, Brown L, Hertzberg M, Greenwood M, Moore J, Gottlieb D, Huang G, Tan J, Ward C, Kerridge I. "Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia". *Australian Journal of Cancer Nursing* 2017:18(2):16-23.

9.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

9.4. Manuscript

The published version of the manuscript follows.

Prevalence of high-risk health behaviours in long-term survivors of adult allogeneic blood and marrow transplantation in Sydney, Australia

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Abstract

Allogeneic blood and marrow transplantation (BMT) survivors are at a significantly increased risk of many preventable conditions that cause long-term morbidity and mortality. The aim of this multi-centre cross-sectional study was to examine Australian BMT survivors and their engagement in high-risk health behaviour known to contribute to these conditions. Of 441 New South Wales (NSW) participants, smoking, drinking more than recommended, being overweight/obese, and inactivity was reported by 7.5%, 12.1%, 48.1%, and 33%, respectively. Rates of "sun-smart" behaviours were high (77%). Time since transplant, lower levels of education and chronic graft-versus-host disease (GVHD) resulted in decreased odds of good health behaviour. Our results suggest that despite well-defined long-term risks, certain subsets of long-term survivors continue to engage in high-risk health behaviours. Therefore, targeted, lifelong counselling and education by nurses about the importance of adhering to preventative health behaviours is critical to improve long-term outcomes.

Keywords: Bone marrow transplant survivors, cancer survivors, health behaviours, high-risk health behaviours.

Please note that the data presented in this manuscript forms part of the Sydney post-bone marrow transplant survey report produced for the the New South Wales Agency for Clinical Innovation (ACI)1.

Introduction

Allogeneic blood and marrow transplantation (BMT) is a lifesaving medical procedure used for the treatment of many malignant and non-malignant diseases in adults and children. With advances in transplantation techniques and supportive care, up to 85% who are alive at two years post-BMT will survive long-term[2]. However, survival is not without consequence. Many long-term survivors experience chronic morbidity, decreased quality of life (QoL) and late non-transplant related mortality. The effects of graft-versus-host disease (GVHD) — a condition in which the donor T-cells recognise the patient as foreign — combined with late toxicities associated with chemo-radiotherapy and immunosuppression, place survivors at a significantly increased risk of many preventable chronic health conditions. Cardiovascular and respiratory disease, diabetes mellitus, osteoporosis, endocrine and gonadal failure, anxiety, depression and secondary cancers all commonly occur after BMT[3], and result in mortality rates four- to nine-fold higher than those observed in an age-adjusted general population for at least 30 years after BMT[4].

According to international consensus guidelines for the long-term care of survivors of allogeneic BMT, primary preventive behaviours should be espoused in an attempt to mitigate this increased risk of poor long-term health[5]. Specifically, these guidelines state survivors of BMT should eat a healthy diet, not smoke, drink alcohol in moderation (<2 drinks per day), maintain a healthy weight, avoid excessive sun exposure and wear sunscreen, and follow age-specific guidelines for physical activity[5] (Australian physical activity recommendations for 18–64 years are at least 150–300 minutes of moderate intensity exercise or 75–150 minutes of vigorous intensity exercise per week, plus at least 2 days per week of muscle-strengthening activities[6]). Early adoption of these modifiable behaviours, it is argued, may help attenuate a subset of the chronic health conditions that survivors experience and improve survivors' QoL[7].

While these guidelines have been available for a decade[8] and campaigns addressing these behaviours have existed in Australia directed at the general population for many years (for example, *Life be in it*[9], *Slip, Slop Slap*[10], *Every cigarette is doing you damage*[11], *Measure up*[12], *Swap it, don't stop it*[13] and *Live Lighter*[14]), it is recognised that behaviour modification can be difficult, even in the context of cancer survivorship. People are familiar with how to prevent morbidity (or prevent further morbidity in the context of allogeneic BMT survivorship), but knowledge does not necessarily result in a desired behaviour[15]. Indeed, while a cancer diagnosis is thought to represent a "teachable moment", many studies have found that despite the increased risks to health, when compared to non-cancer controls, cancer survivors continue to need education and assistance to help change health behaviour in the longer term[16-22].

Although there is a growing body of literature on health behaviours of cancers survivors[23-27], there is a paucity of data on survivors of BMT and no data regarding the health behaviours of Australian BMT survivors. We report the results of a cross-sectional survey of long-term survivors of allogeneic BMT in New South Wales (NSW) to identify their participation in primary preventive health behaviours; to examine the demographic, socio-economic and transplant factors and sequelae associated with lifestyle and health behaviour choices; to identify gaps where cancer nurses are best able to assist this vulnerable and high-risk patient group; and to use this data to support clinical and health policy decision-making for long-term care.

Methods

Patients and procedures

Potential participants were identified from the databases of all adult allogeneic transplant centres in NSW. Participants were eligible if they were ≥18 years of age (at the time of survey) and had undergone an allogeneic BMT at an adult BMT centre between 1 January 2000 and 31 December 2012, were ≥17 years at the time of transplant, could read and write English and could provide consent. Names and phone numbers were provided to the research team. Consenting participants were given the option to self-complete the questionnaire or complete it via a phone interview with one of the researchers. A second round of telephone calls was made to 178 participants who had not returned the survey within a month. No participant elected to be phone-interviewed. All authors had access to primary clinical trial data. The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Instruments

Engagement in high-risk health behaviours was analysed according to a range of demographic, transplant, psychosocial and lifestyle variables assessed using six survey instruments (five validated and one designed specifically for the study). The five validated instruments included the *Functional Assessment of Cancer Therapy — Bone Marrow Transplant (FACT-BMT Version 4)*[28,29], anxiety stress and depression (*The DASS 21)*[30-32], chronic GVHD (*The Chronic GVHD Activity Assessment — Patient Self Report — Form B)*[33] and *The Lee Chronic GVHD Symptom Scale*[34] and *The Post-Traumatic Growth Inventory score*[35,36].

The sixth survey instrument, the *Sydney Post-BMT Study Survey* was purpose-designed for the study by the research team following literature review and discussion with patients attending BMT late effects clinics — to cover issues not addressed in existing surveys. The survey comprised 402 questions grouped into 20 domains and included questions relating to high-risk health behaviour: smoking, drinking, exercise, diet and body mass index (BMI), and being "sun-smart". ("Sun-smart" behaviour was defined in the survey as "always/routinely wearing sunscreen,

hat, sunglasses, shirts with long sleeves and a collar, and avoiding being in the sun between 11 am and 3 pm".) Other relevant domains included demographics, medical complications, tests and assessments, medications and therapies, infections, vaccinations, complementary therapy use, cancer screening, relationship status, income, and lifestyle factors following allogeneic BMT. The questionnaire used tick-box responses, short-answer questions and five-step Likert scales measuring attitudes and other factors and took approximately one hour to complete. The questionnaire was piloted with BMT survivors to assess face and content validity and to check for comprehension. For each consenting participant, data was collected on dates of diagnosis and transplant, stage/remission status at transplant, transplant conditioning, GVHD prophylaxis, stem cell source and donor type.

Statistical analysis

Categorical responses were summarised using frequencies and percentages. Parametric continuous variables were summarised using means and standard deviations, and non-parametric variables using medians, interquartile ranges (IQR) or ranges. Odds ratios and 95% confidence limits, Pearson chiχ^2 test or Fisher's exact tests were used for comparative analysis of dichotomous categorical variables. Adjusted odds ratios to account for potential confounding effects were determined using multivariable logistic regression analysis. Two sample comparisons of parametric and nonparametric data were determined using the independent t-test, and Wilcoxon Rank Sum tests, respectively; greater than two sample comparisons were determined using one-way Analysis of Variance (ANOVA) and Kruskal Wallis tests. A two-tailed p value <0.05 was used as the level of statistical significance.

Statistical analysis was performed using STATA version 12.1 statistical package (StataCorp, College Station, TX, USA).

Results

A total of 1,475 allogeneic BMT were performed in the study period. Of the 667 recipients known to be alive at study sampling, 581 (87%) were contactable and were sent study packs. Four hundred and forty-one (66% of total eligible, 76% of those contacted) returned the completed survey. Three per cent declined participation (Figure 1).

Of those completing the survey, 250 (57%) were male and 191 (43%) female. The median age of survey respondents was 54 years (range: 19–79). The median age at time of transplant procedure was 49 years (range: 17–71). The median time since BMT was 5 years (range: 1–14) (Table 1)

A range of lifestyle factors were surveyed including smoking, alcohol consumption, weight/BMI, exercise and diet.

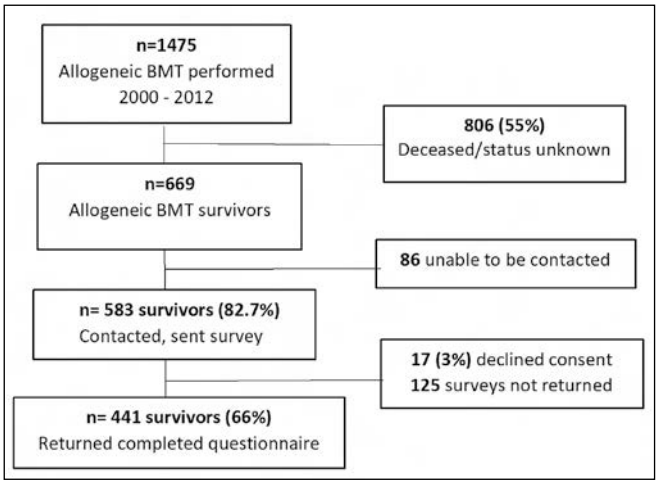

Figure 1: Study flowchart
**Reproduced with permission from the Agency for Clinical Innovation BMT Network Long-Term Follow-Up Group*[1]

Smoking

A total of 33/438 (7.5%) of BMT survivors were smokers — 21/247 (8.5%) males, and 12/191 (6.3%) females. Twelve (36.4%) reported smoking ≤5 cigarettes/day on average; 7 (21.2%) reported 5 to ≤10 cigarettes; and 13 (39.4%) >10 cigarettes per day. One survivor did not report quantity. On univariate analysis factors associated with significantly lower odds of smoking included having some level of university education, having chronic GVHD, and if there had ever been a referral to a respiratory specialist or physiotherapist. There was no significant association between chronic co-morbidities and smoking. The odds of being diabetic and a smoker were lower, though this was not statistically significant.

On multivariate analysis, adjusting for potential confounders, years from date of transplant was associated with increased odds of smoking (OR 1.25; 95% CI 1.08, 1.45; p=0.01) and any level of university education was associated with decreased odds of smoking (OR 0.12; 95% CI 0.03, 0.60; p=0.003).

No measures of personal growth (PTGI), depression stress and anxiety (DASS 21) or QoL demonstrated a significant difference between smokers and non-smokers.

Alcohol

A total of 282/441 (63.9%) of survivors drank alcohol, including 179/250 (71.6%) males, and 103/191 (53.9%) females. Thirty-three (12.1%) of those who drank alcohol reported drinking more than two standard drinks per day on average, (29 male, 4 female). Six (2%) males exceeded four standard drinks per day

On univariate analysis factors associated with significantly lower odds of alcohol use included lower income status and being diabetic. An increased odds of alcohol use was observed in males, those who worked, those with any level of university education and those with mild or no symptoms of GVHD.

Table 1: Demographic, social and clinical characteristics of post-transplant survivors responding to survey (n=441)

Characteristic	Distribution
Socio-demographic	
Gender (Male) n/total (%)	250/441 (57%)
Median age in years (range)	54 (19–79)
Postcode location	
City/inner regional n/total (%)	396/431 (92%)
Income status (A$) n/total responses (%)	
Low income $20,000–$39,999	155/423 (37%)
Middle income $40,000–$79,999	123/423 (29%)
High income >=$80,000	145/423 (34%)
Educational status n/total responses (%)	
Some high school	53/333 (16%)
Completed high school	79/333 (24%)
Trade qualifications/diploma	47/333 (14%)
Some university	24/333 (7%)
Completed university	130/333 (39%)
Transplant factors	
Years since transplant — median (range)	5 (1–14)
Underlying diagnosis n/total responses (%)	
Acute leukaemia	226/423 (53%)
Other *	197/423(47%)
Donor type n/total responses (%)	
Sibling related	250/439 (57%)
Matched unrelated	158/439 (36%)
Haploidentical/mismatched	31/439 (7%)
Conditioning n/total responses (%)	
Myeloablative	214/439 (49%)
Reduced intensity	225/439 (51%)
Post-transplant morbidity and quality of life	
cGVHD	
Total reported cGVHD since transplant n/total responses (%)	301/434 (69%)
Total LEE GVHD score — median (range)	19 (0–77)
Chronic diseases/psychological morbidity n/total responses (%)	
Bone disease (osteopenia, spinal fractures or avascular necrosis)	126/400 (32%)
Cardiovascular risk factors (diabetes, hypertension or elevated cholesterol)	180/414 (43%)
Cancer (mouth, skin, or other)	108/389 (28%)
Anxiety	83/403 (21%)
Depression	95/407 (23%)
Depression, anxiety, stress (DASS 21) — median score (range)	20 (0–118)
Lifestyle n/total responses (%)	
Smoke	33/438 (7%)
Drink alcohol	282/441 (64%)
Exercise/play sport	300/436 (69%)
Always use sun-protection (sunscreen, hat, clothing sunglasses	333/431 (77%)
Median BMI (range) for males	25 (17–63)
Median BMI (range) for females	24 (16–53)
Total FACT BMT — median (range)	110 (32–144)

* CML, CLL, SAA, NHL, HL MM, MDS/Myeloproliferative disease, other (unspecified)

On multivariate analysis adjusting for potential confounders, years from date of transplant was associated with an increased odds of alcohol consumption (OR 1.13; 95% CI 1.01, 1.26; p=0.04) and male gender (OR 2.50; 95% CI 1.18, 5.28; p=0.02).

We further examined associations between alcohol consumption and other measures of personal growth (PTGI), depression stress and anxiety (DASS 21) and QoL. When adjusting for the effects of age, gender and years since transplant, we observed significantly increased odds of improved QoL (FACT BMT score) and alcohol consumption. Significantly lower measures of depression, anxiety and stress were also seen in those consuming alcohol. Comparative measures of personal growth (PTGI scores) were lower in those who consumed alcohol.

"Sun-smart" behaviour

A total of 333/431 (77.3%) of survivors reported sun-smart behaviour, including 192/243 (79.0%) males, and 141/188 (75%) females.

On univariate analysis, those who reported sun-smart behaviour had significantly higher morbidity from GVHD (p=0.03), as measured using the LEE GVHD score. Other factors positively associated with sun-smart behaviours included referral to a dietitian (OR 1.84; 95% CI 0.98, 3.63; p=0.047) and a history of skin cancer (OR 2.39; 95% CI 1.21, 5.07; p=0.008).

On multivariate analysis, no significant associations were observed between socio-demographic variables, co-morbidities, GVHD or referral patterns.

No significant associations were shown between sun-smart behaviours and measures of personal growth (PTGI), depression stress and anxiety (DASS 21) or QoL (FACT BMT), after adjusting for the effects of age, gender and years since transplant.

Weight/BMI

A total of 197/405 (48.6%) of survivors had a normal BMI (≥18.5 to 25), including 103/229 (45.0%) males, and 94/176 (53.4%) females. Thirty-six of those surveyed did not respond to the question on weight and/or height (from which BMI was derived). Thirteen

(3.2%) of survey respondents were underweight (BMI ‹18.5), 128 (31.6%) were overweight (BMI ›25 to ‹30) and 67 (16.5%) were obese (BMI ›30).

On univariate analysis, those with normal BMI had lower odds of diabetes and anxiety.

On multivariate analysis, normal BMI was associated with significantly lower odds of diabetes (OR 0.46; 95% CI 0.23, 0.92; p=0.02) and a trend towards being more years out from the date of the transplant (OR 1.07; 95% CI 1.00, 1.14; p=0.052).

No significant associations were shown between those with normal BMI and measures of personal growth (PTGI), depression stress and anxiety (DASS 21) or QoL (FACT BMT), after adjusting for the effects of age, gender and years since transplant.

Diet

Sixty-five per cent of survivors in the early post-transplant group (‹2 years) reported that their eating habits had returned to normal. In those survivors who were two or more years post-transplant, 77% (292/379) reported that their eating habits had returned to normal.

One hundred and thirty-one survivors reported changing their diet since having a BMT (29.6%). The four most common changes included: avoiding particular food and food groups (37%, n= 48/131), focus on healthy eating (35%, 46/131), reducing meat consumption (16%, 21/131) and choosing organic foods (11%, 14/131). Twelve per cent (52/441) of survivors were taking oral nutritional supplements at the time of the survey.

Physical activity

A total of 300/436 (68.8%) of survivors reported regular exercise post-BMT, including 168/247 (68.0%) males, and 132/189 (69.8%) females.

Two hundred and one (67%) of those who exercised did so at least three times per week.

On univariate analysis, the odds of exercise uptake were significantly lower in those reporting chronic GVHD, hypertension and diabetes. Similarly, referral to a rehabilitation specialist, dietitian or social worker was also associated with lower odds of exercise. An increased odds of exercise was observed in those with no or mild GVHD symptoms

On multivariate analysis, adjusting for potential confounders, diabetes and social worker referral showed a trend towards less exercise, though this association was not statistically significant.

We further examined associations between exercise uptakes and other measures of personal growth (PTGI), depression stress and anxiety (DASS 21) and QoL. When adjusting for the effects of age, gender and years since transplant, we observed that exercise was associated with a significantly better QoL measures (FACT BMT score) and reduced measures of anxiety, depression and stress (DASS 21 scores). No significant association between exercise and personal growth was observed.

Discussion

This study is the first to provide a comprehensive account of high-risk health behaviour in a cohort of long-term survivors of BMT in Australia. Our results reveal that some survivors continue to engage in high-risk health behaviour, despite their increased risks to long-term survival[2,5]. Seven and a half per cent of survivors reported smoking, with nearly 40% of those smoking ›10 cigarettes/day, 12.1% reported drinking ›two standard drinks per day, and almost half had a higher than normal BMI (30% were overweight and almost 17% were obese). Pleasingly, however, 77% reported being "sun-smart", 68.8% were physically active and 35% reported that they had made efforts to eat a healthy diet post-transplant.

In studies of English, Swiss and North American BMT survivors, it was found that when compared to both gender-matched siblings[37] and the general population[38-40], BMT survivors tend to have better health-promoting habits across all health behaviours than comparators with the exception of "active" health behaviours, such as physical activity and eating a healthy diet. When we compare our results to Australian Bureau of Statistics (ABS) data, our survivors also appear to engage less in high-risk health behaviour than the general population[41] (in 2012 the ABS reported that 16% of adults smoked daily, 19.5% of adults consumed ›two standard drinks per day, 62.5% of Australians aged 18 years and over were either overweight (35.3%) or obese (27.5%), only a third were physically active, and 5.1% reported eating the recommended daily amount of fruit and vegetables[37]). However, despite these positive findings, these behaviours do remain concerning, given the significant and pervasive long-term co-morbidities to which BMT survivors are predisposed[42-50].

Our results reveal that time since transplant and being male were significantly associated with smoking and high-risk drinking, whereas higher levels of education, GVHD and referral to a respiratory physician or physiotherapist decreased the odds that a survivor would be a smoker. This is consistent with studies done in other settings, which also reported that younger age at BMT, lower education levels and lack of knowledge of recommendations for post-BMT care are important variables for health behaviours[19,37,39,51,52]. There are several possible explanations for this. Firstly, as the time since BMT increases, survivors generally have less contact with their BMT centres and with other health services, and so may receive fewer reminders about the necessity for adopting and maintaining positive health behaviours. Secondly, as BMT recipients survive beyond the highest risk period (the first two years post-BMT) it is possible that they may begin to believe that they are "in-the-clear" and so free to resume (harmful) pre-BMT behaviour. Importantly, while others have reported that psychological distress is often a trigger for smoking and drinking[53], we found no association

between decreased QoL, depression, anxiety and stress or lower PTGI scores, and, in contrast, found that those who reported drinking alcohol to excess had better QoL and lower depression, anxiety and stress.

While it is reassuring that a high percentage (77.3%) of our survivors reported "sun-smart" behaviours — and that this rate is higher than reported in the Australian general population[54] — there are two important points to stress. The first is that skin cancer in Australia is common; the incidence of melanoma is 11 times that of the average world rate[41]. And the second is that allogeneic BMT further increases the risk of all types of skin cancer due to the long-term use of immunosuppressive drugs, chronic cutaneous GVHD, and the use of azole antifungal agents[55]. Therefore, no amount of sun exposure is acceptable for Australian survivors of BMT. In our study, higher reported GVHD morbidity, a history of skin cancer, and referral to a dietitian were significantly associated with adoption of "sun-smart" behaviour. While it is unsurprising that skin chronic GVHD and previous skin cancer would increase the likelihood that survivors would be more aware of the vulnerability of their skin, the positive association with dietitian referral is less clear, although may simply reflect contact time with health services, and, in particular, with health professionals whose focus is much broader than curing the underlying disease and/or treating the acute side effects of BMT.

At two years post-BMT, a third of survivor reported dietary changes post-BMT — avoiding particular food and food groups, focusing on healthy eating, reducing meat consumption and/or choosing organic foods. The fact that many survivors (77%) returned to their pre-BMT diet, and that only a third had made efforts to improve their nutritional intake is consistent with a recent Japanese, population-based study that was not able to identify differences in nutritional intake between cancer and non-cancer survivors[56]. While this may reflect the complex and intractable nature of eating behaviour, it may also be indicative of the lack of data regarding the impact of diet on chronic non-communicable diseases in cancer survivors and, therefore, both the difficulty that health professionals, and in particular nurses, have in counselling survivors on the most appropriate diet to decrease their long-term health risks, and that survivors have in making dietary choices.

In contrast, regular exercise has been clearly shown to impact QoL, survival and (possibly) cancer progression[17] post-BMT. In our study, 68.8% reported doing some form of exercise. Variables that decreased the odds of exercising included chronic GVHD, hypertension, and referral to a rehabilitation specialist, dietitian or social worker. This data reveals the profound limitations that chronic morbidity, particularly GVHD, which can affect any area of the body, has on survivors of BMT, restricting their mobility and increasing their need for psychosocial support.

Our data reveal that many survivors of BMT appear to be making an effort to maintain their health and wellbeing, compared to the general Australian population. Our results also suggest, however, that given the much greater health risks associated with BMT, much more needs to be done to encourage adoption of positive health behaviours, particularly in certain subsets of survivors. While more research is needed to define the best way to prevent non-communicable disease in survivors of BMT, health-promoting education and support, preferably provided by advanced practice nurses who are uniquely placed to assist cancer survivors, should be rigorously pursued[18].

Despite the large sample size and high response rate (76%) there are a number of limitations to our study that may limit the generalisability of these results to BMT survivors in other countries. Because we relied upon self-reporting and did not capture data on non-responders, we do not know whether BMT survivors who had died prior to study commencement had better or worse engagement with good health behaviour. It is also possible, as with other health surveys, that positive health behaviour may have been over-reported and negative health behaviour under-reported. Another limitation is that we did not ask about pre-BMT behaviour, therefore we are not able to comment on any change in rates of smoking, drinking, BMI or exercise, nor diet type pre- to post-BMT in our survivors. Finally, because only English speakers were eligible to participate in this study, we are not able to comment on other culturally and linguistically diverse (CALD) populations, who may very well have different health knowledge and behaviour.

Conclusion

This study is the largest to explore health behaviours in survivors of BMT in Australia. We found that despite well-defined long-term risks, certain subsets of long-term survivors continue to engage in high-risk behaviours post-BMT, including smoking, drinking alcohol to excess and failing to perform regular exercise. Our results also suggest that adherence to recommendations regarding preventive health behaviours may require ongoing education and counselling and that particular groups of patients — men, those with lower levels of education and those with chronic GVHD, should be the focus of targeted post-BMT nursing education and support.

While the lives of increasing numbers of adults and children are saved by BMT, many survivors bear the burden of chronic and serious illness. While much more research is needed in BMT survivorship and chronic non-communicable diseases to test whether — and which — health behaviour changes make a lasting difference to long-term BMT outcomes, there is no doubt that transplantation clinicians needs to extend their "gaze" beyond the acute phases of transplantation to measures that may prevent, detect and treat modifiable illness in survivors.

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9.5. Synopsis

This manuscript provides the largest and most comprehensive account of health behaviour in Australian allogeneic BMT survivors. The results indicate that survivors may continue to engage in high-risk health behaviour despite well-defined preventive health behaviour recommendations post-BMT.

While rates of high-risk health behaviours in our BMT survivors were comparable to or better than that of the Australian general population (smoking 7.5% vs 16%, drinking > 2 standard drinks per day 12.1% vs 19.5%, overweight 30% vs 35.3%, obese 17% vs 27.5%, physically active 68.8% vs 33.3%) they are still problematic as rates of chronic non-communicable conditions after BMT are almost six times that of sibling comparators(1), with some chronic or malignant diseases including oral and oesophageal cancer occurring up to fifteen times more often than the general population(2). This has significant implications for BMT survivors, health care professionals involved in their long-term care and public health authorities who are responsible for health promotion and preventive health education. In this regard our results clearly suggest that more needs to be done to educate BMT survivors on the increased risk of serious long-term morbidity (the fifteen-year cumulative incidence of severe/life-threatening/fatal conditions has been reported to be 41%(1)). This is particularly important for male survivors, those with lower levels of education and those with cGVHD.

However, as with cancer screening in this population, there are also limited data about the efficacy of preventive health behaviour post-BMT. In particular, we do not know if adopting health behaviours recommended by public health and cancer advocacy bodies for the general population will prevent morbidity and mortality in long term BMT survivors. This is a major lacunae as without this data it may be difficult to convince BMT survivors of the necessity to quit smoking, stop drinking alcohol to excess, maintain a healthy weight, eat a healthy diet, meet physical activity recommendations and avoid excessive UV exposure.

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Chapter 10: Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia

10.1. Chapter overview

This chapter reports on the long-term impact of allogeneic BMT on survivors' work status and household income. It consists of a published manuscript entitled: 'Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia'. The manuscript reports on the pre and post-BMT occupational status and income of BMT survivors and their association with demographic, transplant characteristics and cGVHD.

These results demonstrate that BMT has a significant impact on the work status and household income of long term survivors. Many are unable to remain in full-time work and retire due to ill-health, consequently experiencing a significant reduction in their household income. The impact of this is likely to be profound – exacerbating carer burden, social isolation and medication non-adherence. The findings have implications for the education and support provided to BMT recipients and their carers by health care staff and health care and government agencies including Department of Health, Department of Jobs and Small Business, Department of Human Services (Centrelink), Medical Services Advisory Committee (MSAC), Pharmaceutical Benefits Advisory Committee (PBAC), workers unions and not for profit and charitable patient and carer support services such as the Cancer Council, Arrow Foundation and the Leukaemia Foundation. As this manuscript was published as a letter to the editor, the results are further discussed in the synopsis section of this chapter.

10.2. Publication details

Dyer G, Brice L, Gilroy N, Kabir M, Hertzberg M, Greenwood M, Larsen SR, Moore J, Gottlieb D, Huang G, Hogg M, Brown L, Tan J, Ward C, Kerridge I. "Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia". *Bone Marrow Transplant* 2018;53(7):926-31.

10.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

10.4. Manuscript

The published version of the manuscript follows.

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CORRESPONDENCE

Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia

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As long-term survival following Blood and Marrow Transplant (BMT) improves, it is increasingly important to explore the long-term impact it has on survivors' lives, including their work status and household income.

Previous studies suggest that 50–70% of survivors return to work within 1 year of BMT[1–4] and up to 72% at 10 years post BMT[5]. The accuracy of these estimates are open to question however, as these studies are small, combine survivors of both autologous and allogeneic transplant, reflect historical age-bias in selection for transplantation, and appear inconsistent with reports that more than half of survivors and families report a decline in income post BMT and experience significant financial hardship as a result.[6,7]

In this multi-centre, cross-sectional study we aimed to identify the changes in work status and household income in a large cohort of allogeneic BMT survivors, and examine the demographic, socioeconomic, transplant factors and sequelae associated with those changes.

Eligible participants were allogenic BMT survivors >18 years, transplanted between January 2000 and December 2012 in New South Wales, Australia, who could read and write English, and provide consent. Potential participants were identified from the transplant databases of the adults BMT centres in NSW, and were asked to complete seven questionnaires; the Sydney Post-BMT Study Survey, FACT-BMT Version 4[8,9], DASS21[10–12], The Chronic GVHD Activity Assessment – Patient Self Report (Form B)[13], The Lee Chronic GVHD Symptom Scale[14], the Fear of Cancer Recurrence (FoCR) Scale[15] and The Post Traumatic Growth Inventory (PTGI)[16,17].

The Sydney Post BMT Study Survey (SPBS) was developed by the research team and comprised 402 questions grouped into 20 domains including socio-demographics, pre and post transplant work status, functioning and household income. The questionnaire used tick box responses, short answer questions and 5-step Likert scales to measure attitudes. It was piloted to assess face and content validity and to check for comprehension. For each consenting participant data was also collected on diagnosis and transplant details.

Income and occupational data were stratified by survivor demographics and baseline transplant characteristics using

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Table 1 Demographic, social and clinical characteristics of BMT survivor respondents ($n = 441$)

Characteristic	Distribution
Socio-Demographic	
Gender (Male) *n*/total (%)	250/441 (57%)
Median Age in years (range)	54 (19–79)
Postcode location	
City/inner regional n/total (%)	396/431 (92%)
Household income status (AUD) *n*/total responses (%)	
Low income $20,000–$39,999	155/423 (37%)
Middle income $40,000–$79,999	123/423 (29%)
High income ≥$80,000	145/423 (34%)
Educational status *n*/total responses (%)	
Some high-school	53/333 (16%)
Completed High school	79/333 (24%)
Trade qualifications/diploma	47/333 (14%)
Some university	24/333 (7%)
Completed university	130/333 (39%)
Transplant factors	
Years since transplant- Median (Range)	5 (1–14)
Underlying diagnosis n/total responses (%)	
Acute Leukaemia	226/423 (53%)
Other*	197/423(47%)
Donor type *n*/total responses (%)	
Sibling related	250/439 (57%)
Matched Unrelated	158/439 (36%)
Haploidentical/Mismatched	31/439 (7%)
Conditioning *n*/total responses (%)	
Myeloablative	214/439 (49%)
Reduced Intensity	225/439 (51%)
Post transplant Morbidity and Quality of life	
cGVHD	
Total reported cGVHD since transplant n/total responses (%)	301/434(69%)
Total LEE GVHD score-Median (range)	19 (0–77)
Chronic Diseases/Psychological morbidity n/total responses (%)	
Bone Disease (osteopenia, spinal fractures or avascular necrosis)	126/400(32%)
Cardiovascular risk factors (Diabetes, Hypertension or elevated cholesterol)	180/414 (43%)
Cancer (mouth, skin, or other)	108/389 (28%)
Anxiety	83/403 (21%)
Depression	95/407(23%)
Depression, Anxiety, Stress (DASS21) Median score (range)	20 (0–118)
Lifestyle *n*/total responses (%)	
Smoke	33/438(7%)
Drink alcohol	282/441(64%)
Exercise/play sport	300/436(69%)
	333/431(77%)
Always Use sun-protection (sunscreen, hat, clothing sunglasses	
Median BMI (range) for males	25(17–63)
Median BMI (range) for females	24(16–53)
Total FACT BMT –Median (Range)	110(32–144)

*CML, CLL, SAA, NHL, HL MM, MDS/Myeloproliferative disease, other (unspecified)

descriptive statistics. Categorical responses were summarised using frequencies and percentages. Parametric continuous variables were summarised using means and standard deviations, and medians and interquartile ranges for non-parametric data. Dichotomous categorical variables were tested using the Pearson Chi-square or Fishers' Exact tests, and the relationship between continuous variables were assessed using Pearson's correlation coefficient. The McNemar test was used to assess for significant differences in the distribution of pre and post transplant variables such as full time (FT) employment and low-income status. Means and medians were compared using the independent Student's *t*-test and Wilcoxon Rank Sum tests for two samples; where there were >2 samples one-way analysis of Variance (ANOVA) and Kruskal Wallis tests were used. Multivariable logistic regression was used to assess for significant associations between explanatory and outcome variables after adjusting for potential confounders. A two-tailed P value <0.05 was considered as the level of statistical significance.

Statistical analysis was performed using Stata software (Version12.1).

The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207–217M).

A total of 1475 allogeneic BMTs were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable. In total 441 (66% of total eligible, 76% of those contacted) completed the survey and 17 patients (3%) declined participation.

Respondents included 250 (57%) males and 191 (43%) females. The median age of survey respondents was 54 years (Range: 19–79). The median time since transplant was 5 years (Range: 1–14) (Table 1).

Pre and post transplant employment status was provided by 404 survivors. In total, 261 (64.6%) were in FT employment pre transplant, and only 130 (32.2%) post-BMT (McNemar X^2 (1 df) = 106.6, $P < 0.001$). Three hundred and forty (84.2%) reported being in any paid employment (FT, part-time (PT) or casual) pre transplant which fell to 233 (57.8%) post transplant (McNemar X^2 (1 df) = 88.8, $P < 0.0001$).

Table 2 Changes to emplyment and income status post BMT by demographic and transplant variables

Variable	Changes to FULL TIME (FT) employment post BMT					Changes to ANY PAID employment post BMT					Changes to LOW INCOME status post BMT				
	n/total (%) in FT employment pre transplant	*n*/total (%) in FT employment post transplant	% different	McNemar X^2 (1 df)	*P* value	*n*/total (%) in paid employment pre transplant	*n*/total (%) in paid employment post transplant	% different	McNemar X^2 (1 df)	P value	n/total (%) in low income status pre transplant	n/total (%) in low income status post-transplant	% different	McNemar X^2 (1 df)	*P* value
Age group (years (yrs) at time of transplant)															
<40yrs	78/128 (61.9%)	59/126 (46.8%)	−15.10%	7.68	**0.006**	109/126 (86.5%)	99/126 (78.6%)	−7.90%	3.57	0.06	31/126 (24.6%)	35/126 (27.8%)	3.10%	0.57	0.45
40 < 50yrs	72/99 (72.2%)	33/99 (33.3%)	−38.90%	37.1	**<0.0001**	87/99 (87.9%)	65/99 (65.7%)	−22.20%	18.62	**< 0.0001**	16/102 (15.7%)	33/102 (32.4%)	16.70%	17	**< 0.0001**
50 < 60yrs	83/121 (68.6%)	30/121 (24.8%)	−43.80%	53	**<0.0001**	103/121 (85.1%)	56/121 (46.3%)	−38.90%	47	**< 0.0001**	27/133 (20.3%)	62/133 (46.6%)	26.30%	33.1	**< 0.0001**
>60yrs	28/58 (48.3%)	8/58 (13.8%)	−34.40%	20	**<0.0001**	41/58 (70.7%)	13/58 (22.4%)	−48.30%	28	**< 0.0001**	13/60 (21.7%)	23/60 (38.3%)	16.70%	8.33	**0.004**
Gender															
Male	177/228 (77.6%)	93/228 (40.8%)	−36.80%	73.5	**<0.0001**	199/228 (87.3%)	132/228 (57.9%)	−29.40%	59.8	**< 0.0001**	37/ 238 (15.5%)	82/238 (34.4%)	18.90%	33.2	**< 0.0001**
Female	84/176 (47.7%)	37/176 (21.0%)	−26.70%	34	**<0.0001**	141/176 (80.1%)	101/176 (57.4%)	−22.70%	29.6	**< 0.0001**	50/183 (27.3%)	71/183 (38.8%)	11.50%	13.4	**0.0003**
Marital status															
Married—defacto	210/318 (66.0%)	105/318 (33.0%)	−33.00%	85.5	**<0.0001**	271/318 (85.2%)	187/318 (58.8%)	−26.40%	69.2	**< 0.0001**	53/331 (16.0%)	99/331 (29.9%)	13.90%	33.1	**< 0.00001**
Other	48/80 (60.0%)	23/80 (28.7%)	−31.20%	20.2	**<0.0001**	64/80 (80.0%)	42/80 (52.5%)	−27.50%	18.6	**< 0.0001**	32/84 (38.1%)	49/84 (58.3%)	20.20%	10.7	**0.001**
Income status Pre BMT															
Low income pre BMT	25/82 (30.5%)	17/82 (20.7%)	−9.70%	3.6	0.06	53/82 (64.6%)	38/82 (46.3%)	−18.30%	10.7	**0.001**					
Middle-High income pre BMT	226/305 (74.1%)	109/305 (35.7%)	−38.40%	101.4	**<0.00001**	276/305 (90.5%)	188/305 (61.6%)	−28.80%	77.4	**< 0.00001**					
Chronic GVHD															
Yes	180/272 (66.2%)	83/272 (30.5%)	−35.70%	83.3	**<0.0001**	234/272 (86.0%)	155/272 (57.0%)	−29.00%	67.1	**< 0.0001**	57/291 (19.6%)	104/291 (35.7%)	16.10%	32	**< 0.0001**
No	77/126 (61.1%)	45/126 (35.7%)	−25.40%	22.3	**<0.0001**	100/126 (79.4%)	75/126 (59.5%)	−19.90%	18.9	**< 0.0001**	28/123 (22.8%)	47/123 (38.2%)	15.40%	14.4	**0.0001**
BMT conditioning															
Myeloablative	126/199 (63.3%)	70/199 (35.2%)	−28.10%	40.2	**<0.00001**	173/199 (86.9%)	129/199 (64.8%)	−22.10%	33.4	**< 0.00001**	44/201 (21.9%)	61/201 (30.3%)	8.40%	7.81	**0.005**
Reduced intensity	133/203 (65.5%)	58/203 (28.6%)	−35.90%	65.8	**<0.00001**	165/203 (81.3%)	102/203 (50.2%)	−31.10%	55.9	**< 0.00001**	43/219 (19.6%)	92/219 (42.0%)	22.40%	42.1	**< 0.0001**
Donor type															
Sibling	149/230 (64.8%)	71/230 (30.9%)	−33.90%	66.1	**<0.00001**	190/230 (82.6%)	129/230 (56.1%)	−26.50%	53.9	**< 0.00001**	52/239 (21.8%)	91/239 (38.1%)	16.30%	31	**< 0.00001**
MUD*/ Mismatched/ Haplo	110/172 (63.9%)	57/172 (33.10%)	−30.80%	40.7	**<0.00001**	148/172 (86.0%)	102/172 (59.3%)	−26.70%	35.3	**< 0.00001**	35/180 (19.4%)	62/180 (34.4%)	15.00%	16.2	**< 0.00001**

Table 2 (continued)

Variable	Changes to FULL TIME (FT) employment post BMT					Changes to ANY PAID employment post BMT					Changes to LOW INCOME status post BMT				
	n/total (%) in FT employment pre transplant	*n*/total (%) in FT employment post transplant	% different	McNemar X^2 (1 df)	*P* value	*n*/total (%) in paid employment pre transplant	*n*/total (%) in paid employment post transplant	% different	McNemar X^2 (1 df)	P value	*n*/total (%) in low income status pre transplant	*n*/total (%) in low income status post-transplant	% different	McNemar X^2 (1 df)	*P* value
Time from transplant															
<2 years	33/54 (61.1%)	12/54 (22.2%)	−38.90%	19.2	**<0.00001**	40/54 (74.1%)	24/54 (44.4%)	−29.60%	11.6	**0.006**	8/53 (15.1%)	17/53 (32.1%)	15.10%	7.36	**0.007**
2–6 yrs	121/191 (63.3%)	53/191 (27.7%)	−35.60%	59.3	**<0.00001**	164/191 (85.9%)	99/191 (51.8%)	−34.00%	63.1	**< 0.00001**	43/196 (21.9%)	76/196 (38.8%)	16.80%	27.9	**< 0.00001**
6–10 yrs	69/105 (65.7%)	42/105 (40.0%)	−25.70%	20.8	**<0.00001**	93/105 (88.6%)	75/105 (71.4%)	−17.14%	13.5	**0.0002**	22/114 (19.3%)	38/114 (33.3%)	14.03%	9.14	**0.002**
10–14 yrs	38/54 (70.4%)	23/54 (42.6%)	−27.78%	9	**0.003**	43/54 (79.6%)	35/54(64.8%)	−14.81%	4	**0.04**	14/58 (24.1%)	22/58 (37.9%)	13.79%	4	**0.04**

The bold figures are statistically significant

Ill-health as a cause for being unable to work increased from 14 (3.4%) pre BMT to 55 (13%) post transplant (McNemar X^2 (1 df) = 33.0 $P < 0.001$). Those in retirement increased from 5.4% to 18.8% (McNemar X^2 (1 df) = 54.0 $P < 0.001$).In total 50 of the 76 (65.8%) in retirement post transplant, had retired due to poor health and 89 (54.6%) of the 163 not in retirement reported they were not employed due to health issues.

Household income status was provided by 421 survivors. Those in the lowest household income strata (<$39,999pa) increased from 20.7% pre transplant to 36.3% post transplant (McNemar χ^2 test (1 df = 46.3) $P < 0.0001$). At the same time the proportion in the high-income strata (≥$80,000) fell from 46.1% to 34.4% (McNemar χ^2 test (1 df = 27.6) $P < 0.0001$). There was a non-significant change for those in middle income strata ($40,000–$79,999) (33.2% decreased to 29.2% (McNemar χ^2 test (1 df = 2.5) $P = 0.12$).

Changes to employment status (FT and any paid) and low household income was further compared pre and post transplant, and stratified by a range of variables including age group at BMT, gender, relationship status at BMT, low income status pre BMT, cGVHD, conditioning regimen, donor type, and years since transplant.

Significant declines in FT work status were reported across all income strata other than those already in the low-income strata pre transplant($P = 0.06$). For those moving into a low-income bracket, significant increases were reported across all strata except for those less than 40 years of age at BMT (p = 0.45). (Table 2).

In multivariate analysis the only variable found to have a positive and significant association in maintaining any paid employment was being in paid employment pre BMT (OR 7.87, 95% CI 2.79, 22.24; $P < 0.0001$). For those aged ≥50 years at BMT the odds of being in any paid employment post transplant was significantly reduced (OR 0.20; 95% CI 0.10, 0.40; $P < 0.0001$) with severe GVHD demonstrating a trend towards significance (OR 0.54; 95% CI 0.27–1,05; $P = 0.07$).Longer duration post transplant demonstrated a positive association with being in paid employment, that trended towards significance (OR 1.09; 95% CI 0.99, 1.20; $P = 0.06$)(Table 3).

After adjusting for pre transplant household income status, being in Low income bracket pre transplant (OR 15.3: 95% CI 6.74, 33.8; $P < 0.0001$) and having severe GVHD (OR 3.17; 95% CI 1.61, 6.22; $P = 0.001$) were the only independent variables found to be positively associated with being in a low-income bracket post-BMT. Older patients (age > 50yrs) showed a trend towards having significantly increased odds of being in a low-income bracket (OR 1.85, 95% CI 0.92, 3.69; $P = 0.08$) post-BMT. (Table 3).

Table 3 Variable and their independent association with being in any paid employment and/or in a low income bracket post transplant

Variable	Being in any paid employment post BMT			Being in a low income bracket post BMT		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Paid employment pre BMT	7.87	2.79–22.24	**<0.0001**			
Low income bracket pre BMT	0.72	0.32–1.59	0.41	15.31	6.74, 33.8	**<0.0001**
Age at BMT ≥ 50 years	0.2	0.10–0.40	**<0.0001**	1.82	0.91, 3.66	0.09
Male Gender	0.89	0.49–1.64	0.72	0.84	0.44, 1.59	0.59
Severe GVHD*	0.54	0.27–1.05	0.07	3.17	1.61, 6.22	**0.001**
Married /Defacto	0.79	0.37–1.69	0.54	0.44	0.20, 0.92	**0.03**
Myeloablative conditioning	0.63	0.31–1.26	0.19	0.41	0.20, 0.83	**0.01**
Sibling Donor	0.86	0.48–1.54	0.6	1.13	0.61, 2.08	0.7
Years since BMT	1.09	0.99–1.20	0.06	0.99	0.90, 1.08	0.76

The bold figures are statistically significant

*Severe GVHD was defined as those with LEE GVHD score (>30). This represented LEE GVHD scores in >75th centile

Being in a married/de-facto relationship at transplant (OR 0.44; 95% CI 0.20, 0.92; $P = 0.03$). and having myeloablative conditioning (OR 0.41; 95% CI 0.20, 0.83; $P = 0.01$) were variables associated with a significantly reduced odds of being in a low-income bracket post transplant.

Work type (physical/non-physical) was provided by 376 survivors. There was a significant increase in the proportion of survivors doing non-physical work post BMT (59% pre BMT versus 75.5% post (McNemar X^2 (1 df) = 48.0 $P < 0.0001$)) and a significant reduction in the proportion doing physical work (37.5% pre BMT versus 21% post (McNemar X^2 (1 df) = 49.3 $P < 0.0001$)).

Changes to occupation/field of work post-BMT was reported by 168 (of 396) (42.4%). Reasons reported for not returning to previous field of work included physical limitations (114, 67.9%), concerns about health risks in the workplace (54, 32.1%), psychological/emotional limitations (42, 25%), cognitive limitations (28, 16.8%), employer concerns about ability to undertake required tasks (28, 16.7%), being made redundant (24, 14.3%), employer concerns about liability (21, 12.5%), exhausting sick leave to attend appointments (20, 11.9%), unsatisfactory redeployment/change in work responsibilities (11, 6.6%) and reallocation of hours/shifts (11, 6.6%).

In total 85 (63.9%) of the 133 who reported trying to find employment post-BMT, reported feeling that being a BMT recipient hindered their employability, and 40 (10.2%) employed respondents also described experiencing workplace discrimination including unreasonable limitations being placed upon responsibilities (15, 37.5%), difficulty securing employment (17, 42.5%), workplace harassment (5, 12.5%), forced redundancy (5, 12.5%), job transfer (6, 5.0%), and denial of promotion (5, 2.5%).

Only 9 of 379 (2.4%) respondents had received some form of counselling regarding their legal rights to employment.

This study is the largest ever study to explore the impact of allogeneic BMT on work status and functioning, and household income in long-term survivors. We demonstrate that survival is associated with significant and substantial reductions in FT employment, any paid employment and in household income compared with the general population. (During the study period the Australian general population unemployment rate was 6.3%[18] and the average FT weekly earnings were $1539.40 (equivalent to an annual income of ~$80,000)[19]).

While other studies have found that gender (female), worse physical functioning and age (>25 years) are associated with delayed return to work or unemployment[4,20,21] this was not evident in our population. Our analysis showed that being in paid employment pre BMT, and age <50 years predicted being in employment post BMT. We also found that being in a low-income bracket pre BMT and having severe cGVHD was associated with being in a low-income bracket post BMT, while being in a relationship and receiving myeloablative transplant conditioning were associated with a reduced odds of being in a low-income bracket post BMT. (The effect of cGVHD on employment has been variable, with some studies reporting a negative effect and others finding no association[4,20,22]). There was further trend towards longer survival post BMT being associated with a return to paid employment post BMT.

Although the sample size and high response rate (76%) make it likely that these results represent an accurate account of the impact of BMT on NSW survivor's work status and household finances, there are several limitations to our study that restrict the generalizability of these results to BMT survivors in other settings including participation bias, self-report, exclusion of non-English-speaking survivors and the failure to capture data on non-responders and the financial circumstances of caregivers to household income. Cross-sectional studies like this also have limited

capacity to test inferences about causal or temporal relationships.

Our results suggest that being older (aged over 50 years), single, and developing severe cGVHD are predictive of experiencing an adverse financial impact of BMT and being unable to return to work post transplant. While these data may provide the basis for development of an algorithm to predict the likely impact of BMT on a recipient's occupational and financial status and the likelihood of return to work post-BMT any predictive model will need further testing in a separate validation population. It is crucial that this is done, however, as patients need to understand the full impact that BMT will have on their lives.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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10.5. Synopsis

Previous studies have explored the cumulative effect of post-BMT sequelae on survivors' QoL reporting high rates of anxiety and depression, social isolation, carer burden(1-3) and relationship dysfunction(4-6). These effects also impact upon survivors' capacity to effectively return to their 'pre-BMT' lives(3). While a number of studies have noted the impact that employment difficulties and decreased income may have on QoL(7-10), at the time of publication this study provided the most comprehensive analysis of the occupational and economic impact of BMT.

More specifically, this manuscript presented the largest dataset of the occupational and financial impact of BMT on allogenic survivors reported internationally and the first data on Australian BMT survivors. The results make clear that long term survival following BMT is associated with substantial reductions in full-time employment, any paid employment and in household income. Many survivors are required to change their occupation or field of work post-BMT, mostly due to physical limitations following BMT. Despite this, few received employment counselling post-BMT, even though some experienced difficulties and discrimination in the workplace.

Over 40% of survivors in our study did not return to work post-BMT, with 65% of those retiring doing so because of ill health. These figures are consistent with studies in other BMT populations – as is our finding that up to 10% experience some form of employment discrimination, face challenges finding employment, are inappropriately denied promotion or have limitations placed on their workplace responsibilities(10, 11).

Consistent with international literature on the experience of cancer and BMT survivors(10, 12-14) we found those who were able to return to work, did not have to 'downsize' their career and/or experienced less financial impacts of BMT enjoyed a higher QoL, while age and cGvHD were the strongest predictors of adverse financial and occupational impact of BMT.

These are important findings because work is central to a person's life and identity and 'return to work' is a reliable indicator of physical and social recovery post-BMT(10). But these data are also important because they provide the basis for development of an algorithm that may be used to predict the likely impact of BMT on a recipient's occupational and financial status, and predict the likelihood that they will return to work post-BMT. While any predictive model would need further testing in a separate validation population, these results suggest that being older (aged over 50 years), single, having a RIC BMT and developing severe cGVHD are predictive of experiencing an adverse financial

impact of BMT and being unable to return to work post-transplant, while being in paid employment pre-BMT may increase the likelihood that a BMT survivor will return to work post-BMT.

The results of this manuscript provide a cogent reminder of the necessity for, and importance of LTFU of BMT survivors and the need to prepare BMT recipients for the profound impact that BMT may have on them and on their families, including on QoL, economic and social status and even medication non-adherence(15, 16). For these reasons alone, despite the discomfort physicians may feel about speaking about the financial impacts of treatment(15, 17), finances and occupational issues should routinely be discussed pre-transplant and should remain the focus of continuing education, counselling and support in the longer term to improve outcomes.

Finally, this manuscript provides important insights into the impact that BMT may have on survivors' work status and household income. These data may benefit BMT programs in many ways – enabling BMT patients to make more realistic post-transplant employment plans, informing occupational rehabilitation programmes, occupational health services, and employers and guiding government policy for long-term BMT survivors. Furthermore, if a return-to-work risk prediction tool were to be developed and sensitively deployed so that it does not inappropriately discourage patients at higher risk from seeking BMT or physicians from offering BMT to patients at higher 'financial risk', this may enable BMT physicians to give patients a more accurate picture of the likely socioeconomic and occupation impact of BMT, allow patients and families to realistically prepare for time off work and to arrange their household finances, and give patients, family members and employers the opportunity to prepare for life post-BMT(18).

10.6. Chapter references

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Chapter 11: Oral health and dental morbidity in long-term allogeneic bone marrow transplant survivors in Australia

11.1. Chapter overview

This chapter reports on the incidence and range of oral and dental disease occurring in long-term survivors of BMT. It consists of a published manuscript entitled, 'Oral health and dental morbidity in long-term allogeneic bone marrow transplant survivors in Australia'. The paper discusses the demographic, socioeconomic, transplant factors, and co-morbidities associated with oral and dental disease. It also discusses compliance with dental care, and the impact of oral and dental disease on QoL. Specifically, survivors were asked about oral and dental symptoms and diagnoses of oral disease, including oral cGVHD and oral cancer. Survivors were also asked how often they attended for dental care, the time since their last visit, and, if they did not attend a dentist regularly, the reasons for not doing so.

The results of this study make clear that oral and dental morbidity post-BMT is common and that despite the increased risk, a third of the respondents to our survey were not compliant with either general population recommendations or recommended dental care for BMT survivors(1). Disturbingly, many survivors noted that they did not attend for dental care as they did not feel it was necessary or because they had not been specifically advised to do so by their treating team. Just as worryingly, although perhaps not unsurprisingly, many survivors also reported not attending a dentist due to concerns about its cost. These findings have clear implications for the provision of oral and dental care education and counselling for BMT recipients both pre and post-transplant. But they also have clear implications for health care professionals involved in the long-term care of BMT survivors as there is no doubt that survivors do not seem to be getting the message that dental care is important. And most importantly of all, these findings send a message to health policy makers that public dental care in Australia is in urgent need of reform.

11.2. Publication details

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11.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

11.4. Manuscript

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Oral health and dental morbidity in long-term allogeneic blood and marrow transplant survivors in Australia

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ABSTRACT

Background: Oral and dental disease is a major cause of long-term morbidity following allogeneic blood and marrow transplantation (Allo-BMT). This study aimed to describe the extent and range of oral and dental complications in BMT recipients and to identify gaps in service provision provided to this high-risk group.
Methods: Participants were Allo-BMT recipients, aged >18 years, and received transplants between 2000 and 2012 in NSW. They completed seven surveys, the purpose-designed Sydney Post-BMT Study survey and six other validated instruments.
Results: Of 441 respondents, many reported dry mouth (45.1%), dental caries (36.7%), mouth ulcers (35.3%), oral GVHD (35.1%), gingivitis (16.2%), tooth abscess (6.1%) and oral cancer (1.5%). Regular dental visits were reported by 66.2% of survivors. Middle–high income, older age and geographic location showed a positive association with regular dental visits. Of those who did not visit the dentist regularly, 37% stated they did not feel it necessary, 36% reported cost and 20% stated it was not advised by the treating team.
Conclusion: Despite oral complications commonly occurring after Allo-BMT, many survivors receive inadequate dental care. These results emphasize the need for improved oral health education, the importance of regular dental checks and improvement in the delivery of dental health services for BMT survivors.

Keywords: Blood and marrow transplant, cancer survivors, dental complications, stem cell transplant.

Abbreviations and acronyms: ALLO-BMT = Allogeneic Blood & Marrow Transplant; BMT = Blood & Marrow Transplant.

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INTRODUCTION

Allogeneic blood and marrow transplant (BMT) is increasingly used for many malignant and non-malignant haematological diseases with great success. The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) reports that 10-year survival figures for some conditions now approach 70%.[1] But while survival rates continue to improve, many survivors experience long-term and late morbidity. The 15-year post-BMT cumulative incidence of chronic health conditions is 71%[2] with BMT survivors experiencing a decreased life expectancy compared with an age- and gender-matched normative population.[3] Importantly, the link between chronic health conditions and poor oral/dental health has been well established[4] with oral and dental complications of BMT reported in up to 80% of survivors.[5]

The post-BMT oral and dental manifestations and complications relate specifically to chronic graft vs.

host disease (GVHD) – an immunological condition in which donor-derived T, B and Natural Killer (NK) cells attack normal host tissues. When chronic GVHD involves the mucosal lining of the oral cavity (and oro-pharynx), which occurs in up to 83% of patients who develop chronic GvHD,[6] this may cause characteristic mucosal features of lichen planus, with lichenoid striations, papules, plaques, including depapillation of the dorsal tongue and highly symptomatic oral mucosal atrophy, erosion, excoriation and ulceration with consequent limitation in mouth opening and tongue movement and contribute to oral squamous cell carcinoma.[7–11] Chronic GVHD also can involve the salivary glands (and indeed all of the exocrine glands to a variable degree), in keeping with the clinical presentation seen with Sjogren's syndrome and with the same consequent salivary hypofunction, loss of taste, decreased salivary protection against dental caries and the development of multiple mucoceles.[12,13] The incidence of osteonecrosis of the jaw (ONJ) is also increased in survivors of BMT given the use of bisphosphonates to address osteoporosis resulting from premature gonadal failure and chronic corticosteroid use, and the increased rates of chronic dental disease (dental caries and periodontal disease) necessitating dental extractions.[9,14–16]

Risk factors for post-BMT dental and oral disease include radiotherapy to the head and neck region, age at BMT, underlying diagnosis of Fanconi's anaemia and GVHD.[17] As oral and dental disease can significantly impair quality of life (QoL),[18–20] it is now widely recommended that BMT survivors receive lifelong follow-up including *at least* yearly oral clinical assessments and dental review.[2,17,21]

The routine provision of long-term dental care post-BMT is, however, enormously challenging.[22,23] Barriers to implementing oral care standards for cancer survivors include gaps in knowledge (clinician and patient), reliance on tradition, inconsistent or absent oral assessments, diverse oral care regimens and practices, an insufficient and/or conflicting evidence base, lack of accepted universal standard of care, administrative and clinical issues, and lack of interdisciplinary collaboration.[24,25] In addition, the cost of dental care in Australia also negatively impacts upon the number of patients who receive dental care. Indeed, the Australian Institute of Health and Welfare (AIHW)[26] found that 44.9% of those aged 25–44 years avoided or delayed visiting a dentist due to cost. This cross-sectional study aimed to describe the extent and range of oral complications in allogenic BMT recipients in NSW and identify gaps in dental service provision provided to this high-risk group, in order to support clinical and health policy decision making around long-term care.

METHODS

Potential participants were identified from the transplant databases of the adult transplant centres in NSW. (At the time of study commencement, there were four adult allogeneic transplant centres in NSW, collectively performing approximately 175 BMTs annually[27]). Participants were eligible if they were ≥18 years of age and had undergone an allogeneic BMT between 1st January 2000 and 31st December 2012, could read and write English and could provide consent. Consenting participants were given the option to self-complete the questionnaire or complete it via a phone interview with one of the researchers. A second phone call was made to 187 participants who had not returned the survey within a month. No participants completed the survey via a phone interview. All authors had access to primary clinical trial data. The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Instruments

Participants were asked to complete seven questionnaires

The Sydney Post BMT Study Survey (SPBS) was developed by the research team from a review of the literature and discussions with patients attending BMT clinics. The survey comprised 402 questions grouped into 20 domains including socio-demographics, quality of life and morbidity relating to oral and dental health. The questionnaire used tick box responses, short answer questions and 5-step Likert scales measuring attitudes and other factors. The questionnaire was piloted with six BMT survivors in clinic and phone interviews to assess face and content validity and to check for comprehension. For each consenting participant, data were collected on dates of diagnosis and transplant, stage/remission status at transplant, transplant conditioning, GVHD prophylaxis, stem cell source and donor type.

Oral health and dental morbidity were analysed according to a range of demographic, transplant, psychosocial and lifestyle variables assessed using the *Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4)*,[28,29] chronic GVHD (*The Chronic GVHD Activity Assessment – Patient Self Report (Form B)*[30] and *The Lee Chronic GVHD Symptom Scale)*.[31]

Statistical analysis

Oral and dental health data were stratified by survivor demographics and baseline transplant characteristics

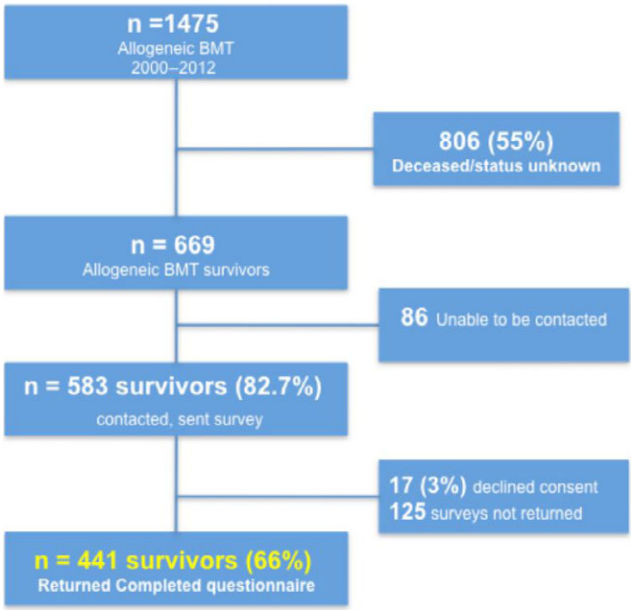

Fig. 1 Study flowchart.

using descriptive statistics. Categorical responses were summarized using frequencies and percentages. Distribution of categorical variables was described using percentages and continuous variables using median, interquartile ranges and range. Odds ratios and 95% confidence intervals, Pearson's chi-square/Fishers' exact tests were used for analysis of dichotomous categorical variables, Wilcoxon rank sum test for two sample comparisons of medians and Kruskal–Wallis test for > 2 sample comparison of medians. Multivariable logistic regression was used to adjust for relevant confounders. A two-tailed $P < 0.05$ determined the level of statistical significance.

Statistical analysis was performed using Stata software (Version12.1).

RESULTS

A total of 1475 Allogeneic BMT were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable. Four hundred and forty-one (66% of total eligible, 76% of those contacted) completed the survey. Seventeen patients (3%) declined participation, while 125 (21%) did not return the survey (Fig. 1).

Respondents included 250 (57%) males and 191 (43%) females. The median age of survey respondents was 54 years (range 19–79). The median time since transplant was 5 years (range 1–14) (Table 1).

Oral health and dental morbidity

The most common dental and oral health problems reported by BMT survivors were dry mouth (45.1%), mouth ulcers (35.3%), tooth caries (36.7%) and oral GVHD (35.1%). Sixteen per cent reported gum disease/gingivitis, 6% had experienced a dental abscess, 4.8% broken teeth or tooth loss, 1.8% gum recession,1.5% a diagnosis of oral cancer and 0.2% osteonecrosis of the jaw. One per cent required root canal therapy (1%), 3.8% had required other dental intervention (wisdom teeth, dental extractions and fillings) (3.8%) but less than two per cent (1.6%) were edentulous.

Table 1. Demographic, social and clinical characteristics of BMT survivor respondents (n = 441)

Characteristic	Distribution
Socio-demographic	
Gender (male) n/total (%)	250/441 (57%)
Median age in years (range)	54 (19–79)
Postcode location	
City/inner regional n/total (%)	396/431 (92%)
Income status (AUD) n/total responses (%)	
Low income $20 000–$39 999	155/423 (37%)
Middle income $40 000–$79 999	123/423 (29%)
High income ≥$80 000	145/423 (34%)
Educational status n/total responses (%)	
Some high school	53/333 (16%)
Completed high school	79/333 (24%)
Trade qualifications/diploma	47/333 (14%)
Some university	24/333 (7%)
Completed university	130/333 (39%)
Transplant factors	
Years since transplant, median (range)	5 (1–14)
Underlying diagnosis n/total responses (%)	
Acute leukaemia	226/423 (53%)
Other*	197/423 (47%)
Donor type n/total responses (%)	
Sibling related	250/439 (57%)
Matched unrelated	158/439 (36%)
Haploidentical/mismatched	31/439 (7%)
Conditioning n/total responses (%)	
Myeloablative	214/439 (49%)
Reduced intensity	225/439 (51%)
Post-transplant morbidity and quality of life cGVHD	
Total reported cGVHD since transplant n/total responses (%)	301/434 (69%)
Total LEE GVHD score, median (range)	19 (0–77)
Chronic diseases/psychological morbidity n/total responses (%)	
Bone disease (osteopenia, spinal fractures or avascular necrosis)	126/400 (32%)
Cardiovascular risk factors (diabetes, hypertension or elevated cholesterol)	180/414 (43%)
Cancer (mouth, skin or other)	108/389 (28%)
Anxiety	83/403 (21%)
Depression	95/407 (23%)
Depression, anxiety, stress (DASS21), median score (range)	20 (0–118)
Lifestyle n/total responses (%)	
Smoke	33/438 (7%)
Drink alcohol	282/441 (64%)
Exercise/play sport	300/436 (69%)
Always use sun protection (sunscreen, hat, clothing sunglasses)	333/431 (77%)
Median BMI (range) for males	25 (17–63)
Median BMI (range) for females	24 (16–53)
Total FACT BMT, median (range)	110 (32–144)

*CML, CLL, SAA, NHL, HL MM, MDS/myeloproliferative disease, other (unspecified).

Of the 69.3% BMT survivors who reported a diagnosis of chronic GVHD, 51.5% of these had oral GVHD (35.1% of all respondents).

Regular dental visits

Overall, 288/436 (66.2%) of patients reported visiting a dentist on a regular basis (at least annually). The proportion of those visiting a dentist was similar across survival cohorts with rates of dental review in early transplant survivors being comparable to rates in late survivors (Table 2).

Factors associated with regular dental review

Patients having regular dental follow-ups were significantly older (adjusted OR 1.02, 95% CI 1.008, 1.04, $P = 0.004$), were more likely to live in the city/metropolitan area (adjusted OR 1.74, 95% CI 1.10, 2.75, $P = 0.02$) and were more likely to be from the middle/high-income group (adjusted OR 1.83, 95% CI 1.18, 2.83, $P = 0.007$). Gender and quality of life (FACT-BMT score) were not significantly associated with regular dental visits (Table 3). Those who visited a dentist regularly also had higher rates of dental pathology (such as caries, dry mouth, oral GVHD) though none of these associations was statistically significant. It is unclear whether higher rates of dental morbidity in those attending a dentist regularly reflected improved diagnosis or the presence of symptoms driving patients to seek dental care.

Time from last dental visit

Two hundred and fifty-six (88.9%) of the 288 patients who visited a dentist on a regular basis reported the time since their last dental review. The median time reported was 10 months (IQR 7, 13, range <1 month, 34 months). Patients who were less than 2 years from transplant were significantly more likely to have had a more recent dental review (median of 8 months) compared with those who were more than 10 years post transplant (median of 13 months, $P < 0.05$, Kruskal–Wallis test) (Table 4).

Table 2. Proportion in survival cohorts (years since transplantation) and regular dental visits

Years since transplant (N = number of responses)	Number visiting dentist on a regular basis (%)
1–2 years (N = 58)	38 (65.5%)
2 < 6 years (N = 203)	139 (68.5%)
6 < 10 years (N = 115)	74 (64.3%)
≥10 years (N = 60)	37 (61.7%)
All (N = 436)	288 (66.1%)

Reasons reported for not regularly attending a dentist

Among the reasons cited by the 148 who did not attend a dentist regularly were cost (54, 36.4%), an assumption that it was not necessary (55, 37.2%), lack of direction to attend for dental care given by the treating team (30, 20.3%) or lack of time (28, 18.9%). Less commonly, survivors noted that they did not regularly attend for dental care because they were edentulous (13, 8.9%), had a fear of dentists (2, 1.3%), had too great a distance to travel,[1] had "more pressing" medical concerns (3, 0.7%) or had low platelets (1, 0.7%).

DISCUSSION

This is the largest study of oral and dental morbidity in allogeneic BMT survivors in Australia. The results of this study demonstrate that oral complications following BMT are common and that one third of BMT survivors are not receiving regular dental reviews according to recommended BMT long-term follow-up guidelines.[17,21] In many cases, this appears to result from ignorance of the need for dental care, inadequate communication from BMT teams regarding the importance of routine post-BMT dental care or the out-of-pocket costs associated with dentistry.

BMT survivors experienced higher rates of tooth caries than the general Australian population (36.7% vs. 28.2% Australian men and 22.7% Australian women).[26] However, rates of dental disease and dry mouth were similar to rates reported in patients treated for head and neck cancer ((36.7% vs. 34% reporting dental disease and 45% vs. 52% experiencing a dry mouth[32]).

In total, 69.3% of our survivors reported a diagnosis of chronic GVHD, and over half of these survivors experienced oral chronic GVHD. This is significant for two reasons. First because our respondents report much higher rates of cGVHD than large international registries (e.g. Japan 41% [33] and the USA 37% [34]). And second because oral cGvHD is a risk factor for developing oral and oesophageal cancer[10] – which occurs with a standard incidence ratio (SIR) of 15.7 in BMT recipients compared with the general population.[33] Together these findings highlight the importance of life-long, vigilant oral and dental care follow-up in those with any history of GVHD.

Interestingly, despite the significant effects that chemo-radiotherapy can have on the oral cavity, in our study dental disease and symptoms were not associated with a reduced quality of life score. This is consistent with other studies of both autologous and allogeneic BMT survivors[11] and onco-haematological patients,[35] which have described weak, non-significant association between dental/oral disease and decreased

Table 3. Socio-demographic factors and association with regular dental reviews

Factors (N = number of responses)	Regular dental visit (N = 288)	No regular dental visit (N = 148)	OR (95% CI) *P* value	Adjusted odds ratio (AOR) *P* value
Age (years)	56	52	*P* = 0.007	1.02 (1.008, 1.04)
Median (IQR)	(IQR 45, 63; 19–79)	(IQR 43, 60; 22–73)		*P* = 0.004
Gender				
Female	131/288 (45.5%)	58/148 (39.2%)	1.3 (0.85, 1.98)	1.37 (0.89, 2.12)
Male	157/288 (54.5%)	90/148 (60.8%)	*P* = 0.21	*P* = 0.14
Household income (AUD)				
Middle/high income (≥$40 000)	185/274 (67.5%)	78/144 (54.2%)	1.76 (1.14, 2.71)	1.83 (1.18 2.83)
Low income ($20 000–39 999)	89/274 (32.5%)	66/144 (45.8%)	*P* = 0.007	*P* = 0.007
Missing	14	4		
Residence				
Metropolitan city	213/281 (75.8%)	94/145 (64.8%)	1.70 (1.07, 2.69)	1.74 (1.10, 2.75)
Other regional/remote	68/281 (24.2%)	51/145 (35.2%)	*P* = 0.02	*P* = 0.02
Missing	7	3		
FACT-BMT score				
High QoL (above 50th centile)	147/288 (51.0%)	68/148 (46.0%)	1.22 (0.81, 1.86)	1.19 (0.78, 1.83)
Low QoL (lower 50th centile	141/288 (49.0%)	80/148 (54.0%)	*P* = 0.31	*P* = 0.40

Table 4. Relationship between years from transplant procedure and time to last dental visit

Time since transplant (N = number of responses)	Months since last visit to a dentist median (range)
1 < 2 years post transplant (N = 27)	8 months (<1–14 months)
2 to <6 years post transplant (N = 128)	10 months (1–29 months)
6 to <10 years post transplant (N = 66)	10 months (1–27 months)
≥10 years (N = 35)	13 months (2–34 months)
All respondents (N = 256)	10 months (<1–34 months)

QoL when compared with healthy controls. The explanation for this finding is uncertain but may be because oral health becomes less of a priority and oral symptoms have less of an impact when a patient has been diagnosed and treated for cancer, has had to face the possibility of dying and has been separated from the family and friends and all that is familiar to them.[35]

Somewhat reassuringly, two thirds (66.2%) of survivors reported that they attended regular dental visits, including survivors <2 years and >10 years post BMT. This rate is similar to dental attendance rates in other cancer survivor populations including adult survivors of childhood cancer.[36–38] The time from last dental visit, however, varied across the cohorts, ranging from 1 to 14 months in those 1–2 years post BMT to 2–34 months in those >10 years post BMT. Differences in longitudinal dental attendance rates were also identified in a US study of 4195 cancer survivors that found that dental visits decreased (statistically and clinically significantly) during and after cancer treatment. Taken together, these studies suggest that the further survivors are from diagnosis/treatment, the less likely they are to attend to dental and oral health – which may reflect decreased contact with the health system and/or education/reminders about the importance of oral health, or the impact of other life priorities.[39]

This study found that middle–high income, older age and geographic location of survivors showed a positive association with regular dental visits and retained significance when adjusting for effects of confounders. This resonates with a 2004 study of adult survivors of childhood cancer which compared survivors to sibling's dental utilization practices.[36] The authors found that minority subjects, those with lower levels of education, no health insurance and annual incomes of less than $US20 000 were less likely to report a recent dental visit. They also noted that males who had cranial radiation were more likely to have seen a dentist recently, than those who had not had cranial radiation. Female gender has been found to have a positive association with more recent dental care[40] and has been supported in a systematic review of patterns and drivers of healthcare use in long-term childhood cancer survivors[41]; higher income, private health insurance, attending follow-up care, chronic health conditions, prior radiotherapy, being female and older age increase survivor healthcare utilization. We did not find that gender had an impact on our study population, however. With regard to the Australian general population, income, health insurance and location do play a role in oral health. Untreated caries is reported as 23.5% in major cities and increases up to 37.6% in remote/very remote areas, and those with higher incomes and insurance had lower rates of caries and periodontal (gum) disease, and fewer missing teeth.[26]

Of our survivors who did not visit the dentist regularly, many (36.4%) attributed this to the personal cost of dental care. In Australia, total expenditure on dental services (excluding hospital services) in 2012–2013 was $8706 million, an increase of over $2761

million from a decade previous,[26] with 58% of this paid directly out of pocket by individuals to private practitioners. Public dental services exist, but are available only to select groups with very low income.[42] In NSW alone, there are over 68 000 adults awaiting public dental treatment,[43] with wait times (varying by state) of between 1 and 2.5 years.[44] These data suggest that the public dental system is simply unable to cope with the current demand. So while the World Health Organisation (WHO) confirm that oral health is integral to overall health and can assist in constraining health costs,[4] Australian policy makers first needs to improve access to dental services and provide comprehensive treatment and continuity of care[45] to those most disadvantaged, before any burden can be eased. For even for those who have private health insurance with dental cover, many Australian residents (77%) still make co-payments towards dental visits and 19% report a large financial burden from doing so.[26,45] Indeed, in this regard, it is little wonder so many BMT survivors avoid dental visits due to cost as 16.8%–40.9% of the Australian general population also avoid or delay visiting a dentist because of cost.[26]

Interestingly, lack of education on behalf of both BMT survivors and clinicians contributed to low compliance with regular dental reviews, 37.2% felt that it was not necessary and 20.3% stated that they were not advised to do so by their treating team. This has the potential to cause avoidable health-related burdens for survivors and is economically costly for the State. In an analysis of Western Australian data, 65 000 hospitalizations with a total cost of $157million occurred over a 10-year period for potentially avoidable oral health conditions.[46] Total numbers and rates of admissions steadily increased over the period with dental caries being the most common preventable condition (53%).[46,47] This is highly relevant given our increasing numbers of long-term survivors and the rates of dental caries they experience. BMT clinicians are not the only healthcare professionals not providing adequate oral health education, however. In a study of head and neck cancer patients, only 53% of survivors reported explicit recommendations for post-treatment dental examinations.[48] Patient education represents a cheap and easily implementable strategy for improving the oral health of BMT survivors. In general, oral health education across the healthcare sector needs to improve; oral morbidity that is exacerbated by a lack of vigilant oral and dental care clearly places unnecessary burdens on patients and the health system.

Although this was a multi-centre study and the sample size and high response rate (76%) make it likely that these results represent an accurate account of the impact of BMT on NSW survivor's oral and dental health, there are a number of limitations to our study that restrict the generalizability of these results to BMT survivors in other countries and other settings. Participation bias, self-report, only surveying those who can read and write English and not capturing data on non-responders are all limitations. In addition, we did not ask respondents if they had private health insurance (which includes dental cover), which may have provided insightful information about dental visits as lack of; lack of dental insurance has been shown to delay dental care in other studies of cancer survivors.[40] Also, as our survivors received transplants prior to 2013, and were surveyed in late 2014, we are not able to report how many survivors had a dental review within 1 year of BMT, as per follow-up recommendations. Furthermore, previous studies have reported that recipient HLA haplotype impacts oral health;[49] unfortunately, we did not have access to tissue typing results for our study, but it may be worth further consideration for risk stratified preventative oral health care in an overburdened heath system. A final limitation to note is that cross-sectional studies like ours restrict inferences about causal or temporal relationships.

This study confirms the significant morbidity associated with oral complications after BMT. Socio-economic status, location and patient education contribute to low compliance with dental care. These results emphasize the need for improved oral health education for both survivors and clinicians, the importance of regular dental checks, and improvement in the delivery of dental health services in Australia for BMT survivors. Potential solutions to address this issue are not necessarily expensive or difficult to implement but will likely to be the subject of intense professional debate. It is also likely that efforts to improve the dental health of BMT survivors will need to concurrently address deficiencies in funding, workforce and therapeutics. This may include employment of oral medicine specialists by BMT units[50] and specialists in Special Needs Dentistry, increased funding of pre-, peri- and post-BMT dental care – perhaps according to a Medicare fee schedule similar to the Federal Department of Veteran Affairs for Gold Card holders or Totally & Permanently Incapacitated ex-service personnel, and PBS approval of high-intensity, fluoride dentifrices and pharmacological sialagogues to assist BMT patients maintain their oral and dental health. The need to improve dental care for BMT survivors in self-evident – what is required is action.

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DISCLOSURE

The authors declare no conflicts of interest.

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11.5. Synopsis

This paper provides the largest and most comprehensive account of oral and dental morbidity in Australian allogeneic BMT survivors. The results indicate that oral and dental complications post-BMT are common, that many survivors do not receive dental care post-BMT and that urgent attention is required to improve patients and health professionals knowledge of, and compliance with, guidelines for dental care post-BMT.

While it is reassuring that approximately two third of our survivors received regular dental care, given the increased risks to oral health experienced by BMT survivors compared to the general population, this represents very few patients who receive appropriate care. It is also enormously concerning that many survivors are not aware that they should visit a dentist and/or have not been advised to do so by their treatment team. The factors that predict attendance for dental care are sadly predictable, with socioeconomic status (high income and older age), residential location (metropolitan), and patient education the factors that are most positively significantly associated with dental care compliance.

In this regard it is also noteworthy that over a third (36.4%) of BMT survivors in this study do not attend regularly for dental care because of the costs of doing so. This finding and the fact that cost is a major (negative) factor in regards to the adequacy of the general Australian population dental care(2), suggests that improvements in health education and counselling will not be enough to improve the oral health of BMT survivors and that radical policy reform is needed to make dental care more accessible and more affordable.

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Chapter 12: A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia

12.1. Chapter overview

This chapter reports on infectious diseases and adherence with guidelines for post-BMT vaccination in our survivors. It consists of a manuscript entitled 'A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia'. The manuscript reports on rates of self-reported infectious diseases experienced post-BMT and vaccination uptake according to the Australian Immunisation Handbook (AIH) schedule, and describes the demographic, transplant, psychosocial and lifestyle factors that influence rates of adherence.

These results demonstrate that vaccine preventable disease (VPD) post-BMT are common (41.7%), and that despite their increased risks of infection, very few survivors (31.8%) completed the recommended AIH post-BMT vaccination schedule. No factors significantly and reliable predicted rates of vaccination post-BMT. While income strata showed a trend towards lower vaccination rates, it was not significant, nor was the education level of survivors or rates of cGVHD.

It seems likely that a number of factors contributed to rates of post-BMT vaccination. Importantly, despite many survivors (69.8%) reporting that they received their post-BMT vaccinations from their GP, only 50% of respondents reported that their GP received any documentation or advice with regard to the vaccination schedule. These findings have profound implications for the organisation of post-BMT care, for communication between BMT centres and primary care practitioners, and for the education of BMT survivors and health providers. Critical improvements in communication, funding and support between tertiary and primary health services, and between public and private practices are clearly required to improve vaccination adherence. It is likely however, that rates of adherence may also be increased if future research can clearly demonstrate proof of post-BMT vaccination and outline the clinical, social and economic benefits that accrue from routine vaccination.

12.2. Publication details

Dyer G, Gilroy N, Brice L, Kabir M, Gottlieb D, Huang G, Hogg M, Brown L, Greenwood M, Larsen S, Moore J, Hertzberg M, Tan J, Ward C, Kerridge I. "A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia" *Transplant Infectious Diseases,* In press (accepted 10th December 2018).

12.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

12.4. Manuscript

The version of the manuscript which has been accepted for publication follows.

Title: A survey of infectious diseases and vaccination uptake in long-term Haematopoietic Stem Cell Transplant survivors in Australia

Running title: Infections and vaccinations post HSCT

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Abstract

Background

This cross-sectional survey aimed to establish the prevalence of infectious diseases and vaccination uptake in long-term allogeneic hematopoietic stem cell transplants (HSCT) survivors in New South Wales, in order to reduce long-term post-HSCT morbidity and mortality and enhance long-term care.

Patients and methods

HSCT survivors aged over 18 years and transplanted between 2000–2012 in New South Wales (NSW) were eligible to participate. Survivors self-completed the Sydney Post BMT Study survey, FACT-BMT (V4), Chronic Graft versus Host Disease (cGVHD) Activity Assessment Self Report, Lee Chronic GvHD Symptom Scale, DASS21, Post Traumatic Growth Inventory, and the Fear of Recurrence Scale.

Results

Of the 583 HSCT survivors contacted, 441 (78%) completed the survey. Respondents included 250 (57%) males and median age was 54 years (range 19-79 years). The median age at time of transplant was 49 years (Range: 17-71), the median time since HSCT was 5 years (Range: 1-14) and 69% had cGVHD. Collectively, 41.7% of survivors reported a vaccine preventable disease (VPD) with the most common being influenza-like-illness (38.4%), varicella zoster/shingles (27.9%), pap smear abnormalities (9.8%), pneumococcal disease (5.1%) and varicella zoster (chicken pox) (4.6%). Only 31.8% had received the full post-HSCT vaccination schedule, and the majority (69.8%) of these had received the vaccines via their General Practitioner. cGVHD was not found to be a significant factor on multivariate analysis for those who were vaccinated. There was a trend towards lower vaccination rates in patients in a lower income strata.

Conclusions

Vaccinating post-HSCT survivors to prevent infections and their consequences has an established role in post-HSCT care. Improving rates of post-HSCT vaccination should be a major priority for BMT units.

Keywords: Haematopoietic Stem Cell Transplant, Survivors, Vaccinations, Vaccine preventable diseases, infectious diseases.

Main text

Introduction

As worldwide application and frequency of allogeneic hematopoietic stem cell transplantation (HSCT) has increased[1,2], long-term survival has become more commonplace – over 80% of recipients who are alive at 5 years post-HSCT can expect to be alive ten years post-HSCT[3,4]. Simulating these trends, prevalence estimates of HSCT survivors in the US (alone) by 2030 is 500,000[5]. Notwithstanding the

success of HSCT, this ever growing population of long-term survivors experiences long-term and late-effects of transplant including ongoing acute and chronic graft versus host disease (GVHD), increased risks of infections, chronic illnesses and secondary malignancies[6-9]. Long-term HSCT survivors report twice as many medical problems when compared to case matched controls, are 3.5 times more likely to develop a severe/life-threatening condition than siblings (this increases up to 4.7 times in those with GVHD),[7,10] and have higher rates of hospitalisations and late mortality[11].

Despite advances in supportive care and anti-infective strategies and treatments, infectious diseases remain a challenge and contribute substantially to this excess morbidity and mortality. The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) report infection to be a contributing cause of transplant related mortality (TRM) in the first-year post HSCT in 61%, as well as in 46% and 55% of matched sibling, and other related and unrelated donor transplants respectively[12]. The most common infections reported include Pneumocystis jirovecii, encapsulated bacteria, fungi, varicella-zoster virus (VZV), cytomegalovirus, and respiratory viruses[13,14]. Notwithstanding some questionable efficacy may be reduced in the face of prolonged immune dysregulation, delayed immune reconstitution and GVHD[15], nevertheless, revaccinating HSCT survivors against vaccine preventable diseases (VPD) is universally recommended[16].

Schedules for re-vaccination post-HSCT have existed for over two decades[17] however these have varied considerably between and within countries (including time points and choice of vaccine). In 2009 a global collaboration involving nine major HSCT, infectious diseases and public health bodies published guidelines for preventing infectious complications, and in so doing harmonised the revaccination schedule based on HSCT calendar (time post HSCT) and event status (GVHD, immunosuppressive therapy)[16]. Since HSCT is an expensive, lifesaving, increasingly utilised complex medical procedure[18] mitigating infection risk by vaccinating post-HSCT recipients against VPD should be routinely employed. However, international data suggests that HSCT survivors are not routinely vaccinated and adherence to post-HSCT re-vaccination schedules is frequently poor[19-22].

Australian specific vaccination guidelines are published in the Australian Immunisation Handbook (AIH)[23]. These are online, free and easily accessible and are based on the international recommendations[16,24]. In this study we aimed to ascertain the prevalence of infectious diseases and rate of vaccination uptake (according to the AIH schedule) in a large cohort of long-term HSCT survivors in New South Wales (NSW), the largest state in Australia.

Methods

This cross-sectional survey of HSCT survivors in NSW included questions regarding post HSCT infections, vaccination uptake, cGVHD and demographic and social characteristics. Potential participants were identified from the transplant databases of all four adult allogeneic transplant centres in NSW (there are now 5 allogeneic adult HSCT centres in NSW). Participants were eligible if they were $\geq$18 years of age and had undergone an allogeneic HSCT between 1st January 2000 and 31st December 2012, could read and write English and could provide informed consent. Names and phone numbers were provided to the research team and in each case the study was verbally explained to the patient over the phone or when attending their BMT clinic. Consenting participants were sent study packs (which included a patient information sheet, an informed consent form and the survey instrument) in the post and were given the option to self-complete the questionnaire and return it via a stamped self-addressed or complete it via a phone interview with one of the researchers. A second round of telephone calls was made to 187 participants who had not returned the survey within a month. No participant wished to complete the survey via a phone interview. Phone calls and discussions in BMT clinics with potential participants and sending of the study packs via the post occurred over a 3-month period between September - December 2013. Survey close date was March 2014. All authors had access to primary clinical trial data. The study protocol was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Instruments

Participants were asked to complete seven instruments.

The Sydney Post BMT Study Survey (SPBS) was developed by the research team from a review of the literature and discussion with patients attending HSCT long-term follow-up clinics. The survey comprised 402 questions grouped into 20 domains and included questions relating to socio-demographics, co-morbidities, infections, vaccine uptake, HSCT complications, quality of life, and household income. The questionnaire used tick box responses, short answer questions, and 5-step Likert scales measuring attitudes and other factors, and took approximately 1 hour to complete. The questionnaire was piloted with six HSCT survivors in clinic and phone interviews to assess face and content validity and to check for comprehension. For each consenting participant, data was collected on dates of diagnosis and transplant, stage/remission status at transplant, transplant conditioning, GVHD prophylaxis, stem cell source and donor type.

Infectious diseases and vaccine update were analysed according to a range of demographic, transplant, psychosocial and lifestyle variables assessed using the *Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4)*[25,26], anxiety stress and depression (*The DASS 21)*[27-29], chronic GVHD (*The Chronic GVHD Activity Assessment – Patient Self Report (Form B)*[30] and *The Lee Chronic GVHD Symptom Scale)*[31] and the *Fear of Cancer Recurrence (FoCR) Scale*[32] and *The Post Traumatic Growth Inventory (PTGI)* score[33,34]. For ease of completion all instruments were combined into one booklet.

Statistical Analysis

Infectious diseases and vaccine uptake were stratified by demographic data, and baseline transplant characteristics using descriptive statistics. Categorical responses were summarised using frequencies and percentages. Parametric continuous variables were summarised using means and standard deviations, while medians and interquartile ranges were used for non-parametric data. The Pearson Chi-square or Fishers' Exact tests were used for dichotomous categorical variables and Pearson's correlation coefficient enabled assessment of the relationships between continuous variables. Comparisons of means and medians were determined by the independent t-test and Wilcoxon Rank Sum tests for 2 samples; one way analysis of Variance (ANOVA) and Kruskal Wallis tests were used when there were >2 samples. Multivariable logistic regression was used to assess for significant associations between explanatory and outcome variables after adjusting for potential confounders. A two-tailed *P* value <0.05 was considered as the level of statistical significance.

Statistical analysis was performed using Stata software (Version12.1).

Results

A total of 1,475 allogeneic HSCT were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable and were sent study packs. Four hundred and forty one (66% of total eligible, 76% of those contacted) returned the completed survey. Three percent (17) declined participation. (Figure 1)

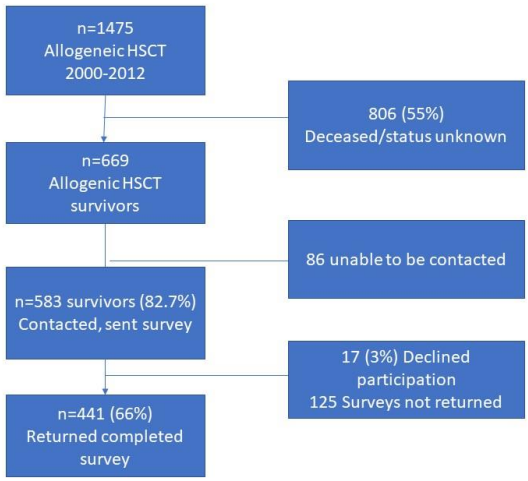

Figure 1: Study Flowchart

Of those completing the survey, 250 (57%) were male and 191 (43%) female. The median age of survey respondents was 54 years (Range: 19-79). The median time since transplant was 5 years (Range: 1-14) cGVHD was reported by 69% (Table I).

Table 1. Demographic, social and clinical characteristics of HSCT survivor respondents (n=441)

Characteristic	**Distribution**
Socio-Demographic	
Gender (Male) n/total (%)	250/441 (57%)
Median Age in years (range)	54 (19-79)
Postcode Location	
City/inner regional n/total (%)	396/431 (92%)
Income status (AUD) n/total responses (%)	
Low income $20,000-$39,999	155/423 (37%)
Middle income $40,000-$79,999	123/423 (29%)
High income >=$80,000	145/423 (34%)
Educational status n/total responses (%)	
Some high-school	53/333 (16%)
Completed High school	79/333 (24%)
Trade qualifications/diploma	47/333 (14%)
Some university	24/333 (7%)
Completed university	130/333 (39%)
Transplant factors	
Years since transplant- Median (Range)	5 (1-14)
Underlying diagnosis n/total responses (%)	
Acute Leukaemia	226/423 (53%)
Other*	197/423(47%)
Donor type n/total responses (%)	
Sibling related	250/439 (57%)
Matched Unrelated	158/439 (36%)

Haploidentical/Mismatched	31/439 (7%)
Conditioning n/total responses (%)	
Myeloablative	214/439 (49%)
Reduced Intensity	225/439 (51%)
Post transplant Morbidity and Quality of life	
cGVHD	
Total reported cGVHD since transplant n/total responses (%)	301/434(69%)
Total LEE GVHD score-Median (range)	19 (0-77)
Chronic Diseases/ Psychological morbidity n/total responses (%)	
Bone Disease (osteopenia, spinal fractures or avascular necrosis)	126/400(32%)
Cardiovascular risk factors (Diabetes, Hypertension or elevated cholesterol)	180/414 (43%)
Cancer (mouth, skin, or other)	108/389 (28%)
Anxiety	83/403 (21%)
Depression	95/407(23%)
Depression, Anxiety, Stress (DASS21) Median score (range)	20 (0-118)
Lifestyle n/total responses (%)	
Smoke	33/438(7%)
Drink alcohol	282/441(64%)
Exercise/play sport	300/436(69%)
Always Use sun-protection (sunscreen, hat, clothing sunglasses	333/431(77%)
Median BMI (range) for males	25(17-63)
Median BMI (range) for females	24(16-53)
Total FACT BMT –Median (Range)	110(32-144)

* CML, CLL, SAA, NHL, HL MM, MDS/Myeloproliferative disease, other (unspecified)

Infectious diseases

Frequency and distribution of post-transplant infections

Patients were asked about what infections they had been diagnosed with since transplantation (Table 2). The most frequently reported infections included influenza-like illness/recurrent colds (45.7%), herpes zoster (27.9%), fungal infection (15.2%) and pneumococcal disease (5.1%). Female patients were asked about Pap smear abnormalities detected since transplant; 9.8% reported a Pap smear abnormality. Genital warts were reported in 5% of males and 1.6% of female transplant recipients.

HSCT survivors who reported having had pertussis or pneumococcal disease were significantly older than those without these diseases (Table 3). The median age of those with pertussis was 65 years

compared to 54 years of those without the disease (p=0.01). The median age of those with pneumococcal disease was 62 years compared to a median of 53 years for those without the disease (p=0.01). Females reporting Pap smear abnormalities were significantly younger than those reporting no Pap smear abnormalities (42 years compared to 52 years, p=0.01). The median time since transplant for those reporting common infections such as influenza and zoster was six years (Table 3).

Hepatitis B, Bordetella pertussis (whooping cough), Haemophilus influenzae type b (Hib), Streptococcus pneumoniae (pneumococcus), Neisseria meningitidis (meningococcus) and Influenza A/B are infections for which vaccination is recommended in the first post-transplant year. Overall, 41.7% of the transplant cohort reported having had at least one of these vaccine preventable infections. Most of these were due to influenza. Excluding influenza, this rate decreased to 10.6%.

Hepatitis B, hepatitis C and tuberculosis were reported in six, four and three patients, respectively. It is not known whether these infections represented reactivated disease or de novo infections.

Table 2: Post-transplant infectious diseases

Infectious disease (N=number of responses)	Number reporting the disease (%)
Bacterial	
Pertussis (412)	11 (2.7%)
Pneumococcal disease (N=415)	21 (5.1%)
Haemophilus influenzae type B (N=411)	12 (2.9%)
Meningococcal disease (N=412)	0 (0%)
Tuberculosis (N=412)	3 (0.7%)
Viral	
Influenza-like-illness/recurrent colds (N=429)	197 (45.9%)
Varicella zoster Infections: – primary (chicken pox) (N=416) – herpes zoster/shingles (N=420)	 19 (4.6%) 117 (27.9%)
Hepatitis A (N=414)	1 (0.2%)
Hepatitis B (N=413)	6 (1.5%)
Hepatitis C (N=414)	4 (0.9%)
Measles (N=413)	3 (0.7%)
Mumps (N=414)	2 (0.5%)
Rubella (N=413)	2 (0.5%)
Human papillomavirus-related disease: – Pap smear abnormalities (females, N=184)	 18 (9.8%)

Genital warts:	
– Male (N=230)	12 (5.2%)
– Female (N=182)	3 (1.6%)
Fungal	
Fungal infections (N=408):	62 (15.2%)
– Mucocutaneous (thrush/candida/skin)	29 (7.1%)
– Aspergillosis/ Lung/sinus	12 (2.9%)
– Onychomycosis (nails)	7 (11.3%)
– Invasive mycosis (prosthetic valve)	1 (1.6%)
– Not specified	14 (1.9%)
Unspecified	
Recurrent colds (N=402)	92 (22.9%)

Table 3: Distribution of post-transplant infections by age and years post-transplant

Infection N=number of responses	Number reporting infection (%)	Median age (range)	p value	Median years since transplant for those with disease (range)
Recurrent colds (N=402)			0.32	6 (1–14)
Yes	92 (22.9%)	52 (19–74)		
No	310 (77.1%)	54 (21–79)		
Influenza-like-illness (N=419)			0.97	6 (1–14)
Yes	161 (38.4%)	54 (19–79)		
No	258 (61.6%)	53 (21–75)		
Influenza/ Recurrent colds (N=429)			0.42	6 (<2-14)
Yes	197 (45.9%)	54 (19-79)		
No	232(54.1%)	54 (21-75)		
Pertussis (412)			0.01	7 (4–11)
Yes	11 (2.7%)	65 (43–73)		
No	401 (97.3%)	54 (19–79)		
Pneumococcal disease (N=415)			0.01	8 (1–13)
Yes	21 (5.1%)	62 (30–73)		
No	394 (94.9%)	53 (19–79)		
Haemophilus ib (N=411)			0.87	3 (<2–8)
Yes	12 (2.9%)	52 (29–68)		
No	399 (97.9%)	54 (19–79)		
Tuberculosis (N=412)			0.09	7 (4–10)
Yes	3 (0.7%)	70 (51–71)		
No	409 (99.3%)	54 (19–79)		
Hepatitis A (N=414)			N/A	9
Yes	1 (0.2%)	34		
No	413 (99.8%)	54 (19–79)		
Hepatitis B (N=413)			0.28	5 (<2, 11)
Yes	6 (1.5%)	60 (47–66)		
No	407 (98.5%)	54 (19–79)		

Hepatitis C (N=414) Yes No	 4 (0.9%) 410 (99.1%)	 60 (52–62) 54 (19–79)	0.31	6 (<2–14)
Varicella zoster infections Primary (chicken pox) (N=416) Yes No	 19 (4.6%) 397 (95.4%)	 56 (27–69) 54 (19–79)	0.72	5 (<2, 11)
Zoster/shingles (N=420) Yes No	 117 (27.9%) 303 (72.1%)	 56 (21–74) 53 (19–79)	0.09	6 (<2–14)
Measles (N=413) Yes No	 3 (0.7%) 410 (99.3%)	 61 (40–70) 54 (19–79)	0.46	2 (3–11)
Mumps (N=414) Yes No	 12 (0.5%) 412 (99.5%)	 61 (40–70) 54 (19–79)	0.09	3, 11
Rubella (N=413) Yes No	 2 (0.5%) 411 (99.5%)	 61 (40–70) 54 (19–79)	0.09	3, 11
Pap smear abnormalities (females, N=184) Yes No N/A	 18 (9.8%) 150 (80.6%) 16 (8.6%)	 42 (22–65) 52 (19–75)	0.01	8 (<2–14)
Genital warts – Male (N=230) Yes No	 12 (5.2%) 218 (94.8%)	 55 (29–70) 55 (21–79)	0.74	7 (3–13)
– Female (N=182) Yes No	 3 (1.6%) 179 (98.4%)	 50 (30–58) 52 (19–75)	0.31	9 (3–11)
Meningococcal disease (N=412)	0 (0%)			
Fungal infection (N=408) Yes No	 62 (15.2%) 346 (84.8%)	 55 (21–73) 54 (19–79)	0.83	5 (<2–14)

Vaccination uptake

Pre-transplant vaccination uptake and setting

Forty-seven per cent of patients reported having received an annual influenza vaccination pre-transplant. Of these, 50% were older than 51 years of age at transplant. A much smaller proportion

(15%) reported having ever had pneumococcal vaccination, and of these the median age at transplant was 53 years. Human papillomavirus vaccine (HPV) had been administered to a total of four females, three of whom were aged 17 to 25 years at transplantation, and one aged 58 years.

Pre-transplant vaccination was most often administered by a GP (40.4%), followed by hospital (5.4%) or a community clinic (0.5%).

Post-transplant vaccination: uptake and setting

The uptake of inactivated vaccines in HSCT recipients was reported as follows (Figure 2): influenza 82%, dTpa 72%, polio 67%, hepatitis B 65%, pneumococcal vaccine 55%, Haemophilus influenzae 56% and Neisseria meningitidis 49%. Overall, 136 (30.8%) of HSCT recipients had received all inactivated vaccines recommended on the post-transplant schedule.

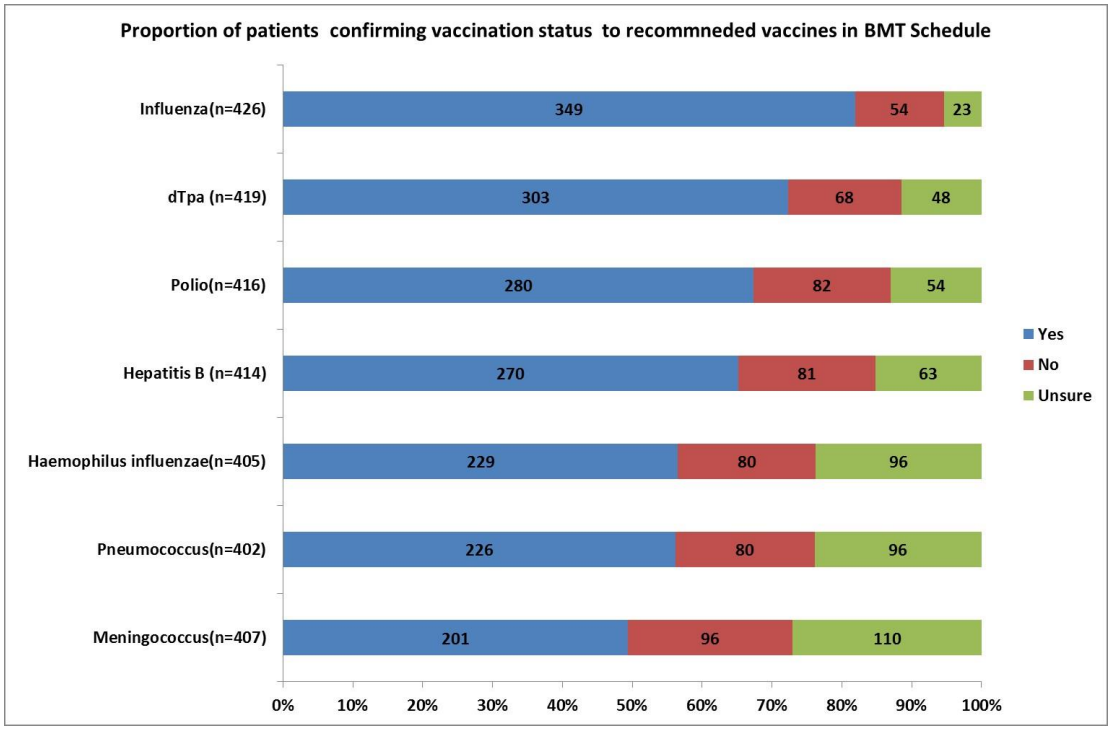

Figure 2: Uptake of recommended inactivated vaccinations post HSCT

The uptake of live-attenuated vaccinations was reported as follows: MMR 55% and varicella 26.4%. The proportion of those on immunosuppression at the time of survey reported lower uptake; 38.7% for MMR and 14.8% for varicella. For HSCT recipients that reported ever having had a diagnosis of cGVHD, the rates of live attenuated vaccination was 49.5% for MMR and 20.9% for varicella. Sixteen (27.6%) and 11 (19%) of the 58 HSCT recipients who were less than 2 years post-transplant reported

receiving MMR and varicella vaccination respectively. This compares to 210 (54.8%) and 95 (24.8%) of the 383 HSCT recipients who were more than 2 years post-transplant.

Patients with lower income showed a trend towards having not completed the recommended post HSCT vaccination schedule (adjusted OR 3.32, 95% CI 0.83, 13.4; p=0.09). Non-completion of the recommended schedule of inactivated vaccines showed no significant association with education (adjusted OR 0.5, 95% CI.13, 1.91 p=0.31) or cGVHD (adjusted OR2.33; 95% CI 0.62, 8.75) on multivariable analysis (Table 4).

Table 4: Comparison of patients who have received no vaccines and those who have received all inactivated vaccines (excepting HPV) recommended post-transplant

Factors (N=number of responses)	No vaccines (N=31)	All vaccines** (N=136)	OR (95% CI)	p value	Adjusted OR (95% CI) (p value)
Age (years) Median (IQR)	57 (48,63)	53 (45,62)		0.45	1.00 (0.94, 1.06) 0.93
GENDER			2.60 (1.05, 6.85)	0.03	
Male (N=88)	22 (71%)	66 (48.5%)			2.74 (0.81, 9.35)
Female (N-79)	9 (29%)	70 (51.5%)			0.11
Income strata			2.38 (0.92, 6.14)	0.04	
Income Low (N=58)	14/26 (53.8%)	44/134 (32.8%)			3.32 (0.83, 13.4)
Middle/High (N=102)	12/26 (46.1%)	90/134 (67.2%)			0.09
RESIDENCE			1.51 (0.57, 4.48)	0.51	
City/metro (N=117)	24/31 (77.4%)	93/134 (69.4%)			1.27 (0.36, 4.52)
Regional/remote (N=48)	7/31 (22.6%)	41/134 (30.6%)			0.71
MARITAL STATUS			0.82 (0.28, 2.75)	0.79	
Married/defacto (N=136)	25/31 (80.6%)	111/133 (83.5%)			2.87 (0.45, 18.4)
Other (N=28)	6/31 (19.4%)	22/133 (16.5%)			0.26
EDUCATION			0.62 (0.21, 1.72)	0.35	
Higher (N=64)	9/22 (40.9%)	55 (52.8%)			0.50 (0.13, 1.91)
Other (N=62)	13/22 (59.1%)	49 (47.1%)			0.31
cGVHD					
Yes (N=111)	21 (67.7%)	90 (66.7%)		1	2.33 (0.62, 8.75)

No (N=55)	10 (32.3%)	45 (33.3%)	1.05 (0.43, 2.71)		0.21
Early post-transplant (< 2 yrs)					
Yes (N=31)	11/31 (35.5%)	20/136 (14.7%)	3.19 (1.18, 8.24)	**0.007**	12.2 (3.02, 49.0)
No (N=136)	20/31 (64.5%)	116/136 (85.3%)			<0.001
** pertussis, tetanus, diphtheria, haemophilus, pneumococcus, meningococcus, hep B, influenza					

Post-transplant vaccinations were administered by GPs alone for 308 respondents (69.8%), in the hospital setting alone for 48 (10.9%), in community clinics alone for two (0.5%), in other settings (not specified) for two (0.5%). A combination of settings for vaccination (GP + other, hospital + other) was used by 32 respondents (7.2%).

Vaccination records

Two hundred and ninety-nine of the 417, (71.1%) reported having been given a post-HSCT vaccination schedule, 75 (18.0%) had never received a schedule and 43 (10.3%) were uncertain if they had received one. When asked if their GP had received a copy of the post-transplant vaccination schedule, 216 (52.1%) of 414 respondents said yes, 183 (24.9%) said no and 95 (23%) were uncertain. When asked if they had a personal record (book) of any vaccinations they had received, 175 (41.8%) of the 410 respondents said yes, 230 (54.9%) said no and 14 (3.3%) were uncertain.

Discussion

Protecting HSCT survivors against VPD with improved vaccine uptake is an important aspect of post-transplant care. In this study, the largest ever of Australian long-term allogeneic HSCT survivors, we found a high incidence of self-reported VPDs (42%) together with low complete revaccination rates (31%) for recommended inactivated vaccines. While our revaccination rates are poor, they are consistent with international literature and with Australian single centre studies; complete revaccination rates of HSCT survivors range from 20-33%[19,35-37]. Live attenuated vaccinations were analysed separately in this study as the recommendation for their use is limited by levels of post-transplant immunosuppression, and incomplete immune reconstitution in the post-transplant period which is expected to take at least 24 months. So, while 55% and 26.4% of all respondents reported receiving MMR and varicella respectively, it is worthy of note that 27.6% of patients who were less than 2 years post-transplant reported receiving MMR, and 19% receiving the varicella vaccine. Although rates of live attenuated vaccine use was lower in those with a history of cGVHD or those

currently on immunosuppression, the cross sectional nature of this study was unable to determine if these vaccines were given when cGVHD or immunosuppression were contemporaneous.

Despite 82% of our survivors reporting receiving an annual influenza vaccination (and influenza vaccines providing up to 80% efficacy[38]),a high rate (46%) of influenza-like -illness or recurrent upper respiratory tract infections was reported. There may be a number of possible explanations for this finding including reporting bias, misattribution, the inconsistent uptake of annual seasonal influenza vaccination or the variable efficacy of the vaccine, such as that which occurs with seasonal mismatch with circulating strains. In previous studies laboratory confirmed influenza has been reported to occur in 1.3% - 3.5% of HSCT recipients[39-41], which likely underrepresents the true burden of disease. Influenza in the post HSCT setting can result in an increased risk of bacterial pneumonia, hospitalisation, mechanical ventilation and mortality[38,40-42]. It is important therefore that risk mitigation strategies are implemented including improving the uptake of pre and post- influenza vaccination rates in HSCT recipients (only 47% of our population reported receiving influenza vaccination pre-HSCT), annual vaccination of household contacts, and administration of annual influenza vaccination to health care workers caring for HSCT recipients[38].

Pneumococcal disease occurs more commonly post HSCT compared to the general population[35,39]. In this study 5.1% of respondents reported the disease. This is double that of a 2014 Australian study that reported invasive pneumococcal disease (IPD) in 2.3%[39] of HSCT recipients. Our high rates may be explained by reporting bias; we did not ask specifically if the survivor had IPD or non-invasive pneumococcal disease and a number of other factors. Only 15% reported receiving the vaccine pre-HSCT as recommended, only 55% of survivors reported receiving the vaccine post-HSCT, and those who experienced the disease were almost 10 years older than those who did not contract the disease (62yrs vs 53yrs, p=0.01). Vaccine underutilisation, immunosenescence and (where vaccination did occur) vaccine failure may be responsible – a combination of increasing age of survivors[43] and poor maintenance of specific immunity to pneumococcal disease among long-term HSCT survivors[44]. Similarly, in the case of pertussis, the vaccine was administered to 72% of post-HSCT survivors, 2.9% reported the disease and those that did so were >10years older than those that reported not having the disease (65yrs vs 54yrs, p=0.01)).

Notably, in the general Australian population, the uptake of immunisations is relatively high such that the vaccination rate for 5 years olds is 94%[45]. Clearly, however, there must be barriers to vaccination uptake in older persons. Polysaccharide pneumococcal vaccine (PPV) is subsidised on the Pharmaceutical Benefits Schedule (PBS) for transplant recipients of any age, and all Australians 65

years and over are eligible to receive PPV free of charge on the National Immunisation Program (NIP). The protein conjugate pneumococcal vaccine (PCV), recommended as a three-dose schedule post-transplant receives no government subsidy. Influenza vaccines are free on the NIP, for those medically at risk and for all Australians 65 years and over. Despite these funding provisions only 51% of Australian adults over 65 years are immunised against these diseases (AIHW 2009, Australia's health 2018).

On multivariate analysis cGVHD was not associated with vaccination status of our survivors. This implies that there are potential barriers to vaccination uptake in the first two years post-HSCT which is unrelated to the presence or severity of cGVHD. This is important and requires attention since the AIH guidelines recommend that HSCT survivors are fully revaccinated by 12 months post-HSCT (excluding live vaccines), when the risk for some VPDs is highest.

Importantly, lower income showed a non-significant trend towards not completing the revaccination schedule. As the majority of our survivors received their vaccinations via their GP (40.4% pre-HSCT and 69.8% post-HSCT), the effect of cost of revaccination to adherence to recommended post-HSCT must be considered. In Australia, HSCT recipients are not eligible to receive childhood vaccinations free of charge on the NIP. The revaccination schedule requires multiple visits to medical practitioners at 6, 8, 12 and 24 months post-HSCT. Given the cost associated with the purchase of the vaccines, additional consultation costs will add to the out-of-pocket expenses borne by the patient. The lack of financial subsidy for the majority of vaccinations recommended on the post transplant vaccination schedule may therefore be a potentially important barrier to vaccination uptake (It is estimated that the cost for all vaccines post HSCT is >$1,000, depending on what pharmacies chose to charge for individual vaccines and their dispensing fees).

As mentioned, the vast majority of HSCT recipients (69.8%) receive their vaccinations via their GP. Given that this is regularly devolved to local medical officers (LMOs/GPs) [20,46] it is important that HSCT survivors and their GPs are aware of the revaccination schedule. In our study 71.1% of survivors had been given a vaccination schedule, and 52% reported that their GP had been provided with the schedule. The low revaccination completion rates highlights the need for better education and communication between tertiary and primary health services, and between public and private practices.

Our survey also asked survivors if they had received a vaccination record. Only 41.8% had been given written proof of any vaccines they had received post-HSCT. Fortunately, the Australian Government expanded its previous Childhood Immunisation Record (ACIR) to become the Australian Immunisation

Register (AIR) in September 2016. This is a national register that records vaccines given to people of all ages in Australia and theoretically may overcome the lack of vaccine records for HSCT survivors, GPs and BMT centres. This was not available at the time of survey completion. Other strategies used to increase vaccination adherence and education include vaccination cards and reminder telephone calls[36], and dedicated post-HSCT vaccination clinics.[47]

This was a multi-centre study and the sample size and high response rate (76%) make it likely that these results represent an accurate account of the impact of HSCT on NSW survivor's post-transplant infection rates and vaccine uptake. Nevertheless, there are a number of limitations to our study that may limit the general applicability of these results to HSCT survivors in other countries and other settings. Some of the limitations include participation bias, self-reporting and not capturing data on non-responders. Furthermore, we did not verify self-reported infections with patient medical records/pathology reports (this is particularly relevant when considering the high rate of influenza reported and also that we do not know if survivors had IPD or non-invasive pneumococcal disease and therefore cannot be sure of the effectiveness of vaccination in this setting), and nor did we have access to vaccination records. Additionally, we did not ask why survivors had not completed the revaccination schedule. This would be very important data to consider in addressing rates of vaccine uptake (cost, knowledge, health status, physician decision etc all need to be considered). Also, since only those individuals who could read and write English were eligible to participate, we do fail to capture some data from individuals who may derive from diverse ethnic backgrounds. This is an important consideration since culturally and linguistically diverse (CALD) cancer populations often have worse engagement with health services and outcomes than those of their white/Caucasian counterparts[48], and may be at a disadvantage socioeconomically prior to HSCT. Lastly, cross-sectional studies restrict inferences about casual or temporal relationships.

Optimising vaccination adherence post HSCT represents a highly attractive strategy to improve the outcome and the quality of life of long-term survivors[49]. The results of this study necessitate immediate and critical improvements in vaccination practices post-HSCT. Survivors, carers, BMT specialists and GPs require continuing education, as well as infrastructure, funding and support to ensure survivors are vaccinated according to best practices guidelines. Areas for investigation include prospective measurement of the response to vaccines late after HSCT to identify the benefits and limitations of vaccination, particularly for those with GVHD or on prolonged immunosuppressive treatment (IST). Decreasing the rates of VPD has the potential to decrease long term morbidity, mortality, hospitalisations, cost to patients and the health system and minimise antimicrobial drug resistance – a worthy post-HSCT pursuit.

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12.5. Synopsis

This paper presents the most comprehensive account of the prevalence of self-reported infectious diseases and vaccination uptake in an Australian cohort of allogeneic BMT recipients. It provides detailed data on VPD incidence, and AIH vaccination schedule adherence according to established sociodemographic and transplant variables. The results indicate that VPD incidence is high and that few survivors complete the recommended schedule of post-BMT vaccination. Importantly no single factor including cGVHD, education or income predicts vaccination adherence, suggesting that more fundamental factors (e.g. education, communication, service organisation) may explain rates of adherence.

The low rates of post-BMT vaccination reported here are consistent with international literature and with Australian single centre studies (ranging between 20-33%(1-3). This finding is deeply problematic as infection is one of the major causes of post-BMT mortality, with over 40% of survivors in this study reporting a VPD.

The results of this study also suggest that ignorance and inadequate communication between health providers and patients may explain part of the low rates of vaccination adherence, with few GPs receiving advice regarding post-BMT vaccination or details of the post-BMT vaccination schedule. This suggest that much more needs to be done to improve communication with and education of BMT survivors, BMT healthcare professionals, GPs who care for long-term BMT survivors and policy makers involved in supporting and funding community vaccination programs in Australia.

While there is a clear rationale for vaccination of BMT survivors to reduce rates of post-BMT infection, it is noteworthy that there is limited data about the efficacy of vaccination post-BMT(4). This is a major lacunae as without these data it may be difficult to convince clinicians, health services and policy maker to change their practice and/or be willing to fund potentially important, and life-saving vaccines.

The results of this study have important implications for BMT patients, BMT units, local haematologists, GPs, APNs, and others who are involved in the care of BMT survivors. These results are also relevant to Australian and state government policymakers and to those responsible for development and translation of the National Immunisation Program (NIP)(5).

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Chapter 13: Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia

13.1. Chapter overview

This chapter reports on the use of CAM therapies in long-term survivors of BMT. It consists of a published manuscript entitled, 'Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia'. The manuscript reports on the frequency and type of CAM therapy use and its association with demographic, socioeconomic, transplant factors, medical complications, cGVHD and QoL. Specifically, we asked about survivors use of dietary modification, vitamin therapy, mind-body therapy, herbal supplementation, manipulative and body-based therapies, Chinese medicine, reiki and homeopathy.

Our results demonstrate that over half of the BMT survivors in this cohort used at least one form of CAM therapy post-BMT and that approximately 30% used more than two forms of CAM. Vitamin therapies, manipulative body-based therapies (massage, acupuncture, chiropractic and osteopathy) and mind-body therapies (meditation, hypnosis/breathing and spiritual healing) were the CAM modalities most often used by our respondents. While we did not specifically inquire as to the reasons why survivors used CAMS post-BMT, the literature suggests that this may, in part, be because BMT survivors have physical, psychological and/or spiritual needs that orthodox medicine has been unable to address. There may of course be other reasons why survivors choose to use CAMs – they may be consistent with patients 'world view', they represent the only way that patients can express their agency, and they may provide genuine benefit. But CAM use is also expensive and may be associated with risks, due to either CAM itself or because of interactions with allopathic medicines. Additional risks include CAM use leading patients to delay initiation of conventional therapy or to refuse conventional therapy. The problem here is that we have little empirical data regarding the risks and benefits of CAM in group of patients.

Irrespective of the evidence surrounding CAM, the high prevalence of its use revealed in this study suggests that CAM should be the subject of further research and that CAM use should be specifically addressed in the education and counselling pre-BMT and in long-term follow up. Clinicians involved in the long-term care of BMT survivors must be aware that many survivors may seek complementary, and less frequently, alternative therapies, and must therefore be willing to discuss the established and potential harms and benefits of CAM use to ensure that survivors are informed about their choices.

13.2. Publication details

Lindsay J, Kabir M, Gilroy N, **Dyer G,** Brice, L, Greenwood M, Moore J, Hertzberg M, Larsen S, Kwan J, Brown L, Hogg M, Huang G, Tan J, Gifford G, and Kerridge I. "Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia". *Cancer Med.* 2016;5(12):3606-14.

13.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

13.4. Manuscript

The published version of the manuscript follows.

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ORIGINAL RESEARCH

Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia

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Keywords
Blood and marrow transplantation (BMT), complementary and alternative medicine (CAM), hematopoietic stem cell transplantation (HSCT), quality of life, survivors

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Abstract

In addition to prescribed conventional medicines, many allogeneic hematopoietic stem cell transplant (HSCT) survivors also use complementary and alternative medical therapies (CAM), however, the frequency and types of CAMs used by allogeneic HSCT survivors remain unclear. Study participants were adults who had undergone an allogeneic HSCT between 1st January 2000 and 31st December 2012. Participants completed a 402-item questionnaire regarding the use of CAM, medical complications, specialist referrals, medications and therapies, infections, vaccinations, cancer screening, lifestyle, and occupational issues and relationship status following stem cell transplantation. A total of 1475 allogeneic HSCT were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable and were sent study packs. Of 432 participants who returned the completed survey (66% of total eligible, 76% of those contacted), 239 (54.1%) HSCT survivors used at least one form of CAM. These included dietary modification (13.6%), vitamin therapy (30%), spiritual or mind–body therapy (17.2%), herbal supplements (13.5%), manipulative and body-based therapies (26%), Chinese medicine (3.5%), reiki (3%), and homeopathy (3%). These results definitively demonstrate that a large proportion of HSCT survivors are using one or more form of CAM therapy. Given the potential benefits demonstrated by small studies of specific CAM therapies in this patient group, as well as clearly documented therapies with no benefit or even toxicity, this result shows there is a large unmet need for additional studies to ascertain efficacy and safety of CAM therapies in this growing population.

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Introduction

Worldwide, 90,000 [1] allogeneic HSCTs were performed between 2001 and 2011, with 4369 [2] of these procedures occurring in Australia. With improvements in donor selection, conditioning therapies, and supportive care, 35–80% of HSCT recipients can now be expected to become long-term survivors and be cured of their underlying disease [3]. While HSCT provides a clear benefit for many patients with malignant and nonmalignant disease, it is also associated with significant morbidity and mortality [4].

In recent years, there has been growing literature on the long-term (or late) psychosocial and medical complications experienced by HSCT survivors. The impact of these is profound with HSCT survivors experiencing a 30% lower life expectancy than a matched population cohort [4]. While many survivors rate their quality of life highly at 2 years posttransplant, many HSCT recipients experience considerable difficulty coping with the short-, medium-, and long-term physical and psychological sequelae of HSCT and with the uncertainties of their prognosis. Given the extent and impact of late complications of HSCT, ongoing long-term follow-up and multidisciplinary care of HSCT recipients is essential [5].

In addition to prescribed conventional medicines, many HSCT survivors also use complementary and alternative medical therapies (CAM). However, the prevalence and extent of the usage of CAMs in this patient group remains unclear. A review published in 1998 found the prevalence of CAM use among cancer patients ranges from 7% to 64% of patients sampled in 26 studies conducted worldwide [6]. This is consistent with CAM use in the general population, estimated at 40% in Australia, Canada, Europe, New Zealand, and the United States [7].

Studies in the United States have reported that the most common complementary practices and products used by individuals with cancer are vitamin/mineral supplements, prayer for self, intercessory prayer, chiropractic/osteopathic manipulation, and herbal therapies [8]. To date, no studies have reported CAM usage by HSCT patients.

Despite the lack of literature on the epidemiology of CAM use in HSCT patients, there have been a number of small trials, including randomized controlled studies showing a potential benefit for some CAM therapies such as mind and body interventions, although the majority of CAM treatments show inconclusive mixed results [9]. The authors of a recent literature review of these known studies of CAMs in HSCT proposed that a current barrier to the use and research in CAM therapy is the recognition and acceptance of CAM use in this population and that epidemiologic estimates were required [9]. The aim of this study was to describe the frequency and types of CAM used by HSCT survivors, with the intention of enhancing recognition of CAM use.

Methods

Patients and procedures

Study participants were eligible if they were ≥18 years of age and had undergone an allogeneic HSCT between 1st January 2000 and 31st December 2012 in New South Wales (NSW) (NSW is Australia's most populous state – with a population of ~7.5 million [10]), and could read and write English. Potential participants were identified from the transplant databases of all allogeneic transplant centers in NSW, with names and phone numbers provided to the research team. Consenting participants were given the option to self-complete the questionnaire or to complete it via a phone interview with one of the researchers. A second round of telephone calls was made to consenting participants who had not returned the survey within a month. The study protocol was approved by the Northern Sydney Coast Human Research Ethics Committee (NSLHD Reference: 1207–217M).

Instruments

The Sydney Post HSCT Study survey (SPBS) was developed by the research team. Item construction was informed by a review of the literature and discussions with patients attending HSCT long-term follow-up clinics. It consisted of 402 questions, including questions relating to the use of CAMs, specifically: Nutrition and Dietary approaches, Herbal supplements, Vitamin therapies, Mind–Body therapies (e.g., Meditation), Manipulative and Body therapies (e.g., Acupuncture), Traditional medicine (e.g., Traditional Chinese Medicine), Energy medicine (e.g., Reiki), and Homeopathy. Other relevant domains included demographic data, medical complications, specialist referrals, tests and assessments, medications and therapies, infections, vaccinations, cancer screening, close personal contacts, lifestyle, occupation, and relationship status following stem cell transplantation. The questionnaire used tick box response, short answer questions, and 5-step Likert scales measuring attitudes and other factors, and takes approximately 1 h to complete. The questionnaire was piloted in clinic and phone interviews to assess face and content validity and to check for comprehension of the survey questions.

An additional one page HSCT clinical data form (The Sydney Post HSCT Clinical Data Form) was used to collect information from the transplant database including date of transplant, date of diagnosis, stage at transplant, transplant conditioning, Graft-versus-Host Disease (GvHD) prophylaxis, stem cell source, and donor type.

Measures

Participants were classified as CAM users if they used at least one therapy in any of the CAM categories. CAM use was correlated with demographics, medical complications, posttransplant medical therapies, treatments and clinical variables, relationship status, and social determinants including income and occupational status. The relationship of CAM use was further explored against a range of survey instruments that measured quality of life

(Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT Version 4), anxiety, stress, and depression (The DASS 21), chronic GVHD (The Chronic GVHD Activity Assessment – Patient Self Report (Form B) and The Lee Chronic GVHD Symptom Scale), and an assessment of life change in response to traumatic events (The Post Traumatic Growth Inventory score).

Statistical considerations

Categorical responses were summarized using frequencies and percentages. Parametric continuous variables were summarized using means and standard deviations, and nonparametric variables using medians and interquartile ranges. The Pearson's X 2 test or Fishers Exact tests were used for comparative analysis of dichotomous categorical variables. Two sample comparisons of means and medians were determined using the independent t test and Wilcoxon Rank Sum tests, respectively; greater than two sample comparisons of means and medians were determined using one-way analysis of Variance (ANOVA) and Kruskal–Wallis tests, respectively. A two-tailed $P < 0.05$ was used as the level of statistical significance.

Results

Study subjects

A total of 1475 Allogeneic HSCT were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable and were sent study packs. A total of 432 (66% of total eligible, 76% of those contacted) returned the completed survey. Three percent declined participation.

Table 1. Total complementary and alternative medical therapies (CAM) usage.

Overall CAM users	54.2% (239)
Dietary modification	13.6% (59)
Vitamin therapy (ex Calcium/Vit D)	27.3% (109)
Mind–body therapy (inc spiritual)	17.2% (74)
Herbal supplementation	13.5% (58)
Manipulative and body-based therapies	26.0% (112)
Chinese medicine	3.5% (15)
Reiki	3.0% (13)
Homeopathy	3.0% (13)

Transplantation details

Median survival time post-HSCT was 5 years (range: 1 year 4 months–22 years). The main indication for transplantation was acute leukemia (AML/ALL) in 226 (52.3%). Remission status was reported in 406 HSCT, of which 271 (66.8%) were CR1 or CR2. Donor type was reported in 432 transplant procedures of which the majority were siblings (57.1%) and matched unrelated donors (35.8%). Peripheral blood stem cells were used in 381 (88.1%) of transplants. Myeloablative conditioning regimens were used in 216 (50.0%) and of these 103 (47.7%) employed total body irradiation (TBI). T-cell depleting therapy was reported in 122 (28.2%). Antithymocyte globulin (ATG) accounted for 92.6% of T-depleting modalities, with Alemtuzumab accounting for 3.3%.

Usage of complementary and alternative medicine therapies

A total of 239 (54.2%) of HSCT survivors used at least one form of CAM, including dietary modification (13.4%), vitamin therapy (including minerals and oils) (29.3%), spiritual and mind–body therapy (17.2%), herbal supplements (13.2%), manipulative and body-based therapies (25.4%), Chinese medicine (3.4%), reiki (3%), and homeopathy (3%) (Table 1). One hundred and seventeen (27.2%) patients used more than one form of CAM, ranging up to seven forms of CAM (Table 2).

Characteristics of CAM users are shown in Table 3. There was no age difference between CAM users and nonusers. Women ($P = 0.019$), people living in a major city ($P = 0.017$), those with a university education ($P = 0.001$), and those with bone disease ($P = 0.029$) were significantly more likely to use at least one CAM. When comparing pretransplant diagnosis, type of conditioning or time from transplant, cGvHD, diabetes, cardiovascular risk, thyroid problems, anxiety, and depression, no difference in CAM use was seen.

Additionally, patients taking antibacterial, antiviral, or antifungal treatment were significantly less likely to use CAMs ($P = 0.041$), whereas patients taking other prescription drugs, including immunosuppressant, cardiovascular, hormone replacement, or psychotropic medications, were no more or less likely to use CAMs. Patients who routinely saw a Psychologist ($P = 0.024$) or Physiotherapist ($P = 0.010$) were more likely to use CAMs, as were those who did regular exercise ($P = 0.049$). There was no

Table 2. Total complementary and alternative medical therapies (CAM) burden.

Number of CAMs	Nil	At least 1	1	2	3	4	5	6	7
Patients	43.8% (193)	54.2% (239)	26.0% (116)	14.5% (62)	6.6% (27)	4.3% (17)	0.9% (4)	0.9% (4)	0.7% (3)

Table 3. Characteristics of CAM users.

Variables	CAM users (%)	Nonusers (%)	*P* value	OR (CI)
Demographic				
Gender			0.019	0.63 (0.42–0.92)
Male (*n* = 244)	123/239 (51.5)	121/193 (62.7)		
Female (*n* = 188)	116/239 (48.5)	72/193 (37.3)		
Age (years)			0.73	1.06 (0.73–1.56)
<54 (*n* = 221)	124/239 (51.9)	97/193 (50.3)		
≥54 (*n* = 211)	115/239 (48.1)	96/193 (49.7)		
Postcode			0.017	1.68 (1.0–2.5)
City – metro (*n* = 305)	180/234 (76.9)	125/188 (66.5)		
Regional or remote (*n* = 117)	54/234 (23.1)	63/188 (33.5)		
Socioeconomic				
Education				
Some high school (*n* = 53), completed high school (*n* = 78), Trade/diploma (*n* = 44), Some university (*n* = 24), completed university (*n* = 126)			0.018	–
University education (*n* = 150)	98/179 (54.7)	52/146 (35.6)	0.001	2.18 (1.36–3.42)
Other (*n* = 175)	81/179 (45.3)	94/146 (64.4)		
Posttransplant income			0.43	0.85 (0.57–1.27)
Low income (*n* = 153)	81/230 (35.2)	72/185 (38.9)		
Middle-high income (*n* = 262)	149/230 (64.8)	113/185 (61.1)		
Occupational status				
Full/Part time (*n* = 211)	118/220 (53.6)	93/194 (47.9)	0.24	1.25 (0.85–1.85)
Unemployed, Retired or Casual (*n* = 203)	102/220 (46.4)	101/194 (52.1)		
Transplant factors				
Pretransplant cancer diagnosis			0.78	1.05 (0.71–1.55)
Acute leukemia (*n* = 219)	122/228 (53.5)	97/186 (52.2)		
Other (*n* = 195)	106/228 (46.5)	89/186 (47.8)		
Years since transplant	*N* = 239	*N* = 193	0.053	–
<2 years (*n* = 57)	27 (11.3)	30 (15.5)		
2 < 6 years (*n* = 199)	105 (43.9)	94 (48.7)		
6 < 10 years (*n* = 115)	64 (26.8)	51 (26.4)		
≥10 years (*n* = 61)	43 (18)	18 (9.3)		
Conditioning			0.213	–
Myeloablative (*n* = 216)	239	193		
Reduced intensity (*n* = 225)	122 (51)	88 (45.6)		
Missing (*n* = 2)	115 (48.1)	105 (54.5)		
Clinical factors				
cGvHD	*N* = 233	*N* = 192	0.39	1.23 (0.82–1.87)
Yes (*n* = 294)	166 (71.2)	128 (66.7)		
No (*n* = 131)	67 (28.8)	64 (33.3)		
Diabetes	*N* = 209	*N* = 180	0.75	0.91 (0.51– 1.6)
Yes (*n* = 56)	29 (13.9)	27 (15)		
No (*n* = 333)	180 (86.1)	153 (85)		
Thyroid	*N* = 205	*N* = 176	0.40	1.50 (0.57–3.9)
Yes (*n* = 19)	12 (5.9)	7 (4.0)		
No (*n* = 362)	193 (94.1)	169 (96.0)		
CV Risk	*N* = 219	*N* = 186	0.49	1.14 (0.77–1.70)
Yes (*n* = 175)	98 (44.7)	77 (41.4)		
No (*n* = 230)	121 (55.3)	109 (58.6)		
Self-reported anxiety or depression	*N* = 215	*N* = 185	0.142	1.38 (0.89–2.15)
Yes (*n* = 1160	69 (32.1)	47 (25.4)		
No (*n* = 284)	146 (67.9)	138 (74.6)		
Bone disease	*N* = 214	*N* = 178	0.029	1.62 (1.04–2.52)
Yes (*n* = 121)	76 (35.5)	45 (25.3)		
No (*n* = 271)	138 (64.5)	133 (74.7)		

(*Continues*)

Table 3. Characteristics of CAM users. (Continued)

Variables	CAM users (%)	Nonusers (%)	*P* value	OR (CI)
Skin/Mouth cancers	*N* = 215	*N* = 183	0.59	1.13 (0.71–1.85)
Yes (*n* = 94)	53 (24.7)	41 (22.4)		
No (*n* = 304)	162 (75.3)	142 (77.6)		
Other medication use				
Med group 1 (penicillin, antiviral drug, bactrim, antifungal drug)	*N* = 239	*N* = 193	0.041	0.66 (0.45–0.98)
Yes (*n* = 176)	87 (36.4)	89 (46.1)		
No (*n* = 256)	152 (63.6)	104 (53.9)		
Med group 2 (immune drug, prednisolone)	*N* = 239	*N* = 193	0.31	0.81 (0.54–1.21)
Yes (150)	78 (32.6)	72 (37.3)		
No (282)	161 (67.4)	121 (62.7)		
Med group 3 (any blood pressure drug)	*N* = 239	*N* = 193	0. 16	0.73 (0.47–1.13)
Yes (107)	53 (22.2)	186 (77.8)		
No (325)	54 (28)	139 (72)		
Med group 4 (antidepressant, any sleeping tablet, antianxiety drug)	*N* = 239	*N* = 193	0.50	1.17 (0.73–1.88)
Yes (89)	52 (21.8)	187 (78.2)		
No (343)	37 (19.2)	156 (80.8)		
Calcium	*N* = 239	*N* = 193	0.27	1.23 (0.84–1.50)
Yes (205)	119 (49.8)	86 (44.6)		
No (227)	120 (50.2)	107 (55.4)		
Vitamin D	*N* = 239	*N* = 193	0.43	1.16 (0.79 –1.7)
Yes (244)	139 (58.2)	105 (54.4)		
No (188)	10 (41.8)	88 (45.6)		
Bone strengthening drug	*N* = 239	*N* = 193	0.41	1.25 (0.73–2.14)
Yes (65)	39 (16.3)	26 (13.5)		
No (367)	200 (83.7)	167 (86.5)		
Med Group 5 (hormonal replacement)	*N* = 239	*N* = 193	0.116	1.55 (0.89–2.73)
Yes (62)	40 (16.7)	22 (11.4)		
No (370)	199 (83.3)	171 (88.6)		
Psychosocial				
Psychiatrist	*N* = 220	*N* = 181	0.99	0.99 (0.47–2.08)
Yes (*n* = 31)	17 (7.7)	14 (7.7)		
No (*n* = 370)	203 (92.3)	167 (92.3)		
Psychologist	*N* = 221	*N* = 185	0.024	1.82 (1.07–3.09)
Yes (*n* = 74)	49 (22.2)	25 (13.5)		
No (*n* = 332)	172 (77.8)	160 (86.5)		
Social worker	*N* = 221	*N* = 183	0.21	1.4 (0.79–2.67)
Yes (*n* = 51)	32 (14.5)	19 (10.4)		
No (*n* = 353)	189 (85.5)	164 (89.6)		
Dietician	*N* = 222	*N* = 185	1.00	1.0 (0.63–1.57)
Yes (*n* = 99)	54 (24.3)	45 (24.3)		
No (*n* = 308)	168 (75.7)	140 (75.7)		
Physiotherapist	*N* = 220	*N* = 183	0.010	1.8 (1.1–3.0)
Yes (*n* = 97)	64 (29.1)	33 (18)		
No (*n* = 306)	156 (70.9)	150 (82)		
Exercise physiologist	*N* = 218	*N* = 182	0.067	2.0 (0.93–4.3)
Yes (*n* = 33)	23 (10.6)	10 (5.5)		
No (*n* = 367)	195 (89.4)	172 (94.5)		
Lifestyle				
BMI group	*N* = 239	*N* = 193	0.519	–
Normal (193)	112 (46.9)	81 (42)		
Obesity (66)	36 (15.1)	30 (15.5)		
Overweight (125)	66 (27.6)	59 (30.6)		
Underweight (13)	9 (3.8)	4 (2.1)		
Missing (35)	Median 24.48	Median 25.1		
Median (IQR)	(22.1–28.03)	(22.5–28.3)		

(*Continues*)

Table 3. Characteristics of CAM users. (Continued)

Variables	CAM users (%)	Nonusers (%)	*P* value	OR (CI)
Doing exercise	*N* = 236	*N* = 191	0.076	1.45 (0.96–2.19)
Yes (*n* = 296)	172 (72.9)	124 (64.9)		
No (*n* = 131)	64 (27.1)	67 (35.1)		
>3times/Week (199)	124 (73.4)	75 (62.3)	0.049	0.60 (0.36–1.00)
<3 times /Week(90)	45 (26.6)	45 (37.5)		
FACT-BMT total score	108.3 (89.7–120)	104.6 (90–119)	NS	–
Total lee	17.2 (8.5–31.1)	20.85 (10.3–29.9)	NS	–
Uncertainty score	13.5 (9–17)	14 (10–17)	NS	–
Factor total	58 (40–68)	50 (30–66)	0.001	–

FACT-BMT, functional assessment of cancer therapy – bone marrow transplant, CAM, complementary and alternative medical therapies. Lee cGVHD scale, a valid measure of cGVHD manifestations.

significant relationship with FACT-BMT and patients' use of CAMs.

Dietary modification

Fifty-Nine (13.6%) HSCT survivors modified their diet in some way, including caloric supplementation (3; 0.7%), low calorie diet (6; 1.4%), gluten-free diet (6; 1.4%), lactose-free diet (3; 0.7%), probiotic usage (4; 0.9%), low carbohydrate diet (2; 0.5%), vegetarian or pescetarian diet (8; 1.8%), low cholesterol diet (4; 0.9%), and use of organic food (14; 3.2%). Women were more likely to make modifications to their diet post-HSCT than men, with 32 (17%) of women and 27 (11%) of men (Male: OR: 0.59 [0.34–1.03]). Nine HSCT survivors consulted a dietician (2%).

Diagnosis, comorbidities (diabetes mellitus, cardiovascular disease), bone disease, and posttransplant cancer diagnosis were not significantly associated with dietary modification. Those using dietary modification were significantly more likely to be further out from their transplant date (median 6.6 years compared to 5.0 years [$P = 0.04$]) and reported significantly higher FACT-BMT scores (Median 109, IQR 99–121), indicative of better quality of life.

Herbal therapy

Herbal therapies were uncommonly used by HSCT survivors, with the most common therapies including Ginseng (5; 1.1%) and Garlic (3; 0.7%). Women were more likely to use herbal therapies (Male: $P = 0.056$, OR: 0.58 [0.33–1.01]) as were patients living in an urban area (Rural: $P = 0.051$, odds 2.0 [0.98–4.14]). Although not significant, patients using herbal supplements had higher odds of having a pretransplant diagnosis of AML/ALL (OR: 1.42 [0.798–2.55]), cardiovascular risk factors (OR: 1.32 [0.73–2.39], bone disease (OR: 1.7 [0.95–3.31]), and of seeing a psychiatrist (OR: 1.35 [0.49–3.70]). Those using herbal supplements had lower odds of being diabetic (OR: 0.83 [0.33–2.0]) or seeing a social worker (OR: 0.72 [0.21–1.92]) or a dietician (OR: 0.45 [0.19–1.04]). Patients were significantly less likely to take herbal supplements the more prescription medications they took ($P = 0.004$). There was no significant relationship between FACT-BMT and patient's use of herbs.

Vitamin therapy (including minerals and oils)

Self-medication of vitamins (excluding Vitamin D and Calcium) was taken by 129 (29.3%) patients, including vitamin B (24; 5.4%), vitamin C (33; 7.5%), vitamin E (2; 0.5%), fish oil (28; 6.3%), magnesium (15; 3.4%), zinc (8; 1.8%), CoQ10 (3; 0.7%), and multivitamins (38; 8.6%). Calcium was taken by 211 (47.2%) patients and vitamin D by 250 (56.7%) patients (Table 4). Patients were more likely to take vitamin therapies if they had a university degree (OR: 1.36 [0.84–2.19], however, no other correlations were identified. Of the 239 patients taking vitamin supplements, the total number of supplements (supplement burden) varied, with most patients taking one (61; 51%) or two (32; 27%) supplements (Table 5).

Table 4. Vitamin supplementation.

Total Vitamin Modification (ex Vit D/ Calcium)	Vitamin B	Vitamin C	Vitamin E	Fish oil	Magnesium	Zinc	CoQ10	Multivitamin	Calcium	Vitamin D
24.7% (109)	5.4% (24)	7.5% (33)	0.5% (2)	6.3% (28)	3.4% (15)	1.8% (8)	0.7% (3)	8.6% (38)	47.8% (211)	56.7% (250)

Table 5. Vitamin supplementation burden.

Number of vitamin supplements per patient excl calcium +Vit D	1	2	3	4	5	6	7
	51% (61)	27% (32)	13% (16)	5% (6)	3% (4)	0	0.8% (1)

Mind–body therapies (including spiritual healing)

Mind–body therapies were used by 74 (17.1%) patients, including meditation (45; 10.2%), hypnosis/breathing exercise (7; 1.6%), spiritual healing (9; 2.0%), yoga (8; 1.8%), and tai chi (5; 1.1%). Women were more likely to use mind–body therapies (22%) versus men (13%). Patients with university degrees were significantly more likely to use a spiritual and/or mental therapy ($P = 0.008$ OR: 2.20 [0.21–3.99]). Likewise, those who saw a Psychologist ($P = 0.009$, OR: 2.19 [1.21–3.99]), Psychiatrist ($P = 0.015$, OR: 2.62 [1.17–5.86]), Physiotherapist ($P = 0.049$, OR: 1.77[0.99–3.14]), Exercise physiologist ($P = 0.022$, OR: 2.48 [1.11–5.51]), or those who exercised more than three times per week ($P = 0.042$, OR: 0.48 [0.244–0.97]).

Manipulative and body-based therapies

Manipulative and body-based therapies were used by 112 (26%) patients, including acupuncture (28; 6.3%), chiropractic (28; 6.3%), massage (64; 14%), osteopathy (9; 2%), physiotherapy (8; 1.8%), and reflexology (6; 1.4%). There was a marginal difference in genders seen with 58 (31.2%) women and 54 (22%) men using physical therapies. Those patients with university degrees were significantly more likely to use a manipulative and body-based therapy ($P = 0.001$, OR: 2.24 [1.37–3.67]), whereas those with cGVHD also had a greater odds of use (OR: 1.38 [084 –2.26]).

Traditional Chinese/ayurvedic medicine, reiki, and homeopathy

Traditional Chinese/ayurvedic medicine was used by 15 (3.5%) patients, of which 10 (5.4%) were women and 5 (2.1%) were men. The patients were significantly less likely to take herbal traditional Chinese/ayuredic medicine the more prescription medications they took ($P = 0.023$). Reiki (or "energy medicine") was used by 13 (3%) patients, of which 10 (5.4%) were women and 3 (1.2%) were men. Homeopathy was used by 13 (3.1%) patients, of which 8 (4.4%) were women and 5 (2.1%) were men.

Discussion

In this survey of 583 allogeneic Australian HSCT survivors, over half (54.2%) used at least one CAM. The most common CAM therapies used were vitamin therapies (27.3%) and manipulative body-based therapies (26.0%), with survivors also using mind–body therapies (17.2%), dietary modification (13.6%), and herbal supplementation (13.5%). This usage is consistent with internationally reported CAM usage in cancer patients [6, 11]. The types of CAM therapies used by HSCT survivors in our study are similar to those used by cancer patients, with vitamins, manipulative body-based therapies, and herbal supplementation used more often than other CAMs.

Few participants (3.1%) reported using homeopathy compared to other studies in cancer patients, which report usage up to 10% [12]. This may reflect low rates of homeopathy usage in Australia compared to the United States, and/or the results of recent efforts by the Australian NHMRC (National Health and Medical Research Council) which released an advisory noting the absence of evidence for homeopathy and calling for restrictions on education and health insurance subsidies of homeopathy [13]. At the same time it is of some concern that only half of responders reported taking calcium (47.8%) and vitamin D supplements (56.7%), given that these have shown to be beneficial in this high-risk patient group [14].

As has been documented in other studies of CAM use, both in the general population and in cancer patients [6, 11, 12], we found a higher proportion of CAM usage by women (across all CAM subgroups), those with a university education and people living in a major city (which may be due to a lack of access to CAM in remote regions and smaller towns). We did not see any correlation between CAM usage and cGVHD or patient age. Although a cohort study using a questionnaire risks selection bias, with such a large response rate (76%) of our patient cohort of all contactable HSCT survivors over a 13-year period, we believe selection bias is minimal and this is an accurate proportion of CAM usage.

Given the number of HSCT survivors taking CAM therapies, it is important to be aware of the potential harms CAM therapies may have, including interactions with conventional allogeneic therapies, particularly immunosuppressants and antifungals, as well as risks of

manipulative therapies in patients with underlying bone disease and potential harm of overuse of vitamins [15–17]. Other direct toxicity with CAM usage including diarrhea and vomiting are also a particular concern in transplant recipients as they may exacerbate concurrent gastrointestinal disease including cGVHD [16]. It is also possible that by increasing polypharmacy and the pill burden experienced by allogeneic HSCT survivors (a group already taking a large number of supportive care medications), CAM therapies may also increase the likelihood of nonadherence [18]. Alternatively, several randomized controlled studies, particularly mind and body interventions were found to have potential benefits in this patient group [9]. For example, Takatsuka et al. demonstrated a beneficial effect of fish oil on the incidence of graft-versus-host disease (GVHD) in patients after HSCT [19] and two studies have found a significant positive correlation between massage therapy and a decline in anxiety and depression level in patients after HSCT [20, 21]. Although our subgroup analysis did not replicate these results, with no significant differences in CGVHD or FACT-BMT scores, the design of the study was inadequate for this purpose; rather it has demonstrated that a large proportion of HSCT recipients are using these CAMs up to 10 years posttransplant.

It is crucial that CAM usage is routinely assessed as part of HSCT long-term follow-up (LTFU). While the decision to use a CAM always remains the right of the patient, it is essential that this decision to do so is informed. These results definitively demonstrate a large proportion of HSCT survivors are using one or more form of CAM therapy. Given the potential benefits demonstrated by small studies of specific CAM therapies in this patient group, as well as clearly documented therapies with no benefit or even toxicity, this result shows there is a large unmet need for additional studies to ascertain efficacy and safety of CAM therapies in this growing population.

Acknowledgments

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Conflict of Interest

None declared.

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13.5. Synopsis

This manuscript provides the largest and most comprehensive account of CAM use post allogeneic BMT in Australia. The results indicate that CAMs are commonly used by Australian BMT survivors, particularly by women, those who live in metropolitan areas, those with a university degree, those with bone disease and those who routinely see a psychologist or physiotherapist. Interestingly, we did not find any correlation between physical (co-morbidities (excluding bone disease) and cGVHD) and/or psychological (FACT-BMT scores) distress and CAM use, suggesting either that survivors were not using these CAM therapies to relive physical or psychological symptoms, or that CAM therapies were effective in doing so. This raises questions as to the adequacy of BMT care in meeting the psychological, physical and/or spiritual needs of BMT survivors.

The insights provided by the study are critically important both because data relating to CAM therapy use in Australian BMT recipients has previously not been available, and because assessment of CAM use is not routinely a part of post-BMT assessment or BMT care. This is, of course, because assessment of CAM therapy use is not recommended by international or national screening and preventive care guidelines for BMT LTFU(1, 2). Given its wide-spread use in both the general population and in cancer survivors(3) and the lack of data with regard to its safety and efficacy, this study suggests that CAM therapy use can no longer be ignored by researchers, clinicians and policy makers. The results of recent research which suggest that CAM use by patients with cancer may be associated with lower rates of treatment adherence and higher risk of death provide a further incentive to closely examine the use of CAMs in BMT recipients(4).

BMT recipients must have a full understanding of the impact that BMT will have on their lives and must be empowered through education to take steps to improve their post-transplant outcomes. The importance of adhering to therapeutic recommendations made by the transplant team, informing clinicians about their use of over-the-counter (OTC) products and CAM therapies, and avoiding CAM therapies that may compromise their health, must be emphasised to BMT recipients both pre and post-BMT. This requires not only a willingness on the part of BMT clinicians to discuss CAM use, but also an awareness of why BMT patients use CAM and what risks and benefits may be associated with their use. This should be the subject of ongoing research.

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Chapter 14: Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all?

14.1. Chapter overview

This chapter reports on the lived experience of BMT survivorship. It consists of a published manuscript entitled, 'Haematopoietic stem cell transplantation survivorship and QoL: is it a small world after all?'. The manuscript reports on the qualitative analysis of responses to a single question put to BMT survivors, 'What would you say are the three things that have had the most impact on your quality of life since your transplant (or that cause you the most distress)?' The purpose of this open-ended question was to elicit qualitative data not currently captured by standard psychometric measures of QoL post-BMT by allowing BMT survivors to describe in their own words and without direction or constraint, how BMT had impacted upon their lives.

The results of this study demonstrate that BMT has a significant and pervasive impact on the lives of long-term survivors of BMT and on their perceptions of their QoL. In broad terms survivors described a 'shrinking life world' post-BMT with five common themes identified from participant responses; the 'failing body' and diminishing physical effectiveness, the 'changed mind', the 'loss of social connectedness', the 'loss of functional self' and the sense that a BMT patient was a 'patient for life'. These findings have profound implications for many aspects of BMT including the policies and processes and content of consent to BMT, and the education, counselling and support of BMT recipients and their families' pre and post-BMT. The findings are of methodological significance as they also suggest that a single open-ended question may encourage BMT patients to talk about their fears and about the things that are impacting most on their QoL. This is important, not simply because it may be used to study the QoL of BMT survivors, but also because it suggests the clinical utility of a single question in each routine post-BMT clinic appointment, and therefore has clinical utility in routine post-BMT care.

14.2. Publication details

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14.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

14.4. Manuscript

The published version of the manuscript follows.

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ORIGINAL ARTICLE

Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all?

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Abstract
Purpose The aim of this qualitative study was to gain a rich understanding of the impact that haematopoietic stem cell transplantation (HSCT) has on long-term survivor's quality of life (QoL).
Method Participants included 441 survivors who had undergone HSCT for a malignant or non-malignant disease. Data were obtained by a questionnaire positing a single open-ended question asking respondents to list the three issues of greatest importance to their QoL in survivorship. Responses were analysed and organised into QoL themes and subthemes.
Results Major themes identified included the following: the failing body and diminished physical effectiveness, the changed mind, the loss of social connectedness, the loss of the functional self and the patient for life. Each of these themes manifests different ways in which HSCT survivor's world and opportunities had diminished compared to the unhindered and expansive life that they enjoyed prior to the onset of disease and subsequent HSCT.
Conclusions HSCT has a profound and pervasive impact on the life of survivors—reducing their horizons and shrinking various parts of their worlds. While HSCT survivors can describe the ways in which their life has changed, many of their fears, anxieties, regrets and concerns are existential in nature and are ill-defined—making it exceeding unlikely that they would be adequately captured by *standard* psychometric measures of QoL post HSCT.

Keywords Quality of life · Bone marrow transplantation · Haematopoietic stem cell transplantation · Cancer

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Haematopoietic stem cell transplantation (HSCT) is a demanding therapeutic intervention used in the treatment of a range of life-threatening malignant and non-malignant diseases, with high treatment-related mortality. For those who survive, their lives are often complicated by a wide range of debilitating physical sequelae, with over 90 % of HSCT survivors experiencing at least one serious late adverse effect of treatment [1]. The coexistence of multiple late sequelae, particularly chronic graft-versus-host disease (cGVHD), is widely recognised as having a profound impact upon HSCT survivor's quality of life (QoL). Therefore, obtaining QoL information is a crucial part of the assessment of treatment success, as improved overall survival is no longer the only factor relevant to the evaluation of a *successful* medical outcome.

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Recent reviews of QoL post HSCT have concluded that many aspects of the individual's physical, functional, social and psychological QoL improve despite high symptom burden [2–5]. Typical concerns of HSCT survivors include compromised fertility and sexual functioning, fatigue, cognitive declines and physical and emotional distress [2–4, 6, 7]. Fear of recurrence, the challenge of managing uncertainty and frustration at loss of control are also commonly cited psychological sequelae of post-HSCT survivorship [8, 9]. Inevitably, each of these challenges can compromise the survivor's social roles and identity and may have significant implications for their social interactions and relationships [10–13].

Previous research has highlighted the deleterious impact that late-onset and persistent adverse effects of HSCT may have on survivor's daily functioning and the intense frustration that survivors may feel as a consequence of these limitations and the intractable unpredictability of recovery [14]. Despite the challenges that HSCT survivorship brings, many survivors, however, are still able to reflect on the positive, transformative nature of HSCT and experience a renewed appreciation for life, a renegotiation of priorities, an enhanced spirituality, liberation from hospitals and the possibility of returning to study/work [15, 16]. While the experience of illness, survival and limitation may encourage many patients to reflect on their own lives and on the *human condition*, it remains the case that many survivors, particularly those dealing with the effects of chronic GVHD, struggle with the limitations on their lives and functioning as a consequence of the adverse sequelae of HSCT [17, 18]. Indeed, a review of the literature reveals how patients report being surprised by the severity and duration of distressing side effects particularly as it impacts on their ability to return to activities of daily living such as driving and returning to education or employment [14, 19].

While the concept of a 'shrinking life world' has been used to describe the patient's experience in a range of chronic illnesses, including the way in which illness may disrupt or diminish employment, restrict or limit social interactions and erode an individual's self-concept [20], this concept has yet to be explored in the context of HSCT survivorship. In part, this may be a consequence of what is known about long-term survival post HSCT, as the vast majority of studies reporting on the QoL of HSCT survivors are quantitative studies, and often retrospective registry reviews, and rely upon a limited range of measures to assess QoL. While such studies provide important and useful information about QoL, at the same time, they often fail to fully capture the ways in which survivor's lives have changed, including the existential and often ill-defined regrets, concerns, fears and anxieties that they experience. Although a number of important qualitative studies have provided some insights into the *everyday* challenges of survivorship [6, 14, 21, 22], there is also no doubt that more qualitative exploration of HSCT survivorship needs to be done in order to guide the development of models of care to improve symptom management, identify survivors at increased risk of poor QoL, provide opportunities for early intervention and help both health professionals and survivors with medical decision-making. This study describes the qualitative insights gained by asking a population of long-term survivors of HSCT a single open-ended question about the quality of their life post HSCT.

Methods

The study sample was selected from allogeneic haematopoietic stem cell transplantation databases of the four major adult metropolitan hospitals in New South Wales, Australia, that perform HSCT. Participants were eligible if they were ≥18 years of age and had undergone an allogeneic BMT between 1 January 2000 and 31 December 2012 and could read and write English. Consenting participants were given the option to self-complete the questionnaire or to complete a telephone interview with one of the researchers. A second round of telephone calls was made to consenting participants who had not returned the survey within a month. A total of 1475 allogeneic HSCT were performed in the study period. Of the 669 recipients known to be alive at study sampling, 583 were contactable and were sent study packs and 441 returned the completed survey. No respondent opted for a telephone interview. Three percent declined participation. Demographic characteristics of the study respondents are depicted in Table 1. The study was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD Reference: 1207-217M).

In order to capture the diversity of responses and to avoid a positive or negative bias, data was obtained by positing a single open-ended question asking respondents to list the three issues of greatest importance to their QoL post HSCT. Responses to the QoL question were copied verbatim, maintaining confidentiality, into a word document. The analytical framework used for initial coding was guided by the model of QoL conceived by Ferrell et al. [23]. We further refined the thematic scheme through multiple readings and line-by-line coding. Initially 232 codes were identified. The codes were then grouped together with codes of similar meaning. The consolidated codes were further condensed to five common themes: the failing body and diminishing physical effectiveness, the changed mind, the loss of social connectedness, the loss of the functional self and the patient for life. The first and last authors performed the analysis, but final agreement on the themes was only reached after three other authors had independently read and provided commentary on both the codes and the characteristics of each category. Qualitative analysis was performed on NVivo software.

Table 1 Patient demographics and clinical characteristics

Characteristics	No. of patients (%)
Age group	
19–29	30 (6.8)
30–39	49 (11.1)
40–49	83 (18.7)
50–59	130 (29.5)
60–69	127 (28.7)
>70	22 (5.0)
Median; range	54; 19–79
Gender	
Male	250 (56.7)
Female	191 (43.3)
Culture, ethnicity	
Australian/European	323 (73.2)
Indigenous Australian	2 (0.5)
Asian	30 (6.8)
Middle Eastern	7 (1.6)
Other	10 (2.3)
Unknown	69 (15.6)
Years since transplant	
<2	58 (13.1)
2 to >6	204 (46.3)
6 to <10	117 (26.5)
≥10	62 (14.1)
Median; range	5; 1–14
Underlying diagnosis	
AML/ALL	226 (51.2)
CML/MDS/myelofibrosis	60 (13.6)
Other	137 (31.1)
Unknown	18 (4.1)
Remission status	
CR1/CR2	271 (61.4)
>CR2	22 (5.0)
Other	46 (10.4)
Chronic phase	18 (4.1)
Accelerated phase and blast crisis	3 (0.7)
Refractory	22 (5.0)
Partial remission	23 (5.2)
Unknown	36 (8.2)
Donor type	
Sibling	250 (56.7)
Haploidentical	10 (2.3)
Matched unrelated	158 (35.8)
Mismatched unrelated	21 (4.8)
Unknown	2 (0.4)
Stem cell source	
Bone marrow	48 (10.9)
PBSCT	381 (86.4)
Cord	12 (2.7)

Results

While some survivors experienced relatively good QoL post HSCT, many struggled with pervasive and unrelenting side effects. The overwhelming theme evident in the responses of those struggling with QoL was that their world and opportunities had become profoundly diminished compared to the life they enjoyed prior to disease and HSCT. (A selection of participant quotes exemplifying the themes are detailed in Table 2.)

The failing body and diminishing physical effectiveness

The majority of respondents reported that the toxicity and immunosuppression associated with HSCT resulted in a plethora of long-term impairments of survivor's physical, emotional and psychosocial function. A considerable number of survivors reflected on the impact of cGVHD. Reference to GVHD was frequently linked to comments highlighting the unrelenting implications for the individual's physical, social and psychological functioning. A large number of survivors reflected on the physical burden of transplant which was often associated with reduced emotional and social functioning including, inter alia, fatigue, employment, depression and declines in socialisation. Some respondents reflected that their social world had shrunk as a consequence of their physical restrictions and incapacity to regain fitness. Many reflected that the complications of transplant transformed their personal world and their intimate relationships, particularly their sexual identity, sexual functioning and fertility. A large number of women reported early onset of menopause, decreased sexual enjoyment, reduced fertility, vaginal dryness, irritation, pain and bleeding, while some men reported erectile dysfunction, lowered libido and decreased sexual enjoyment. Infertility and reports of sexual dysfunction were often linked to the survivor's low mood, poor self-esteem and relationship difficulties. The impact of HSCT on fertility, sexuality, identity and physical function led some respondents to reflect on the difficulty they faced in trying to secure future relationships. Despite many respondents reflecting on the persistence of significant medical complications and the functional limitations that compromised their QoL, the vast majority of respondents reported feeling a deep appreciation for life post HSCT.

The changed mind

Many survivors noted a range of mood changes post transplant including anger, frustration, anxiety and depression. Some survivors linked mood disturbances to social isolation. Several HSCT survivors also described cognitive changes following HSCT, including memory deficits, decreased concentration and attention, mental fatigue and reduced reaction times. Some survivors linked these cognitive impairments to

Table 2 A selection of participant responses to QoL question: What are the three things that have had the most impact on your quality of life since your transplant?

1. The failing body and diminishing physical effectiveness
"GVHD had the biggest impact on my QoL. In particular it attacked my tear glands and saliva glands – both no longer work. I have dry eyes and much discomfort regularly in my eyes. I can no longer drive, watch TV or read or go on the Internet because focusing my eyes hurts and my eyes are very sensitive to all forms of light. Earlier this year, my eyes really affected my mental health and it made me depressed."
"I just don't have the same amount of energy. I feel as if I only have 60 % of my energy since my SCT. This frustrates me…. It took me a long time to listen to my body and rest when I am tired, It does frustrate me as prior to the SCT I was always on the go. We don't plan things too often. I see how I feel when I wake up and if I have the energy, we go out for the day. I feel like my lack of energy rules my life."
"Prior to my transplant I was fit and healthy and now find I am unable to regain the fitness which means I can only do fitness activities including work, sport and leisure for short periods before tiring and requiring a rest. This lack of fitness makes it difficult to find suitable employment for my trade."
"My hormone levels are all over the place. My libido is very low. I've tried different things to help but nothing is helping and it is becoming a problem in my marriage. I am 28 and going through menopause. It is really hard and depressing. I wish I knew this before treatment."
"Finding a woman who will like me for who I am and not judge me for what I have been through…"
"I enjoy everyday. Some days I need to lie down for a few hours due to fatigue and body aches. But, I am so happy and live my life to the fullest. I have accepted that I will need ongoing health checks and I am very grateful for the opportunity to undergo the transplant."
2. The changed mind
"Anxiety & depression – I don't sleep, am always fearful, nervous and on-guard. I don't cope with little things. It's a big change to my personality. I withdraw from social situations."
"Feels like my memory is foggy. Sometimes unable to find the word or form a sentence properly. Unable to remember as well as I did prior to transplant. I feel I wouldn't be able to cope with a high pressure role. I find multi-tasking difficult and get stressed easier and am unable to juggle tasks and live like I used to."
"Fear of recurrence, further side effects and additional problems with health. This fear has restricted my social life and how I react with my family."
"I feel that my disease has set me back in my life so much for me and my family. We have lost 5 years of our lives and it has crippled our future plans and our dreams as a family. Everyone seems to be moving forward except for us. So much time lost…."
"It took quite a long time to rediscover my old self. Who I am? What am I supposed to do, act and feel? I felt like a non-entity and this was my main concern. Five years after BMT and I am only now coming to terms with my old/new self."
3. The loss of social connectedness
"The most important factor in my successful recovery was the love, support and encouragement of my wife, son and close friends. I cannot imagine how anyone would survive a BMT and the complications that follow it on their own."
"Feeling that I am a major drain on my wife's time and lifestyle, even though she does it all willingly and doesn't feel that way."
"Changes in family relationships – There is a distance between me and my wife and each of my 3 children…. I feel I have a disconnect."
"I am reliant on others. Losing my independence. Not knowing if I may have a dizzy turn means I am restricted as to what I do or try. Having been totally independent and self reliant prior to AML it is difficult to take a complete 180 turn around."
4. The loss of the functional self
"I've tried to work lasted one day put me back 3 months aggravated the GVHD. Working or not working is probably number 1 on the list. I won't go back to the position I held before the illness, or work again unless my mind gets better… It is killing me mentally and physically."
"I have reduced my workload in a limited way. I was formally the managing partner of my law firm – Now I have reduced responsibilities and I sometimes feel I have lost some respect. I also feel my firm has suffered from my new role and I could have done it better."
"Not being able to work. Less household income. Difficult to pay bills and medical expenses. Plus isolation, no longer having access to work, friendships and support. Loneliness and isolation."
"I have lost everything, my home, all my savings because it has been a very long treatment in and out of hospital for about 1 year for blood transfusions and had spleen removed, lots of costs for hospital parking and other things."
5. The patient for life—the unrelenting nature of follow-up
"Travel to the transplant unit sometimes monthly, fortnightly and at the moment twice weekly. I cannot work and my wife has had to stop work to become my full time carer. The large regime of medication I take to try and control GVHD and the side effects of medications are numerous and debilitating. I am always fatigued and cannot get motivated. I get over one thing and something else appears. There seems to be no end."
"I feel I need to be near my medical team and this restricts the distance I can travel from home. I am very wary as to where I go in case the communication with the team is not there, so I live in my safety zone."
"Running to doctors all the time, going to the hospital all the time, doctors in the country hospitals have no idea what's wrong, or what to do, even when told by the transplant team. They just don't care up here in the bush. One of the doctors was told by my team how to treat GVHD, but did nothing for 14 days."
"My local GP has caused me unnecessary anxiety due to his inability to cope with my situation. I feel he is lost and a bit afraid in dealing with me to the extent I have lost confidence in him. An example is my vaccination requirements where I had to fight to get the required vaccinations even though they were listed for him."
"I have a great relationship with my local doctor where I can have a conversation rather than just a consultation – this enables me to make health decisions that are supported an acknowledged."

SCT stem cell transplant, *BMT* blood and marrow transplant (these terms are synonymous with HSCT and can used interchangeably), *AML* acute myeloid leukaemia

problems with employment and relationships. One of the most dominant emotions expressed by many respondents was fear—the fear of disease recurrence, the fear of chronic GVHD and the fear of secondary malignancies occurring post HSCT. According to several subjects, this created enormous distress. For some subjects, this deep and pervasive fear made them reluctant to take risks or plan for the future, which further perpetuated shrinking opportunities in their life.

The loss of social connectedness

Perhaps unsurprisingly, family and friends featured prominently in respondents' descriptions of their QoL post HSCT,

with many emphasising the importance of both the physical and emotional support they received from significant others throughout both treatment and survivorship. At the same time, however, many subjects described the terrible impact that HSCT had had on their loved ones and the guilt that they felt about the way HSCT had changed not only their own lives but also the lives of those close to them. Some respondents also noted the degree to which they were dependent—physically, emotionally, socially and financially—upon others and the way that this made them feel.

The loss of the functional self

Many respondents reported an association between undergoing transplant and the loss of some of the certainties that most people take for granted—like health, stable relationships, sustained employment and financial security. For some, the loss of employment and the loss of capacity to work were linked to their sense of self-worth. Indeed for many subjects, work, while previously a central part of their lives, had become stressful and exhausting. Many survivors reported missing numerous workdays due to ill health, and some reported a loss of career momentum including the necessity to change their job or *downsize* to part-time job. Numerous subjects also reported that they were unable to return to work at all, with many describing how these changes caused them further distress including anxiety, depression and impairments in social functioning. A few survivors also reflected on the financial burden of HSCT including the loss of income. References to the financial burden of transplant were often linked to comments regarding the patient's sense of self-worth and financial security.

The patient for life—the unrelenting nature of follow-up

Many survivors described the burdensome requirement of life-long follow-up to prevent, identify and treat the myriad of late effects that complicate transplant survival. Some reported on the redirection of their attention from broader life issues to an intense focus on health and well-being. Some reflected on the restrictions in their life perpetuated by the unrelenting nature of follow-up including loss of productive function, social isolation and a diminished self-concept. Importantly, while many reflected on the fact that long-term follow-up (LTFU) was onerous, some respondents recognised how necessary it was and described how much they relied upon access to multidisciplinary long-term care and the expertise available through their transplant centre. Some survivors stated their desire to live within a safe distance from their transplant centre. This specification was often linked to the individual's anxiety about the uncertainties and dangers posed by the future.

A few survivors felt that the special expertise, knowledge and care provided by their haematologist and HSCT team were simply not available elsewhere. In many cases, this sense was heightened by adverse experiences that HSCT survivors had experienced before transplant and subsequent to it. This was particularly true for patients living in rural, regional or remote areas. Concerns regarding lack of expertise and knowledge were not, however, specific to those living in rural areas, with a few survivors expressing concerns regarding the lack of knowledge of their general practitioners. Importantly, however, even though some expressed concerns about their local doctor, others were very grateful for their relationship with them.

Conclusions

As survival following HSCT has improved, attention has increasingly turned to the impact of HSCT upon recipients' QoL and their experience of *survivorship*. Although a number of quantitative studies suggest that those who survive at least 1–2 years following HSCT have an acceptable QoL [2–5], it is clear that long-term survivors of HSCT face ongoing challenges and experience limitations in many domains of their life. By asking survivors one simple question—to describe the three complications of HSCT that have had the most impact upon their QoL—we were rewarded with a rich picture of the challenges of survivorship. What was clear from the accounts provided by HSCT survivors in this study was that QoL was most impacted by the physical burden of the failing body, the cognitive and mood changes, the diminished social connectedness, the loss of functionality and the burden of being a patient for life. These QoL challenges were shown to shrink various aspects of the HSCT survivor's world—restricting not only their capacities and function but also their identity and relationships. While existing literature has described the changes in self-concept and the loss of identity associated with reductions in HSCT survivor's ability to perform everyday functions of living, this is the first study to conceptualise these *losses* in terms of a shrinking life world [24, 25].

Many respondents to our study reported feeling a sense of dislocation and isolation in the years following their transplant—a sense heightened and perpetuated by their real or perceived fear of infection and GVHD. The functional impairments suffered as a result of overwhelming fatigue were also ubiquitous. Prior research has identified that GVHD and fatigue often compromise survivor's QoL for many years post transplant and are a frequent cause of mood disturbance [3, 4, 24]. For some survivors, this physical and psychological debility was so severe that they felt they had lost their sense of identity, independence and self-worth and were unable to fulfil the social, familial and professional roles that marked out 'who they were' before their HSCT. For others, fears about

their capacity to cope intensified their degree of dependence—binding them to their transplant centre and to the healthcare professionals that they trusted and preventing them from seeing a world beyond the geographical and emotional 'gaze' of their medical care. Not surprisingly, many survivors were distressed by their loss of function, particularly as it compromised those things that provide certainty and stability, like sustained employment and financial security. This is an important finding and is consistent with other recent studies that have highlighted the ongoing challenges associated with job insecurity, discrimination, career derailment and delayed goals, financial loss and instability and constraints on job mobility [19].

According to the literature, family and friends play an important function in providing social support. However, patients also worry that they may become a burden to others. One study concluded that some survivors felt their inability to contribute to the family and their lack of productivity made them feel useless [11]. These findings were consisted with the results of this study which highlighted both the importance of family to survivors and the guilt they experienced as a result of their physical, emotional, social and financial dependence. While prior to HSCT many haematologists and allied health professionals encourage survivors to consider the possibility that they may become 'a patient for life', in reality, it is difficult, if not impossible, to convey what this actually *means*, what impact transplantation may have on every aspect of a survivor's life, how unrelenting follow-up may feel and how difficult it may be for survivors to adapt to their post-HSCT challenges. Previous studies have concluded that while many survivors report adequate QoL, many do not believe they have returned to normal [25]. However, this is not to say that survivors of HSCT (particularly those that modify their expectations and accept that their lives are different post HSCT than they were beforehand) do not adapt, do not resume *normal activities*, do not cope with the uncertainty implicit in survival post HSCT or do not accommodate the need to cease or downsize their employment or modify their relationships and social roles [23]. Rather, it is to acknowledge that some survivors of HSCT will be more profoundly impacted upon than others by their failing body, impaired cognition, emotional distress and social isolation [3, 4].

Previous research has highlighted the important role that pre- and post-transplant education may play in improving the QoL of HSCT survivors and in enabling them to learn strategies to assist them cope with the changes in their lives [14]. As a result, it is now generally recognised that transplant centres should endeavour to incorporate education, counselling and support into every stage of the transplant recipient's journey [14]. But information in any form is very different to personal experience. It is one thing for a patient who is shortly to undergo a HSCT to be told by the transplant team that they have a 60 % chance of developing chronic GVHD but a very different thing to experience it. And it is one thing to record the frequency or numerical grade or extent of HSCT complications but another thing again to describe in one's own words what it is to experience them. While it is important to collective quantitative measures of QoL, it is also crucial to recognise the limitations of this form of data and supplement it with qualitative data that may reveal the full extent and meaning of the challenges to HSCT survivors' QoL.

The results of this study are important not simply because they contribute to the growing qualitative literature on post-HSCT survivorship but because it suggests that a single question may provide important insights into the experience of survival post HSCT. And this is important, because, unlike hour-long in-depth interviews, time could be found in the *routine* follow-up of HSCT survivors to ask them a question about how they are coping and what is of most concern to them. This study has some very clear limitations that caution against over-generalising the results to all HSCT survivors. Our analysis was based upon written responses to a single question about QoL, and we did not use other qualitative methods, such as in-depth interviews or ethnographic methods that would have undoubtedly provide a more nuanced account of the experience of survival post HSCT. But while other qualitative methodologies may have provided more detailed accounts of the experience of survivorship, the use of a single question prompt in this study to elicit qualitative descriptions of post-HSCT survivorship suggests other benefits. Firstly, our results suggest that asking a single, very specific question of HSCT survivors about their QoL may enrich and triangulate the quantitative description of survivorship provided by other psychometric measures of QoL commonly used in post-HSCT follow-up. And secondly, our results provide the possibility of translation, as unlike complex surveys or in-depth, unstructured interviews, regularly asking a patient to describe the main things that are having an adverse impact upon their QoL may be easily done, have clinical utility and have limited resource costs.

It is clear from the accounts provided by the respondents to this survey that while HSCT provides enormous benefits, it also is enormously challenging and may have a range of complex impacts upon the QoL of HSCT recipients and upon their experience of survivorship. While many will cope, and adapt, and continue to cherish the life they have, the vast majority will face challenges along the way. While better education of HSCT recipients may help the work that survivors need to do post HSCT, it is unlikely that it will ever be able to completely prepare HSCT recipients for what lies ahead. In these circumstances, what may be most important is for HSCT services to acknowledge and understand the pervasive impact of HSCT and offer reassurance that no matter what occurs, whether expected or unanticipated, they will always be available to provide care and support.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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14.5. Synopsis

This manuscript provides the largest qualitative account of the impact of BMT survival on long-term QoL. The results indicate that while survivors QoL scores improve post-BMT(1) and may be similar to quantitative evaluations of the QoL of the general population, when asked to describe the impact of BMT on QoL in their own words, many survivors describe continued and pervasive physical, psychological, social, financial and existential impacts of BMT. Further, while many survivors reported feeling enormously appreciative that they were alive, their experience of survivorship was punctuated by regrets, concerns, fears, anxieties and shrinking opportunities, a result of, *inter alia,* cGVHD, infection risk, under/unemployment, and the loss of family and social roles and identity.

While there are many studies that report quantitative data on the QoL of BMT survivors, there is by comparison relatively little qualitative data. In this regard the results of this study make a significant contribution to what is known about the experience of long-term survivorship. While it is tempting to feel that survivors of BMT have succeeded simply by virtue of 'surviving in the face of death' – data like those described here provide a richer and more complex account of what it is like to live post-BMT and what life is like when constrained by the late effects of BMT. These insights make BMT much more than a medical intervention – reminding us that BMT is personal, intimate, relational and social and profoundly changes survivors' world and world view. The incredible richness of the data here – elicited by asking respondents just one question – also reminds us how the care of BMT patients many be enlightened if clinicians are willing to ask their patients open questions about the impact of treatment on their QoL, and how this may paint a much richer picture than any form of psychometric survey. Indeed if post-BMT care is changed in this small way – by making space for hermeneutic enquiry – post-BMT care may be transformed and the education, counselling and support provided to this vulnerable and high-risk group can be made more targeted and more personal.

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Chapter 15: Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia

15.1. Chapter overview

This chapter reports on issues relating to nutrition, body weight and body image in long-term survivors of BMT, and their impact on QoL. It consists of a published manuscript entitled, 'Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia'. The manuscript reports on demographics, socioeconomics, transplant factors and co-morbidities associated with gastrointestinal symptoms (GI), body weight and body image and the correlation of these with BMT survivors' QoL. Specifically, survivors were asked about nausea, vomiting, constipation/diarrhoea, taste and smell alterations, poor appetite, mouth ulcers and dry mouth post-BMT, to report their current height and weight (to allow calculation and categorisation of BMI), and to reveal whether they were happy with their current weight.

The results of this study demonstrate that survivors of BMT continue to experience GI and oral and nutritional symptoms long after transplant, and that some symptoms do not diminish even years after BMT. The results also demonstrate that QoL is significantly negatively impacted by GI symptoms, that many (almost half) of long-term BMT survivors are overweight or obese, and that most report returning to (healthy and unhealthy) pre-BMT eating habits. These findings highlight the importance of dietary education, nutrition review, and weight assessment long-term post-BMT, and suggest that an integrated, multi-disciplinary approach may be needed to reduce the prevalence of obesity, metabolic syndrome and CVD post-BMT.

15.2. Publication details

Smith J, Poon C, Gilroy N, Kabir M, Brice L, **Dyer G**, Hogg M, Greenwood M, Moore J, Hertzberg M, Brown L, Tan J, Huang G, Kwan J, Larsen S, Ward C and Kerridge I. "Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia". *Support Care Cancer.* 2017;25(1):137-44.

15.3. Authors' contributions

GD co-designed the study, recruited study participants, collected data, interpreted the results and drafted the manuscript. A signed Statement of Contribution from all authors is in Appendix A.

15.4. Manuscript

The published version of the manuscript follows.

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ORIGINAL ARTICLE

Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia

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Abstract

Purpose The aims of this study were to describe the long-term nutrition, body weight and body image issues facing survivors of Allogeneic Blood and Marrow Transplant (BMT) and their impact on quality of life. It also describes survivors' perception of enteral feeding during BMT.

Methods Four hundred and forty-one survivors who had undergone a BMT in NSW, Australia between 2000 and 2012 (n = 441/583) completed the Sydney Post BMT Study Survey (SPBS).

Results Forty-five percent of survivors less than 2-year post-transplant reported a dry mouth, 36 % reported mouth ulcers and 19 % had diarrhoea. This was consistent across all survivor groups, regardless of time since transplant. Patients with one or more gastrointestinal (GI) symptoms had significantly lower quality of life scores. There was a significant difference in quality of life scores when comparing those with no GI symptoms to those with one or more symptoms (P = <0.0001). Quality of life was significantly higher in those who once again enjoyed mealtimes (P < 0.0001). Males were more likely to be satisfied with their body weight compared to females (P = 0.009). The median body mass index (BMI) for all patients reporting body weight satisfaction was significantly lower (BMI 23.5) than those reporting dissatisfaction (BMI 27.5) (P = <0.0001). Survivors who had a normal BMI had significantly higher rates of body weight satisfaction compared to underweight, overweight and obese survivors (P = <0.0001). Those survivors who were overweight or obese were significantly more likely to be diabetic (P = 0.008).

Conclusion This study revealed an important relationship between gastrointestinal symptoms, body weight and body image and survivor's quality of life. It provides further support for the importance of nutrition therapy post-BMT.

Jennifer Smith and Christine Poon contributed equally to this work

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Keywords Blood and marrow transplantation- BMT · Cancer survivorship · Nutrition · BMI · Late complications · Quality of life

Introduction

Survivorship from allogeneic Blood and Marrow Transplant (BMT) continues to improve through advances in histocompatibility testing, conditioning regimes, supportive care and the management of Graft-versus-Host Disease (GVHD) [1]. Although BMT provides children and adults with a range of malignant and non-malignant disease with their best chance of survival, it is still associated with significant rates of morbidity and mortality [2–4]. There is increasing recognition that the survivors of BMT experience a wide range of complications including cardiovascular disease [5], metabolic syndrome [6], endocrine dysfunction [7], renal impairment [8], liver dysfunction [7], chronic Graft-versus-Host Disease (cGVHD) [9] and compromised functional status [7].

Routine nutritional assessment and management is an essential component of supportive care for patients undergoing BMT [10]. Malnutrition prior to BMT has been linked to an increased length of stay and trend towards higher mortality [11]. Early adverse side effects such as oral and gastrointestinal complications can induce nutrition-related symptoms which in turn reduce a patient's ability to tolerate adequate oral intake leading to weight loss and a decline in nutritional status. For these reasons, it is generally accepted that oral, enteral or parenteral nutritional support during BMT is essential to prevent further deterioration in nutritional status [12]. Impaired nutritional status is associated with reduced quality of life, lower activity levels, an increase in treatment related symptoms, reduced tumour response to treatment and reduced survival [13].

Although nutrition support is an established part of supportive care prior to and during BMT [14], little is known about the long-term nutritional issues facing survivors. Urbain et al. [15] described the nutritional status and body composition in the first 100-day post-BMT, but there is limited published data describing nutrition status beyond this. Few studies have also investigated the link between nutritional, body weight and body image issues on survivors' quality of life.

The primary aim of this study was to describe the nutritional, body weight and body image issues facing survivors of allogeneic BMT and the impact these have on quality of life. Nutritional issues of interest included salient gastrointestinal symptoms, changes in dietary habits post-BMT, use of nutritional supplements/natural therapies and rates of overweight and obesity. The secondary aim was to describe BMT survivors' perception of enteral feeding during BMT.

Methods

Study population

All adult survivors (≥17 years) who had undergone an allogeneic BMT between 1 January 2000 and 31 December 2012 in New South Wales, Australia, and who were at least 12-month post-transplant were eligible to participate in this cohort study. Patients were excluded if they could not read or write English. Signed informed consent was obtained from all participants. This study was approved by the Northern Sydney Coast Human Research Ethics Committee (NSLHD Reference: 1207-217M).

Study design

Eligible participants were identified from the BMT databases at each of the allogeneic transplant hospitals in NSW, Australia. Patients were informed about the study at their clinic visit or via a telephone call from one of the researchers. Participants were given the study pack containing an invitation letter, a patient information sheet and consent form, the questionnaires and a stamped self-addressed envelope. All participants were given the option to self-complete the questionnaire or to complete it via a phone interview with one of the researchers.

Participants completed the Sydney Post BMT Study Survey (SPBS), the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT Version 4) [16], the Chronic GVHD Activity Assessment–Patient Self Report (Form B) [17], the Lee Chronic GVHD Symptom Scale [18], DASS21 [19], the Post Traumatic Growth Inventory [20], and the Fear of Recurrence Scale [21, 22]. These seven survey instruments were amalgamated into one 20-page document for ease of completion by participants. Once written consent was received from participants, researchers completed the Sydney Post BMT Clinical Data form.

The Sydney Post BMT Study Survey (SPBS) The SPBS was developed by the research team. Item construction was informed by a review of the literature and discussions with patients attending BMT long-term follow-up clinics. It consisted of 402 questions grouped into 20 sections including demographics, medical complications, referrals, tests and assessment and time, medications and treatments, oral and dental health, infections, vaccinations, complementary therapy use, cancer screening, travel history, close personal contacts, lifestyle, diet/nutrition, occupation, infection risk, occupation–work status and functioning, fertility and sexual function, relationships, long-term follow-up care, social, occupational attitudes, physical and psychological concerns and an open text qualitative question. The questionnaire was piloted in clinic and phone interviews to assess face and content validity and to check for comprehension of the survey questions.

Functional assessment of cancer therapy—bone marrow transplant (FACT-BMT version 4) The FACT-BMT is a validated questionnaire for measuring quality of life in BMT recipients [16]. It combines two instruments: the FACT-G and a BMT subscale. The FACT-G (Version 4) is a 27-item self-report instrument that measures quality of life (QOL) in cancer patients [23]. It consists of five subscales measuring physical (seven items), functional (seven items), social (six items) and emotional wellbeing (six items) and satisfaction with the doctor/patient relationship. The BMT subscale includes 10 items designed to test QOL in BMT patients. The FACT-BMT plus the BMT subscale provides an overall quality of life score. Patients rate themselves over the past 7 days using 5-step Likert scales with responses used to calculate overall quality of life and subscale wellbeing scores.

The Sydney Post BMT Clinical Data form A one-page BMT Clinical Data form was developed by the research team to collect information regarding the date of transplant, date of diagnosis and stage at transplant, transplant conditioning, GVHD prophylaxis, stem cell source and donor type of BMT survivors. It contained 10 questions and was completed by the research team.

Statistical analysis

Categorical responses were summarised using frequencies and percentages. Chi squared tests of significance was used for categorical data. Two sample comparisons of means and medians were determined by the independent *t* test and Wilcoxon Rank Sum tests, respectively. Regression analysis was used for examining associations between continuous variables such as FACT-BMT and multivariable regression analysis to control for potential confounders. A two-tailed *P* value <0.05 was considered as the level of statistical significance. Statistical analysis was performed using Stata®_Version 12.1 (Statacorp, Texas). For the purpose of analysis, time periods were separated into three categories: less than 2 years, 2 to 5 years and greater than 5 years. BMI was categorised as per the World Health Organisation: ≤18.5 underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight, ≥30.0 obese [24].

Results

Study population

Patient demographics

A total of 1475 allogeneic BMT were performed during the study period (1 January 2000 to the 31 December 2012). Of those, there were 669 BMT survivors known to be alive at the time of study sampling (29/04/2014). Of the 669 survivors, 583 (83 %) were contactable and were sent study packs. Four hundred and forty-one BMT survivors returned the completed survey, 76 % (441/583) of the total number who were sent the survey. Three percent (17/583) explicitly refused consent.

The median age of the study group was 54 years (range 19–79). Fifty-seven percent of respondents were male (250/441) and 43 % (191/441) female, and the most common cultural group was Australian/European (73 %, 323/441) (Table 1).

Transplant characteristics

The median years post-transplant was 5 years (range 1–14), and the most common underlying diagnosis was acute myeloid leukaemia (AML)/acute lymphoblastic leukaemia (ALL) (51 %, 226/441). The majority of patients (61 %, 271/441) were in complete response/remission 1 (CR1) or complete response/remission 2 (CR2). Fifty-seven percent of patients (250/441) had undergone a transplant from a sibling donor and the most common source of stem cell collection was peripheral blood (86 %, 381/441). Forty-eight percent (214/441) underwent myeloablative conditioning treatments (Table 1).

Cardiovascular comorbidities post-BMT, including hypertension, high cholesterol and diabetes mellitus were reported by 29 % (118/409), 24 % (96/402) and 14 % (57/308) of survivors, respectively. Sixty-nine percent (301/434) of patients reported whether or not they had a chronic GVHD diagnosis since transplant. Of this number, 20 % (61/301) had involvement of the stomach and/or intestines.

Gastrointestinal symptoms and quality of life post transplant

Gastrointestinal symptoms, including nausea, vomiting, constipation, diarrhoea, taste alterations, smell alterations, poor appetite, mouth ulcers and dry mouth, are listed in Table 2. Of note, 48 % (26/58) of survivors less than 2-year post-transplant report an altered taste and a dry mouth, 36 % (21/58) reported mouth ulcers and 33 % (19/58) reported altered smell (Table 2). The prevalence of mouth ulcers and a dry mouth was similar across all survivors regardless of time since transplant whereas alterations in smell and taste were less common in longer term survivors. A poor appetite was particularly common in early transplant survivors (28 %, 16/58) but was reportedly less of an issue in the longer term survivors (18 %, 40/224).

The proportion of survivors with diarrhoea was consistent (~19 %) across all time categories (less than 2 years, 2 to 5 years or greater than 5-year post-transplant). There was a reduction in those survivors reporting nausea and vomiting from less than 2 years to greater than 5 years.

FACT-BMT scores, as a measure of quality of life, declined as the number of gastrointestinal symptoms reported by survivors escalated (Fig. 1). The association between number of gastrointestinal symptoms and quality of life (FACT-BMT

Table 1 Patient demographics and clinical characteristics

Characteristics	No. of patients (%)
Demographics	
Age group	
19–29	30 (6.8 %)
30–39	49 (11.1 %)
40–49	83 (18.7 %)
50–59	130 (29.5 %)
60–69	127 (28.7 %)
>70	22 (5.0 %)
Median; range	54; 19–79
Gender	
Male	250 (56.7 %)
Female	191 (43.3 %)
Culture, ethnicity	
Australian/European	323 (73.2 %)
Indigenous Australia	2 (0.5 %)
Asian	30 (6.8 %)
Middle Eastern	7 (1.6 %)
Other	10 (2.3 %)
Unknown	69 (15.6 %)
Years since transplant	
<2 years	58 (13.2 %)
2 to 5 years	159 (36.0 %)
≥5 years	224 (50.8 %)
Median; range	5; 1–14
Underlying diagnosis and remission status	
Underlying diagnosis	
AML/ALL	226 (51.2 %)
CML/MDS/myelofibrosis	60 (13.6 %)
Other	137 (31.1 %)
Unknown	18 (4.1 %)
Remission status	
CR1/CR2	271 (61.4 %)
>CR2	22 (5.0 %)
Other	46 (10.4 %)
Chronic phase	18 (4.1 %)
Accelerated phase and blast crisis	3 (0.7 %)
Refractory	22 (5.0 %)
Partial remission	23 (5.2 %)
Unknown	36 (8.2 %)
Transplant characteristics	
Number of transplants by year	
2000–2006	136 (30.8 %)
2006–2012	305 (69.2 %)
Donor type	
Sibling	250 (56.7 %)
Haploidentical	10 (2.3 %)
Matched unrelated	158 (35.8 %)
Mismatched unrelated	21 (4.8 %)
Unknown	2 (0.4 %)
Stem cell source	
Bone marrow	48 (10.9 %)
PBSCT	381 (86.4 %)
Cord	12 (2.7 %)
Conditioning	
Myeloablative	214 (48.5 %)
With TBI (*n*, % of myeloablative regimens)	101 (47.2 %)
Non-myeloablative	225 (51.0 %)
With TBI (*n*, % of myeloablative regimens)	26 (11.5 %)
Not known	2 (0.5 %)
Cardiovascular comorbidities and chronic Graft-versus-Host Disease (cGvHD)	
Hypertension	118/409 (28.8 %)
Hypercholesterolaemia	96/402 (23.9 %)
Diabetes mellitus	57/398 (14.3 %)
Chronic GvHD	301/434 (69.3 %)

n = 441

AML acute myeloid leukaemia, *ALL* acute lymphoblastic leukaemia, *CML* chronic myeloid leukaemia, *MDS* myelodysplastic syndrome, *CR1* clinical remission 1, *CR2* clinical remission 2, *PBSCT* peripheral blood stem cell transplant, *TBI* total body irradiation

scores) using simple regression analysis showed a significant negative correlation (regression coefficient −5.8; 95 % CI −6.7, − 4.9: $P < 0.001$). This negative correlation maintained significance even after adjusting for the effects of age, gender and years from transplant in a multivariable regression model (regression coefficient −5.8; 95 % CI −6.9, −4.9: $P < 0.001$).

Eating habits, dietary choices and nutritional supplements post-transplant

Almost 65 % of survivors (37/57) in the early post-transplant group reported that their eating habits had returned to normal. In those survivors who were two or more years post-transplant, 77 % (292/379) reported that their eating habits had returned to normal. Survivors who were two or more years post-transplant were significantly more likely to have returned to their normal eating habits (odds ratio (OR) 1.81 95 % CI 0.94 to 3.39; $P = 0.05$). Eating habits were significantly more likely to have returned to pre-transplant levels in survivors who were two or more years post-BMT compared to those survivors less than 2-year post-BMT (OR 1.94 95 % CI 1.06 to 3.56; $P = 0.01$). Quality of life was significantly higher in those participants who experienced a return to enjoyment of meals with a P value < 0.0001. (Fig. 2).

One hundred and thirty-one survivors reported changing their diet since having a BMT (29.6 %). The four most common changes included avoiding particular food and food

Table 2 Prevalence of gastronitestinal symptoms after transplantation

Symptom	<2 years (% < 2 year post-transplant with symptom) $n = 58$	2–5 years (% 2–5 year post-transplant) with symptom $n = 159$	>5 (% > 5 years post-transplant with symptom) $n = 224$	Total
Nausea	8 (13.8 %)	21 (13.2 %)	21(9.4 %)	50
Vomiting	3 (5.2 %)	10 (6.3 %)	6 (2.7 %)	19
Constipation	10 (17.2 %)	15 (9.4 %)	41 (18.3 %)	66
Diarrhoea	11 (19.0 %)	29 (18.2 %)	43 (19.2 %)	83
Taste alterations	26 (44.8 %)	53 (33.3 %)	55 (24.5 %)	134
Smell alternations	19 (32.8 %)	34 (21.4 %)	35 (15.6 %)	88
Poor appetite	16 (27.6 %)	29 (18.2 %)	40 (17.9 %)	85
Mouth ulcers	21 (36.2 %)	46 (28.9 %)	77 (34.4 %)	145
Dry mouth	26 (44.8 %)	65 (40.9 %)	93 (41.1 %)	184
Median number symptoms (range)	2 (0–9)	1 (0–9)	1 (0–7)	1 (0–9)

groups (37 %, $n = 48/131$), focus on healthy eating (35 %, 46/131), reducing meat consumption (16 %, 21/131) and choosing organic foods (11 %, 14/131).

Twelve percent (52/441) of survivors were taking oral nutritional supplements at the time of the survey. The use of nutritional supplementation in the early post-transplant period (less than 2 years) was significantly higher than those in the late (greater than 2 years) post-transplant group (OR 2.58 95 % CI 1.17 to 5.40; $P = 0.006$).

In contrast to the use of nutritional supplements, the proportion of survivors consuming 'natural' therapies such as nutrition and dietary therapies, herbal supplements, vitamin therapies and manipulative therapies increased over time post-transplant (Table 3).

Body weight and body mass index (BMI)

Self-reported height and weight for BMI revealed that 3 % (13/405) of patients were underweight, 49 % (197/405) were of normal weight, 32 % (128/405) were overweight and 16 % (67/405) were obese. Figure 3 shows the distribution of weight ranges by years post-transplant. The proportion of survivors who were overweight was the highest in the early post-transplant group. The proportion of survivors who were obese was the greatest in survivors more than 5-year post-transplant.

Those survivors who were overweight or obese were significantly more likely to be diabetic compared to those who were underweight or with normal BMI (OR 2.25, 95 % CI 1.18 to 4.41; $P = 0.008$).

Perceptions of body weight and body image

In terms of survivor perception of their own BMI, the highest agreement between actual and perceived BMI was seen with those survivors who thought they were overweight (84 %, 122/146) and the lowest agreement was with those patients who felt they were underweight (20 %, 10/51). When comparing body perception between male and females, females had a body perception that was more likely to align to the

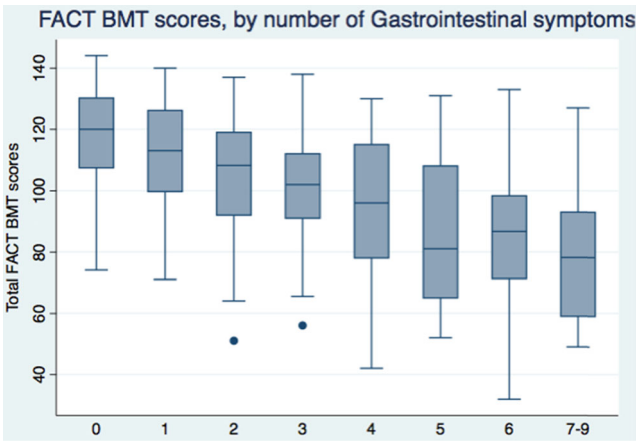

Fig. 1 FACT-BMT scores compared with number of gastrointestinal symptoms

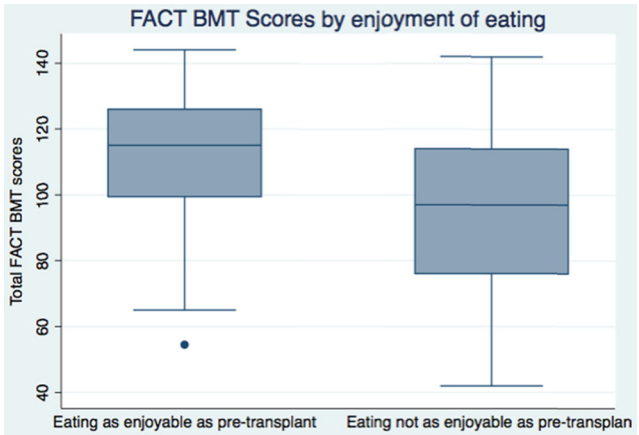

Fig. 2 FACT-BMT scores compared with survivors enjoyment of eating

Table 3 Use of natural therapies

Natural therapies	<2-year post-transplant	2–5-year post-transplant	>5-years post-transplant	Total
Nutrition/dietary approaches	5/54 (9.3 %)	17/157 (10.8 %)	37/222 (16.7 %)	59/433 (13.6 %)
Herbal supplements	4/56 (7.1 %)	17/153 (11.1 %)	37/218 (17.0 %)	58/427 (13.6 %)
Vitamin therapies	14/55 (25.5 %)	41/155 (26.4 %)	73/214 (34.1 %)	128/424 (30.2 %)
Mind-body therapies	11/55 (20.0 %)	27/156 (17.3 %)	36/216 (16.7 %)	74/427 (17.3 %)
Manipulative therapies	12/56(21.4 %)	39/156 (25 %)	61/217 (28.1 %)	112/429 (26.1 %)
Traditional whole medicine systems	2/54 (3.7 %)	4/156 (2.6 %)	9/215 (4.2 %)	15/425 (3.5 %)
Energy medicine	1/55 (1.8 %)	5/156 (3.2 %)	7/216 (3.2 %)	13/427 (3.0 %)
Homoeopathy	2/55 (3.6 %)	3/155 (1.9 %)	8/214 (3.7 %)	13/424 (3.1 %)

BMI reference ranges than male survivors (77 % 135/176 females; 59 % 133/228 males; OR 2.35 95 % CI 1.49 to 3.74, $P = 0.0001$).

Overall, 56 % (244/435) of patients were satisfied with their current body weight. Males were more likely to be satisfied with their body weight compared to females (OR 1.7 95% CI 1.11 to 2.50; $P = 0.009$). The median BMI for all patients reporting body weight satisfaction was significantly lower (BMI 23.5) than those reporting dissatisfaction (BMI 27.5) ($P = <0.0001$). Those that had a normal BMI had significantly higher rates of body weight satisfaction compared to underweight, overweight and obese survivors (OR 3.76 95 % CI 2.43 to 5.83; $P = <0.0001$).

Body mass index was compared to the FACT-BMT total scores. This revealed no significant difference in the total FACT-BMT score across each BMI category ($P = 0.11$), or when stratified by years post-transplant (<2 years $P = 0.12$, 2–5 years $P = 0.95$, >5 years $P = 0.28$). Survivors who were underweight, however, had consistently lower FACT-BMT scores compared to those who were normal, overweight or obese. This was seen across all time periods post-transplant.

Use of dietetic services post-transplantation

Overall, 23 % (99/416) of survivors had been referred to a dietitian after transplantation. Referral to a dietitian was more likely in the early (less than 2 years) survivor group (30.4 % 17/56), though this was not significant ($P = 0.21$). Those survivors with a diagnosis of diabetes (OR 3.28 95 % CI 1.73 to 6.17; $P = <0.0001$), high blood pressure (OR 1.97, 95 % CI 1.16 to 3.17; $P = 0.007$), gut chronic GVHD (OR 1.92, 95 % CI 1.00 to 3.80; $P = 0.03$) or high cholesterol (OR 1.90, CI 95 % 1.09–3.29; $P = 0.01$) were significantly more likely to be referred to a dietitian.

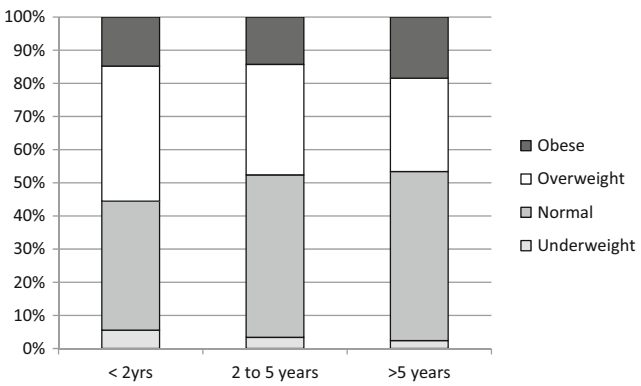

Fig. 3 BMI categories based on time categories

Enteral feeding

One hundred and twenty-eight patients (30 %, 128/432) reported that they were enterally fed during their BMT. One hundred and nine of these survivors (87 %) reported that enteral feeding was beneficial to their care and 75 % (92/122) said they would recommend it to others. There was no significant difference in reported rates of cGVHD ($P = 0.57$) or in gastrointestinal GVHD ($P = 0.63$) in those who had or had not received enteral feeding.

Discussion

This study provides the first comprehensive experience of long-term survivors of allogeneic BMT. It demonstrates clearly that gastrointestinal symptoms such as altered taste and smell, dry mouth, mouth ulcers, anorexia and diarrhoea are not limited to the early post-BMT period but remain problematic for long-term survivors, many of whom are still experiencing the unpleasant complications of their treatment years after transplant. These findings are consistent with those of Lenssen et al. [25] who documented nutritional issues affecting survivors during the first 12 months after transplant. As this study yielded a high response rate, 76 % of total eligible survivors, it is likely that the results presented here provide an accurate picture of nutritional issues facing survivors of allogeneic BMT. However, the results may not be transferrable to other ethnic groups as 73 % of survivors were from an Australian/European ethnic background. Additionally, the fact that the

study relied upon self-reporting and did not capture data on non-responders also limits the findings. It should also be noted that as only two of the respondents had a recurrence of the malignancy for which they were transplanted, the findings only apply to survivors who remain disease free following BMT. Also, as respondents were not asked about nutritional status, gastrointestinal symptoms, body image and exercise pre-BMT, correlation between pre-and post-BMT beliefs and behaviours were not able to be made .

More than 20 % of survivors who were five or more years post-BMT reported taste alterations, mouth ulcers and dry mouth. These symptoms had a significant adverse impact upon quality of life with survivors reporting lower quality of life as the number of gastrointestinal symptoms increased. Reasons for food avoidance particularly mouth sensitivity caused by spicy/hard/rough or hot foods caused many BMT survivors to alter their diet following transplant. There was also a notable association between return of appetite and enjoyment of eating to pre-transplant levels and FACT-BMT scores indicating that nutrition impacts quality of life in BMT survivors.

In the study population, the rates of overweight and obesity were found to be lower than in the general Australian population (48.2 % verse 63 %) [26]. Although BMI scores did not correlate to QOL outcomes, the fact that almost half of the long-term survivors of BMT are overweight and obese remains a significant concern as this adds to the comorbidities experienced by survivors including metabolic syndrome, accelerated vascular disease, diabetes mellitus and musculoskeletal disorders [2]. Further research is needed to establish whether assisting survivors to maintain or achieve a normal body weight, to eat healthily and exercise regularly militates against the burden of disease experienced by the long-term survivors of allogeneic BMT.

While this study was not designed to assess the impact of nutritional support on BMT outcomes, including GVHD and infection (11, 27, 28) this study provides useful data on patient perspectives on enteral feeding. Interestingly, a large majority of patients surveyed thought enteral feeding was beneficial to their care, and they would recommend it to other transplant patients.

It is generally accepted that a comprehensive nutritional assessment should be performed prior to BMT and that nutrition monitoring during transplant plays an important role in preventing nutrition decline [27]. This study provides further support for the roles of nutrition therapy (within a comprehensive multidisciplinary survivorship clinic setting) post-BMT, particularly for survivors with diabetes, obesity, hypercholesterolemia, hypertension and gastrointestinal symptoms. Future studies are required to investigate the effectiveness of nutrition therapy in managing nutritional issues facing survivors of BMT and how this impacts quality of life.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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15.5. Synopsis

This manuscript provides the only published account of nutrition, body weight and body image and its association with QoL in allogeneic BMT survivors. The results indicate GI symptoms post-BMT are common, with some (dry mouth, mouth ulcers and diarrhoea) continuing more than five years post-BMT. Importantly, the results also highlight the negative impact that GI symptoms and poor nutritional status have on the QoL of long-term survivors.

While rates of overweight and obesity in our BMT survivors were less than that of the Australian general population (overweight 32% vs 35.3%, obesity 16% vs 27.5%) these rates are still deeply problematic, both for BMT survivors as they are significantly associated with metabolic syndrome and DM – and for society more generally given the enormous health and financial impact of DM (with direct costs and government subsidies directed to the impact of DM totalling more than A$14.6 billion in 2010(1)).

Interestingly, while GI symptoms negatively impacted upon BMT survivors' QoL, BMI did not. This provides a cogent reminder that simply recording a patients' weight and height does not reveal what it means to them and that discriminatory judgement based on assessment of BMI or morphology are unjustifiable and unhelpful. In this regard it was also noteworthy that only 23% of survivors has been referred to a dietitian post-transplant which, given the prevalence and duration of GI symptoms, high rates of overweight and obesity, predisposition to DM and associated cardiovascular complications, and the negative impact of symptoms on QoL, would seem inconsistent with high quality long-term care. These results, and those of other studies of the endocrine and cardiovascular late-effects of BMT (detailed in Chapter 2), suggest that there is an urgent need to improve nutritional and dietary services post-BMT and to include dietary assessment in the routine care of BMT recipients.

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PART VI: Discussion and Conclusion

Chapter 16: Discussion and Conclusion

Chapter 16: Discussion and Conclusion

16.1. Chapter overview

This chapter summarises how the research reported in this thesis meets the aims of the study. As each of the papers reported here are already discussed in Chapters 5-15, this chapter integrates the main findings of this thesis and their implications for improving the experience of survival following allogeneic BMT in NSW, outlines the strengths and limitations of this study, and makes recommendations for future research, clinical practice, and education.

16.2. Study background

While impressive progress has been made in clinical BMT over the past fifty years, with more and more patients offered BMT for conditions previously thought untreatable or incurable, and more and more patients gaining years of the disease-free survival(1-3), the long term and late effects of BMT remain a major cause of morbidity and mortality. And despite publication of international and local guidelines for BMT LTFU (The ACI, BMT Network published clinical guidelines for BMT LTFU in 2016(4)), and efforts by international, national and local agencies to emphasis life-long follow-up of BMT survivors(4-6), the establishment of sustainable LTFU services and effective MOCs for post-BMT care have proven enormously difficult. A number of factors have mitigated against the development and integration of BMT LTFU services including the increasing numbers of BMTs being performed, the increasing numbers of survivors requiring LTFU, the capacity (human, infrastructure, cost) and preference of BMT centres/clinicians, the complexity and fragmentation of the health care system, the complexity of complications following BMT, and the lack of empirical data regarding the experience of BMT survivorship.

This research sought to provide a comprehensive description of the experience of survival following allogeneic BMT in NSW, Australia. In order to obtain as much meaningful data as possible from the largest feasible sample size, the study consisted of a large cross-sectional analysis using seven survey instruments (six validated and one purposed designed for the study) which asked a total of 518 questions. It was a state-wide multicentre study of a contemporary cohort of adult BMT survivors with data collection occurring at one point in time.

Specifically, the study aimed:

1. to describe the incidence and range of late complications of BMT and their association with the health and functional status of survivors in NSW;
2. to address limitations in BMT survivorship literature – particularly with regard to the financial, occupational and psychosocial impact of BMT;
3. to identify gaps in service provision provided to this vulnerable and high-risk patient group;
4. to provide better information to patients contemplating BMT, and to their families and guardians, regarding the possible long-term sequelae of BMT; and
5. to support clinical and health policy decision-making around BMT through the provision of more comprehensive data regarding the late sequelae of BMT in an Australian setting.

16.3. Main findings

The findings of this research make clear the large burden of morbidity following BMT and the deficiencies in support that long-term survivors of allogeneic BMT in NSW currently receive. The results of this study provide a comprehensive account of the long-term physical and psychosocial impact of BMT in Australia, contribute significant insights into the experience of post-BMT survivorship, and address major deficiencies in the existing literature surrounding LTFU post-BMT. The results provide the case for building and strengthening LTFU services and for changing the way that we design and deliver health services for those undergoing BMT and for those that survive it.

This research revealed that the most common problems reported by long-term survivors of BMT were cGVHD affecting the skin, eye, vagina and/or mouth (69.3%), sexual dysfunction (66% of females and 51% of males), VPD (41.5%), tooth decay (36.8%), iron overload (32.5%), alterations in taste (30.9%), osteoporosis/osteopenia (29.1%), cataracts (28.9%), HTN (29%), high cholesterol (24.0%), secondary malignancy (24.5%), depression (23.3%), anxiety (20.6%), altered smell (20.7%) poor appetite (20.2%), diarrhoea (19.4%), and DM (14.3%).

The study also revealed that despite their increased risks of chronic diseases and infection, survivors continue to engage in high risk health behaviours, including smoking, drinking (>14 standard drinks/week), and not being 'sun smart', in 7.5%, 7.7% and 22.9% of cases respectively. Thirty two percent reported being overweight, 16% were obese and only 45.1% reporting doing regular exercise (at least 3 time/week). Many recipients also did not receive appropriate post-BMT vaccinations with 7.2% reporting being completely unvaccinated, 57.9% receiving only some of the recommended vaccines and only 31.8% receiving the full vaccination schedule. Furthermore, despite the risks of secondary malignancies, adherence with cancer screening following BMT was low with 32.4% of survivors following screening guidelines for bowel cancer, 63.4% of eligible female survivors having a

PAP smear and 53.5% a mammogram, and only 52.3% attending for regular skin cancer 'checks'. Importantly, the most commonly cited reason for not complying with cancer screening was lack of advice to do so by the treating team.

This work also revealed that compliance with recommended assessment for non-malignant or chronic conditions of BMT was also suboptimal. While approximately three-quarters of the survey respondents had had BMD scans and lung function tests (LFT) post-BMT, cardiac function assessment (gated heart pool scan (GHPS) or echocardiography (ECG)) was less commonly reported (49.3%), and thyroid assessment (palpation, ultrasound or scan) even less so (23.8%). Almost 10% of patients reported having no formal screening assessments post-BMT. Together, these data provide a rich picture of the incidence and range of late-stage complications in BMT survivors in NSW.

In contrast to the vast majority of extant literature on BMT survivorship, this study provides important data about the changes in social, occupational and financial status that many BMT survivors experience. Full time employment post-BMT decreased from 64% to 32.5%, and those in the lowest income strata increased from 21% to 36%. Ill-health as the cause for not working increased almost four-fold pre to post-transplant. Over 15% of survivors also reported a change in relationship status post-transplant. CAM therapy was used by 54.1% of respondents and survivors often required care from many specialist medical practitioners (median three), with the most common being dermatologists (60.3%), ophthalmologists (43.6%) and respiratory physicians (28.2%).

When survivors were asked about their preference for LTFU three quarters reported a preference for LTFU with their transplant physician and in a location that either included, or was linked with, the transplant centre (such as a satellite clinic or telemedicine facility).

16.4. Strengths and limitations

The research that provided the data for the papers reported in this thesis had a number of major strengths. The study presented was a comprehensive, multi-centre, state-wide survey of a contemporary cohort of long-term BMT survivors, with a large sample size (n=441) and high response rate (76%). It also used a range of validated instruments to assess the experience of survival and enable comparisons with other cohorts of BMT survivors. This makes it highly likely that these results provide an accurate account not only of the experience of survival following allogeneic BMT in NSW, but also of the experience of BMT survivors across Australia. This is turn, lends support for the use of the results to inform the education and counselling of BMT recipients and their families, health care professionals, and policy makers in Australia.

Nevertheless, there are a number of limitations to this study that may limit the applicability of these results to BMT survivors in other countries and other settings. Some of the limitations include participation bias, inclusion of self-reported data, and failure to capture data on non-responders or those who had died (thereby missing data on BMT recipients who may have experienced 'earlier' or more severe complications of BMT). We also did not correlate self-reported medical and psychosocial issues with medical records, employment records, or financial statements, or assess pre-BMT health risk behaviour or cancer and health screening adherence. Furthermore, we did not explicitly consistently ask *why* survivors had not completed all screening and preventative recommendations, adhered with re-vaccination schedules, complied with health promotion messages, or followed recommendations for screening for chronic conditions, and psychosocial issues. This limits any conclusions that can be made about low rates of screening/health promotion adherence, and about the differential impact of different influences on adherence including the cost of care, knowledge about disease precautions and health promotion, health status of survivors and adequacy of existing services and communication from health care professionals. Importantly, while we explored survivors' preference for post-BMT care we did not specifically explore survivors' views regarding nurse-led clinics for BMT survivors. This is a significant omission as evidence has shown that nurse-led clinics may provide important resources for BMT survivors - improving health outcomes, reducing waiting times for patients and decreasing rates of hospital admission(7, 8). Australia's geographical size, predominantly urban population, climate, and health care system (which includes universal publicly funded and private health care) make the findings most relevant to Australian survivors and inevitably may limit conclusions that can be drawn about LFTU care in other settings.

Additionally, since only those individuals who could read and write English were eligible to participate, we may have failed to capture data from individuals from diverse ethnic backgrounds. This is an important consideration because Australia is a highly diverse nation (49% of Australian's population were born overseas or have a parent who was born overseas, and more than 300 languages are reported to be spoken in Australia homes(9)), because haploidentical transplantation (which is increasingly being undertaken(10)) is often done where patients lack a suitable matched related or unrelated donor – many of whom often come from minority populations, and because patients from culturally and linguistically diverse (CALD) populations often have worse engagement with health services and outcomes than those of their white/Caucasian counterparts, and may be at a disadvantage socioeconomically prior to BMT(11).

Finally, because this was a cross-sectional study, this research has the methodological limitations of all such studies. Firstly, inferences about casual or temporal relationships are restricted; it is not

possible to definitively comment on which complications arose from the BMT procedure, from complications of cGVHD, or from complications resulting from cGVHD treatment. (It is possible however, to use these data to develop hypotheses to test causal relationships). And secondly, as this research is historically defined, it reflects the experience of survival following BMT at a particular point in time. Thus, while these results provide a rigorous account of the issues facing BMT survivors currently, as BMT practices change, prevention and treatments of infection and cGVHD improve, and effective LTFU MOC are implemented and assessed, the long-term and late effects of BMT and the experience of survival following BMT may profoundly change.

16.5. Discussion

The burden of post-BMT morbidity and the experience of BMT survival described in this study is broadly consistent with the international literature. Cardiac and circulatory disease, endocrine dysfunction, genital disease and sexual dysfunction, lung and respiratory disease, renal impairment, liver dysfunction, skeletal disorders, oral and dental disease, immunodeficiency and infection, secondary cancers, ocular disease, neurocognitive impairments, anxiety and depression, and changes to QoL, social and functional status all commonly occur post BMT(12-34). More than half of the respondents in this study reported one or more chronic medical co-morbidities post-BMT, with cGVHD in particular being associated with many long-term complications and profoundly impacting upon the QoL of BMT survivors(35, 36). All of this is congruent with other studies of BMT survivors from across the globe(37, 38).

What is significant about this study is that the data reported here provides the first comprehensive picture of allogeneic BMT survivorship in a contemporary Australian cohort. Prior to this research being published long-term health related data on Australian adult allogenic BMT survivors were scarce. The CAST (Cancer After Stem Cell Transplantation) study had been undertaken but not yet published (manuscripts were published in 2015 and 2016 and included population data on cancer occurrence post BMT for both adult and paediatric autologous and allogeneic survivors(39-41)). A single centre retrospective study of ninety-nine allogenic BMT survivors had also been published (in 2014)(42). While this reported a high incidence of cGVHD and high burden of chronic illness post BMT, it did not analyse the outcomes by socio-demographic or transplant factors. A small survey of Australian haematologists (n=20, response rate 18%) and BMT recipients (n=34, response rate 28%) on post-BMT vaccination practices(43) demonstrated wide variation in vaccination practices across Australia but lacked rigour or power. In sum, prior to this study there was much that remained unknown about Australian BMT survivors.

The data reported in this thesis provides a rich and comprehensive account of the incidence and range of late complications experienced by Australian BMT survivors, and the impact these have on survivors' health and functional status. Consequently, clinicians can now provide BMT recipients and BMT survivors, and those who care for them, with a more informed description of the range of possible long term and late complications that Australian survivors may experience. In addition, following this study, we now have empirical data on the potential financial, occupational and psychosocial impact of BMT which clearly shows that financial insecurity and occupational vulnerability is a very real issue for long-term BMT survivors. This is important information because it can be used by not only clinicians, but also by a range of government agencies including the Department of Health, Department of Jobs and Small Business, Department of Human Services (Centrelink), MSAC, PBAC, as well as workers unions and not-for-profit and charitable patient and carer support services such as the Cancer Council, Arrow Foundation and the Leukaemia Foundation, to prepare potential BMT recipients and BMT survivors and their families for financial, occupational and social life changes post BMT.

Importantly, this study also suggests that currently available 'standard' psychometric measures of post-BMT QoL, such as FACT-BMT, may not necessarily provide a meaningful or sufficient account of the QoL, the health, personal and social challenges that survivors of BMT may experience. While post-BMT QoL scores reported by BMT survivors are often 'good' to 'excellent', and return to pre-BMT levels with time(44, 45), the qualitative data provided by BMT survivors in this study suggest that the physical burden of the 'failing body', the cognitive and mood changes, the diminished social connectedness, the loss of functionality and the burden of being a 'patient for life' profoundly 'shrink' the life world of BMT survivors and impact upon their QoL. None of this, of course, is currently captured by the FACT-BMT or other validated QoL questionnaires. And lastly, this study makes clear that (at least at the time of data collection) LTFU of BMT survivors was not routinely implemented across NSW, with a high burden of unmet need and profound deficiencies in the care provided to BMT survivors, and in the screening they received.

Indeed, this research reveals that despite the adult cancer survivorship movement being more than twenty years old, and the BMT LTFU movement being more than 12 years old(6, 46), the care provided to long-term survivors of allogeneic BMT in NSW is clearly suboptimal. LTFU is not consistent with either international LTFU recommendations or NSW specific LTFU guidelines(4, 5), and varies enormously between patients and centres. This is particularly evident in the assessment and management of sexual dysfunction post-BMT, in the utilisation of fertility sparing procedures offered to BMT recipients of child bearing age pre-BMT, and in the failure to ensure adherence with post-BMT

testing, cancer screening and oral and dental health checks. The fact that survivors continue to engage in high risk health behaviour, do not complete revaccination schedules post-BMT, suffer high rates of VPD, do not undergo all recommended screening tests and assessments, and do not receive expert or nutritional advice post-BMT, and frequently use CAM therapies suggests that LTFU care is lacking and that much more can be done to improve the experience of BMT survivorship.

In this regard it is noteworthy that deficiencies in LTFU in this study were often attributed to a lack of knowledge and awareness on behalf of health care professionals and a lack of education and counselling provided to BMT recipients, survivors and their families. While these explanations are undoubtably true, and are consistent with the international literature, they are not the only barriers or challenges to LTFU care. Health care providers and patients themselves, and the health care system itself, all contribute to the barriers, challenges and frustrations faced by those wanting to improve LTFU care(47-50).

Cancer/BMT, haematology and other health care providers may contribute to suboptimal LTFU because they lack resources for LTFU care, lack interest in LTFU, lack time for LTFU or for developing LTFU programs, lack awareness of the clinical and psychosocial needs of survivors, lack awareness of screening and preventive care guidelines, lack evidence-based tools to facilitate care, are provided insufficient reimbursement for providing care for survivors, and are unwilling to 'let go' of their patients. Poor communication between specialist health care providers, the patient and their carers, and GPs may also compromise LTFU and lead to a lack of clarity regarding responsibility for LTFU(48-50). In this regards, it is noteworthy that GPs specifically report inadequate training in survivorship and LTFU, and that Cancer/BMT specialists report uncertainty regarding general preventive care and the responsibility to oversee it(51, 52).

Patients themselves may also lack awareness of the long-term and late effects of BMT and the magnitude of risk of complications, lack awareness of screening and preventive care guidelines, lack trust in health care professionals other than their cancer/BMT specialist, have competing priorities (eg. employment/schooling status) that erode their willingness to adhere with recommendations for LTFU, and socio-demographic barriers (eg. socioeconomic status, residential location distance from BMT centre) and experience economic hardship, particularly related to insurance coverage and out-of-pocket costs, that reduce the possibility of optimal follow-up(51, 53).

Healthcare system barriers to the provision of optimal LTFU include inadequate funding of LTFU services, insufficient financial and professional incentives for health professionals to participate in LTFU care, a lack of resources and specialists with an interest in LTFU, insufficient 'political' will to

overcome 'cultural', professional and structural obstacles to the introduction of new MOCs for LTFU, and insufficient prospective randomized trials to guide the care of survivors or identify the optimal organisation of health care services post-BMT(47, 48, 54).

16.6. Implications

Given the increasing numbers of BMTs being performed and the increasing numbers of people surviving long-term post-BMT (Chapter 1), the high incidence of complex late morbidity leading or contributing to early death (Chapter 2), and the burden of LTFU testing, care and education required (Chapter 3), and the existing deficiencies in care of long-term survivors of BMT, there is an urgent need to implement new and effective MOC for BMT LTFU.

Models of care for BMT LTFU

As discussed in Chapter 3, there are many ways in which LTFU care can be delivered. Commonly identified service models include:

- *LTFU care provided during routine follow-up in the BMT Clinic:*
  BMT specialist/BMT advanced practice nurse continues to see the survivor in the BMT clinic.

- *LTFU care undertaken as a 'stand-alone' assessment/clinic visit either within the BMT clinic or in a dedicated BMT LTFU clinic:*
  The survivor is transitioned to a dedicated LTFU clinic/team. This is distinct from the early post-BMT clinic, is often held in an alternate space or on a different day, (but may be run alongside the early post-BMT clinic), and may be staffed by a multidisiplinary team.

- *Collaborative LTFU care shared between the BMT centre and other providers (eg. sub-specialists, local haematologists, GPs):*
  The survivor is seen infrequently in the BMT centre (often for purposes of LTFU review and data collection) with the majority of follow-up tests and assessments and health care delivered by the survivors local haematologist/GP and community health care providers.

- *LTFU care with local haematologist/GP:*
  The survivor is transitioned or discharged from the BMT service to the care of their local haematologist or GP with a care plan and recommendations for follow up.

Although it is neither possible nor necessary to dictate the type of LTFU MOC/clinic that individual BMT centres adopt (due to variability in infrastructure, capacity, patient numbers and 'case-mix'), there are some elements of LTFU that *must* be included within any MOC. These include screening for, and treatment of, late effects of BMT; surveillance for disease recurrence and second cancers; education to prevent late effects of BMT; psychosocial support; health promotion; data collection to enable reporting to national and international transplant registries and to facilitate continuous quality improvement, audit and research; and co-ordination of care for survivors both within BMT centres and as survivors transition between services.

In this regard it is noteworthy that following publication of data from this study, and increasing recognition of the need for comprehensive BMT LTFU care, that there have been substantial improvements in the delivery of post-BMT services in NSW. An informal survey of BMT LTFU service provision in mid-2018 found that all allogeneic BMT units in NSW now provide some form of BMT LTFU services and almost all have employed APNs to provide and co-ordinate BMT LTFU (Table 16.1). While this has undoubtably improved the long-term care provided to survivors of BMT in NSW, all services report facing the same barriers and challenges described above. Furthermore, while establishment of LTFU services represent great progress, much more needs to be done to improve long-term outcomes following BMT.

16.7. Recommendations for research and practice

This thesis has highlighted a number of areas where BMT LTFU can be improved and identified areas for future research.

Improve data collection

Prior to this study there were no comprehensive LTFU data on Australian BMT survivors, with the ABMTRR collecting limited data date last seen, cGVHD, second malignancies and death. While this data provides some information on survival, it is not overly helpful when trying to identify, plan for, benchmark or improve long-term BMT survivor medical and psychosocial outcomes. In 2018, recognition of the limitations of the existing dataset led to a pilot project conducted by the ABMTRR and the ACI, in which comprehensive, state-wide, real-time data was collected on long-term survivors (ASTRO BMT LTFU Module). Despite some problems with implementation, this provided important data on local adherence with clinical guidelines for BMT LTFU and reduced the number of patients who were lost to follow-up in the BMT centres in which it was trialled (personal communication). Since this time however, no further progress has been made in implementing this BMT LTFU module

state- or nation-wide, and APNs that co-ordinate the LTFU services at each centre have returned to collecting data on their own 'databases'.

Implementation of a standardised platform for collecting data on LTFU should be a priority as collection of data will enable audit of contemporaneous long-term outcomes, and facilitate retrospective and prospective post-BMT research, and enable health economists to calculate the cost of long-term care and the potential benefits of LTFU.

Conduct more research

As BMT practices change these may impact upon long-term sequalae of BMT and the experience of BMT survivors. These impacts however, will only be visible if data on LTFU is routinely collected as part of care.

But, as this study makes clear, more research is also needed to inform the understanding of BMT survivorship. This should include research on CALD BMT survivors and research to ascertain exactly *why* the care of BMT LTFU survivors is suboptimal.

Randomised clinical trials of interventions to prevent and treat long-term and late effects should also be a priority as many of the recommendations for LTFU care are currently based on expert consensus opinion.

Importantly, research is also needed on the MOC best able to improve long-term and late effects of BMT. For while the IOM and other BMT societies recommend that BMT LTFU care include a MDT approach that utilises the expertise of BMT clinicians, referring physicians, GPs and other relevant health care providers and advise provision of treatment summaries and survivorship care plans to survivors and their carers(55-57), there is limited data to support these recommendations or to assess their impact. This is an important area for ongoing study as there is little doubt that in the coming years clinicians and health services will increasingly use emerging technologies to deliver BMT LTFU, including telemedicine, patient owned health records, online support and education resources/portals.

Perform an economic evaluation

Allogeneic BMT is enormously expensive(58). Improving LTFU and reducing the long-term and late effects of BMT may therefore produce economic benefit to justify their ongoing support. Once robust, validated, comprehensive data has been collected on survivors, economic evaluation of the true cost

of long-term post-BMT care can be performed (including all health outcomes and psychosocial impacts such as absenteeism, lost work days, hospital admissions). This can evaluate the cost (including the disability and years of life lost) of providing inadequate and fragmented care to BMT survivors, and the cost-saving that follows practice improvement(59).

This in turn may support applications for funding for LTFU care, and to applications to the MSAC and the PBAC to fund care and treatments for long-term BMT survivors.

Increase the capacity for nurse-led BMT LTFU services

Nurse-led services offer a holistic and cost-effective solution to some of the barriers mentioned. Evidence has shown nurse-led clinics provide vital access to health advice and treatment and result in improved health outcomes(7, 8). In the context of care provision for children and adults with cancer, nurses have been able to address unmet survivorship needs, and provided leadership in defining, implementing, and evaluating MOCs to advance survivorship research and clinical practice(60). With a plateauing BMT physician workforce(61-63), and increasing health care costs, nurses are arguably best placed to deliver care focussed on health promotion, education, chronic disease management and psychosocial concerns.

Placing APNs at the centre of BMT LTFU is likely therefore to optimise post-BMT care, improve compliance with BMT LTFU guidelines, standardise reporting of post-BMT outcomes, allow the development of evidence-based clinical improvement activities, enable audit and research of post BMT care, improve cost-efficiency and sustainability of BMT LTFU across NSW through the identification and use of shared resources and services, assist in the transition of survivors from the transplant program to local haematologists/oncologist/GPs and support advocacy for increased resourcing for BMT LTFU services in NSW(57).

Develop and disseminate LTFU clinical guidelines and education materials

This study demonstrated that health care professional, BMT survivors and their carers all had deficient knowledge about the need for LTFU care. The development and dissemination of high quality, evidence-based survivor and carer education and guidance regarding the prevention and management of the late effects of allogeneic BMT is therefore greatly needed.

BMT recipients and their carers should be provided with information on the importance of LTFU and long-term complications both as part of the pre-BMT consent process and at discharge post-BMT. And clinicians should be constantly reminded the importance of life-long follow-up at regular intervals.

Health professional undergraduate, post-graduate and professional and other CPD earning curriculums should also include LTFU and survivorship information on cancer and BMT(64). These courses should be readily available for all healthcare professionals who care for BMT recipients, including nurses, allied health professionals, subspecialists, GPs and local haematologists.

Increase the capacity of BMT centres to provide and assist with LTFU care

By 2030 it is predicted that there will be over half a million BMT survivors in the US alone(65). In recognition of this fact, FACT-JACIE guidelines require that BMT centres have infrastructure, policies, and standard operating procedures (SOPs) in place for the provision of appropriate LTFU treatment and care planning(66). There are a number of ways in which BMT centre can increase their capacity to provide better LTFU. This includes implementation of and support for nurse-led clinics; establishment of a register of subspecialists, allied health professionals and community services who are willing to treat survivors of BMT; increased funding on LTFU and support care delivery and communication between all providers and the survivor; and the use of standardised, validated, evidence-based tools for LTFU assessment, including use of qualitative questions inviting accounts of the 'lived experience' of BMT survivorship.

16.8. Conclusion

This study successfully achieved all of its aims, elucidating the incidence and range of late complications of BMT and their association with the health and functional status of survivors; addressing limitations in the literature regarding the financial, occupational and psychosocial impact of BMT; exposing gaps in service provision provided to this vulnerable and high-risk patient group; and providing comprehensive data regarding the long-term and late sequelae of Australian survivors of BMT . This means, really for the first time, that we have comprehensive and rigorous data to improve the design and deliver of post-BMT care, and the experience of BMT survivorship.

Table 16.1: BMT LTFU Models of Care employed across NSW at study completion (2018)

Centre	# Allos/ year 2017	BMT LTFU FTE	Clinic Type	Delivery mode (Led by)	Located within	Provider involvement	1st BMT LTFU visit (mo)	Frequency of LTFU
WH	60	0.6 CNS2	Specialised LTFU Clinic – Multi-disciplinary	Specialised LTFU care (BMT LTFU CNC)	BMT LTFU Clinic	BMT LTFU CNC2 BMT physicians Dermatology Gynaecology Endocrinology Concurrent Respiratory medicine clinic runs in private rooms	1-year post	Annually
			Late Effects Clinic – Multi disciplinary	Routine post-BMT care (BMT LTFU CNC)	BMT LTFU Clinic	BMT CNC2 BMT Physicians Runs concurrently with LTFU Clinic on 1st & 3rd Thursday/month	Patient status depen-dent	
		0.3 CNC	Post-BMT Clinic – Satellite Clinic (Newcastle)	Routine post-BMT care (Newcastle BMT-Co-ordinator)	Westmead pt specific Post-BMT Clinic	BMT-Coordinator BMT Physician from Westmead (rotating physicians on a monthly basis)	3mo post	Annually
SVH	42	0.6 VMO	Specialised LTFU Clinic – BMT only	Specialised LTFU Clinic (VMO BMT-Co-ordinator arranges blood tests, FACT-BMT questionnaire, other investigations)	LTFU Clinic (operates Tuesdays, Wednesday & Thursdays) Referral required from BMT Physician to VMO	VMO In-house referrals to: Respiratory clinic Endocrinology Ophthalmology Private provider referrals Gynaecology	Not defined	
			Post-BMT Clinic	Routine post-BMT care (BMT Physician)	Haematology Clinic	BMT Physician Referrals made within and outside SVH as required/per physician discretion	Physician discretion	

RNSH	33	0.8 NP (0.2 Myeloma care)	BMT LTFU Clinic	Collaborative and specialised LTFU care (BMT NP)	Post BMT clinic (fortnightly)	BMT Physician BMT NP BMT Psychologist In-house referrals Dermatology Ophthalmology Endocrinology Respiratory medicine In-house private referrals (but agreeing to bulk bill BMT patients): Gynaecology Cardiology Referrals outside of RNSH: Dentist	6mo post	6mo, 12mo then Annually
RPA	21	0.5 CNC (0.5 lymphoma)	Specialised LTFU – BMT only	Collaborative and Stand-alone LTFU assessments/ Review – piggybacked on to routine post-BMT care (BMT LTFU CNC)	Haematology Clinic	BMT LTFU CNC BMT physician In-house referrals: Gynaecology Ophthalmology Endocrinology Neurology Dermatology Referred outside RPA: Vaccinations, skin checks/cancer screening - GP Dentist Andrology (Concord Hospital)	3mo post	3mo, 12mo, then Annually
LH	6	0.6 CNS2	Post-BMT Clinic	Routine Post-BMT care (BMT CNS)	Post-BMT Clinic	BMT Physician BMT CNS2 BMT CNS organises blood tests etc and refers on to specialist inhouse)	Physician discretion	
CNS, Clinical Nurse Specialist; CNC, Clinical Nurse Consultant; NP, Nurse Practitioner; VMO, Visiting Medical Officer.								

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Appendix A: Statement of contributions for each publication presented in this thesis

Statement of Contribution

We, the undersigned, attest that Research Higher Degree candidate Gemma Dyer contributed substantially to the conception and design of the study, co-ordinating ethics and governance approvals, securing funding for survey printing and data analysis, and in conducting the study including participant recruitment, gaining consent, survey completion, data collection and cleaning, interpretation of the analysis, and writing the manuscript:

Gifford G, Gilroy N, **Dyer G**, Brice L, Kabir M, Greenwood M, Larsen S, Moore J, Hertzberg M, Kwan J, Huang G, Tan, Brown L, Hogg M, Ward C & Kerridge I. 2016. "The Experience of Survival following allogeneic Haematopoietic Stem Cell Transplantation (allo-HSCT) in New South Wales, Australia". *Blood and Marrow Transplantation* 51(10):1361-8.

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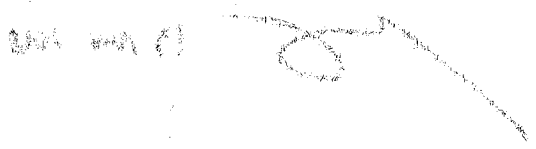

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Dyer G, Gilroy N, Brown L, Hogg M, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Huang G, Tan J, Ward C & Kerridge I. 2016. "What They Want: Inclusion of Blood and Marrow Transplantation Survivor Preference in the Development of Models of Care for Long-Term Health in Sydney, Australia." *Biol Blood Marrow Transplant* 22(4):731-743.

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Dyer G, Gilroy N, Bradford J, Brice L, Kabir M, Greenwood M, Larsen SR, Moore J, Hertzberg M, Kwan J, Brown L, Hogg M, Huang G, Tan J, Ward C & Kerridge I. 2016. "A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia." *Br J Haematol* 172(4):592-601.

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Dyer G, Larsen SR, Gilroy N, Brice L, Greenwood M, Hertzberg M, Kabir M, Brown L, Hogg M, Huang G, Moore J, Gottlieb D, Kwan J, Tan J, Ward C & Kerridge I. 2016. "Adherence to cancer screening guidelines in Australian survivors of allogeneic blood and marrow transplantation (BMT)." *Cancer Med* 5(7):1702-16.

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Dyer G, Larsen SR, Gilroy N, Brice L, Kabir M, Hogg M, Brown L, Hertzberg M, Greenwood M, Moore J, Gottlieb D, Huang G, Tan J, Ward C & Kerridge I. 2017. Prevalence of high-risk health behaviours in long-term survivors of allogeneic blood and marrow transplantation in Sydney, Australia. *Australian Journal of Cancer Nursing* 18(2): 16-23.

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Dyer G, Brice L, Gilroy N, Kabir M, Hertzberg M, Greenwood M, Larsen SR, Moore J, Gottlieb D, Huang G, Hogg M, Brown L, Tan J, Ward C & Kerridge I. 2018. Changes to work status and household income of long-term allogeneic blood and marrow transplant survivors in New South Wales, Australia. *Bone Marrow Transplant* 53(7):926-931.

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Dyer G, Brice L, Schifter M, Gilroy N, Kabir M, Hertzberg M, Greenwood M, Larsen SR, Moore J, Gottlieb D, Huang G, Hogg M, Brown L, Tan J, Ward C, Kerridge I. 2018. Oral health and dental morbidity in long-term allogeneic bone marrow transplant survivors in Australia. *Aust Dent J.* https://doi.org/10.1111/adj.12627

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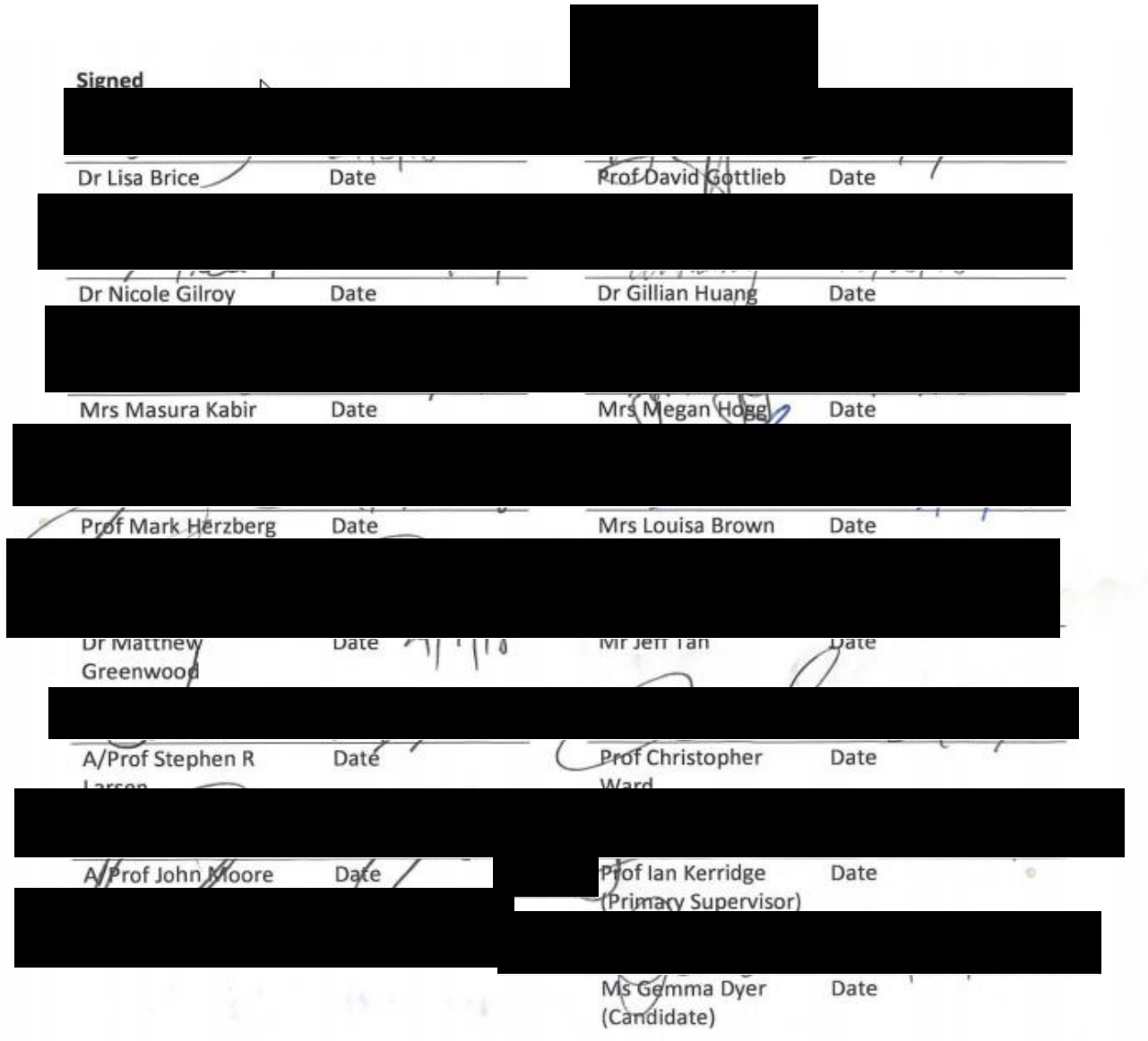
A/Prof Mark Schifter	Date	Dr Gillian Huang	Date
Dr Nicole Gilroy	Date	Mrs Megan Hogg	Date
Mrs Masura Kabir	Date	Mrs Louisa Brown	Date
Prof Mark Herzberg	Date	Mr Jeff Tan	Date
Dr Matt Greenwood	Date	Prof Christopher Ward	Date
A/Prof Stephen R Larsen	Date	Prof Ian Kerridge (Primary Supervisor)	Date
A/Prof John Moore	Date	Ms Gemma Dyer (Candidate)	Date

Statement of Contribution

We the undersigned, attest that Research Higher Degree candidate Gemma Dyer contributed substantially to the conception and design of the study, co-ordinating ethics and governance approvals, securing funding for survey printing and data analysis, and in conducting the study including participant recruitment, gaining consent, survey completion, data collection and cleaning, interpretation of the analysis, and writing the manuscript:

Dyer G, Gilroy N, Brice L, Kabir M, Gottlieb D, Huang G, Hogg M, Brown L, Greenwood M, Larsen S, Moore J, Hertzberg M, Tan J, Ward C & Kerridge I. 2018. "A survey of infectious diseases and vaccination uptake in long-term haematopoietic stem cell transplant survivors in Australia", *Transplant Infectious Disease, in press.*



Statement of Contribution

We, the undersigned, attest that Research Higher Degree candidate Gemma Dyer contributed substantially to the conception and design of the study, co-ordinating ethics and governance approvals, securing funding for survey printing and data analysis, and in conducting the study including participant recruitment, gaining consent, survey completion, data collection and cleaning, interpretation of the analysis, and writing the manuscript:

Lindsay J, Kabir M, Gilroy N, **Dyer G,** Brice, L, Greenwood M, Moore J, Hertzberg M, Larsen S, Kwan J, Brown L, Hogg M, Huang G, Tan J, Gifford G, Kerridge I. Epidemiology of complementary and alternative medicine therapy use in allogeneic hematopoietic stem cell transplant survivorship patients in Australia. *Cancer Med* 2016;5(12):3606-14.

Signed

[redacted]

Mr Julian Lindsay Date

Dr John Kwan Date

[redacted]

Mrs Masura Kabir Date

Mrs Louisa Brown Date

[redacted]

Dr Nicole Gilroy Date

Mrs Megan Hogg Date

[redacted]

Dr Lisa Brice Date

Dr Gillian Huang Date

[redacted]

Dr Matthew Greenwood Date

Mr Jeff Tan Date

[redacted]

A/Prof John Moore Date

Dr Grace Gifford Date

[redacted]

Prof Mark Hertzberg Date

Prof Ian Kerridge (Primary Supervisor) Date

[redacted]

A/Prof Stephen Larsen Date

Ms Gemma Dyer (Candidate) Date

Statement of Contribution

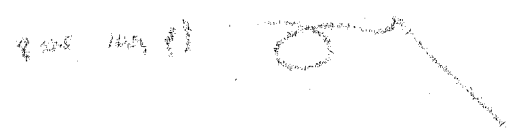
We, the undersigned, attest that Research Higher Degree candidate Gemma Dyer contributed substantially to the conception and design of the study, co-ordinating ethics and governance approvals, securing funding for survey printing and data analysis, and in conducting the study including participant recruitment, gaining consent, survey completion, data collection and cleaning, interpretation of the analysis, and writing the manuscript:

Brice L, Gilroy N, **Dyer G,** Kabir M, Greenwood M, Larsen S, Moore J, Kwan J, Hertzberg M, Brown L, Hogg M, Huang G, Tan J, Ward C, Gottlieb D & Kerridge, I. 2017. Haematopoietic stem cell transplantation survivorship and quality of life: is it a small world after all? *Support Care Cancer* 25(2):421-7.

Signed

[redacted]

Dr Lisa Brice	Date	Mrs Louisa Brown	Date
Dr Nicole Gilroy	Date	Mrs Megan Hogg	Date
Mrs Masura Kabir	Date	Dr Gillian Huang	Date
Dr Matt Greenwood	Date	Mr Jeff Tan	Date
A/Prof Stephen R Larsen	Date	Prof Christopher Ward	Date
A/Prof John Moore	Date	Prof David Gottlieb	Date
Dr John Kwan	Date	Prof Ian Kerridge (Primary Supervisor)	Date
Prof Mark Hertzberg	Date	Ms Gemma Dyer (Candidate)	Date



Statement of Contribution

We, the undersigned, attest that Research Higher Degree candidate Gemma Dyer contributed substantially to the conception and design of the study, co-ordinating ethics and governance approvals, securing funding for survey printing and data analysis, and in conducting the study including participant recruitment, gaining consent, survey completion, data collection and cleaning, interpretation of the analysis, and writing the manuscript:

Smith J, Poon C, Gilroy N, Kabir M, Brice L, **Dyer G**, Hogg M, Greenwood M, Moore J, Hertzberg M, Brown L, Tan J, Huang G, Kwan J, Larsen S, Ward C, Kerridge I. Nutritional issues and body weight in long-term survivors of allogeneic blood and marrow transplant (BMT) in NSW Australia. *Support Care Cancer* 2017;25(1):137-44.

Signed

[redacted]

Mrs Jennifer Smith Date

Mrs Louisa Brown Date

[redacted]

Mrs Christine Poon Date

Mr Jeff Tan Date

[redacted]

Dr Nicole Gilroy Date

Dr Gillian Huang Date

[redacted]

Mrs Masura Kabir Date

Dr John Kwan Date

[redacted]

Dr Lisa Brice Date

[redacted]

A/Prof Stephen R Larsen Date

[redacted]

Mrs Megan Hogg Date

[redacted]

Prof Christopher Ward Date

[redacted]

Dr Matt Greenwood Date

[redacted]

Prof Ian Kerridge (Primary Supervisor) Date

[redacted]

A/Prof John Moore Date

[redacted]

Ms Gemma Dyer (Candidate) Date

[redacted]

Prof Mark Hertzberg Date

Appendix B: Human research ethics committee approval letter for the study

Health
Northern Sydney
Local Health District

30th August 2012

A/Prof. Ian Kerridge
Royal North Shore Hospital
Haematology Department
Level 4
Pacific Highway
St Leonards
2065
Australia

Dear A/Prof. Kerridge,

1207-217M: *The ExperienceOf Survival Following Bone Marrow Transplant in Sydney Australia*

Thank you for providing additional information as requested at the meeting on **24th July 2012** by the Northern Sydney Local Health District (NSLHD) Human Research Ethics Committee (HREC). Following a review of the additional information provided and the HREC Executive have determined that the proposal meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). The HREC Executive is pleased to advise that your study has now granted scientific and ethical approval.

The documentation included in the approval is as follows:

- National Ethics Application Form Version AU/1/A38E010 dated 8th August 2012.
- Participant Information Sheet and Consent Form Version 1.0,8.08.12
- Sydney Post BMT Survey Version 1.0 dated 8th August 2012
- FACT-BMT (Version 4), dated 16 November 2007
- Chronic GVHD Activity Assessment-Patient Self Report
- Chronic GVHD Symptom Scale

It is noted that the approval covers the following NSW Health sites:

- Westmead Hospital
- Royal North Shore Hospital
- St Vincent's Hospital
- Royal Prince Alfred Hospital

It is noted that the study has been assessed by the HREC for *ethical* and *scientific review* ONLY and that clearance on the Site Specific aspects of the trial (local sign-off's, legal documentation etc) MUST be obtained from the above listed sites prior to commencement of research. Each site has different requirements; NSW Area Health Service sites require submission and approval of a Site Specific Assessment (SSA), which can be completed at: **www.ethicsform.org/au**. Please contact the local site for advice on what will be required.

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

AURED NEAF REF: *HREC/12/HAWKE/209*
NSLHD REF NO: 1207-217M,

2. *The HREC is notified of all Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reactions (SUSARs) in accordance with the Serious Adverse Event Reporting Guidelines. Please refer to the Research Office website.*
3. *Proposed amendments to the research protocol or conduct of the research that may affect the ethical acceptability of the project are submitted to the HREC on an amendment form (including any relevant attachments). For multi-centre studies, the Chief Investigator should submit to the Lead HREC and then send the amendment approval letter to the investigators at each of the sites so that they can notify their Research Governance Officer.*
4. *Proposed changes to the personnel involved in the study are submitted to the HREC on a Change in Personnel Form (accompanied by the investigator's CV where applicable).*
5. *The HREC must be provided with an annual progress report for the study by the 31st October each year. For multi-centre studies the Chief Investigator should submit to the Lead HREC on behalf of all sites.*
6. *The HREC must also be provided with a final report upon completion of the study. For multi-centre studies the Chief Investigator should notify the Lead HREC and the investigators at each site should notify the relevant Research Governance Officer.*
7. *The HREC must be notified, giving reasons if the project is discontinued at a site before the expected date of completion.*

Please refer to the NSLHD Research Office website to access forms such as the amendment form, Annual/Final Report Form, Change in Personnel Form and Serious Adverse Event Guidelines and Forms;

Internet:
http://www.northernsydneyresearch.com.au

HREC approval is valid for five (5) years from the date of the approval letter. **Your approval will therefore expire on the 24/08/2017. Your first progress report is due on the 31st October 2013.**

Yours sincerely,

[redacted]

Dr Liz Newton
Co Chairperson
NSLHD HREC

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

AURED NEAF REF: *HREC/12/HAWKE/209*
NSLHD REF NO: 1207-217M,

Appendix C: Sydney post-BMT study invitation letter, Patient information sheet (PIS), Informed consent form (ICF)

[Insert institutional letterhead]

[insert name of local institution/s where research is being conducted]

19 December 2018

[insert name & address]

Dear ..

The Experience of Bone Marrow Transplant (BMT) in Sydney, Australia

Thank you for agreeing to participate in the Experience of Bone Marrow Transplant (BMT) in Sydney study and for your time in completing these forms. Your feedback regarding your own experience will provide an invaluable insight that will assist us caring for patients undergoing BMT in the future.

Please read the Patient Information Sheet attached and if you are still happy to participate please sign the consent form and complete the survey. When you have finished please return the consent form and survey to us in the stamped self-addressed envelope at your earliest convenience. The Patient Information Sheet is for you to keep.

Yours sincerely,

[insert BMT director details]

Westmead Hospital, Royal North Shore Hospital, St Vincent's Hospital & Royal Prince Alfred Hospital

PARTICIPANT INFORMATION SHEET

The Experience of survival following BMT in Sydney, Australia

1. Invitation

You are invited to participate in a research study because you have previously had a bone marrow transplant at one of the BMT hospitals in Sydney (Westmead Hospital, Royal North Shore Hospital, St Vincents Hospital and ROayl Prince Alfred Hospital). You have been identified as a potential candidate for this study by your treating haematologist. This research will help us to understand the effect that transplant had had on you and the challenges or problems that you have faced since your transplant. This information will assist us in designing and delivering the services that people who are undergoing BMT will need in the future. This project will also help people like you to make difficult decisions about whether or not to undergo a bone marrow transplant.

The study is being conducted by clinicians and researchers from all the allogeneic transplant centres in NSW including:

- A/Prof Ian Kerridge, Staff Specialist & BMT Physician, Royal North Shore Hospital.
- Dr Matthew Greenwood, Staff Specialist & Director Stem Cell Transplant Program, Royal North Shore Hospital.
- Dr Mark Hertzberg, Director of Blood and Marrow Transplant Services, Westmead Hospital.
- Dr John Moore, Senior Staff Specialist, St Vincent's Hospital & BMT Network NSW.
- Dr Stephen Larson, Director of BMT Services, Royal Prince Alfred Hospital.
- Dr Nicole Gilroy, Senior Staff Specialist, St Vincent's Hospital, Royal North Shore Hospital & Blood and Marrow Transplant Network NSW.
- Dr Lisa Brice, Clinical Psychologist, Royal North Shore Hospital.
- Ms Gemma Dyer, Clinical Nurse Consultant - BMT Long Term Follow Up Project, Blood & Marrow Transplant Network.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. If you don't wish to take part, you don't have to. You are not required to participate in this study in order to receive care and services.

2. ‘What is the purpose of this study?’

The purpose of this research is to:

- examine the physical and psychosocial impact of BMT and the quality of life of allogeneic bone marrow transplant patients;
- to identify gaps in services provided to survivors of bone marrow transplant;
- to provide better information to patients about the possible late effects of BMT and to healthcare professionals.

3. ‘Why have I been invited to participate in this study?’

You are eligible to participate in this study because you have undergone a allogeneic bone marrow transplant as part of your treatment for a malignant or non-malignant disease at the BMT unit of Westmead Hospital, Royal North Shore Hospital, St Vincent’s Hospital or Royal Prince Alfred Hospital

.

4. ‘What if I don’t want to take part in this study, or if I want to withdraw later?’

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

5. ‘What does this study involve?’

Procedures

If you agree to participate in this study, you will be asked to fill out 4 questionnaires. These questionnaires cover a number of areas which will assess medical complications of BMT, quality of life, medications, oral and dental health, infections, vaccinations, complementary therapies, cancer screening, travel, health behaviours, diet/nutrition, fertility and sexual function, relationships and long term follow up care. The 4 questionnaires will take approximately 30 minutes to complete.

Once you have completed the survey you will be asked to return it to is in a self-addressed postage-paid envelope. You can contact the investigators to ask any questions you might have about any aspect of this study.

The consent to access your personal medical records is also required. The records will be used to collect information about your transplant, including details about your diagnosis.

Reimbursement

You will not be paid for your participation in this research.

6. **'Are there risks to me in taking part in this study?'**

This research poses no physical risks. Very rarely, people may find questions about their diagnosis or transplant, or their life since transplant upsetting. If this occurs we suggest that you discuss your thoughts or feelings with your partner, family or friends or raise them with your transplant team.

7. **'Will I benefit from the study?'**

This study aims to further medical knowledge about issues that affect survivors of bone marrow transplant and the results will be used to inform the design and delivery of healthcare services to BMT patients in NSW. The results of this study may not, however, be of direct benefit to you.

8. **'How will my confidentiality be protected?'**

Surveys will use an identification number and will not ask for your name, therefore none of your normal treatment team will know whether or not you participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be locked in an office or stored on a password protected database. Only the researchers named above will have access to your details and results that will be held securely in the Haematology Department of the Royal North Shore Hospital.

9. **'What happens with the results?'**

Following completion of this study we plan to publish the results in academic medical publications and present them at scientific meetings. In all publications and presentations, study information will be provided in such way that you cannot be identified. Results of the study will be provided to you, if you wish.

10. **'What should I do if I want to discuss this study further before I decide?'**

When you have read this information, the researchers, Gemma Dyer or Lisa Brice, will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact Gemma on 0459 805 603.

11. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by Northern Sydney Coast Human Research Ethics Committee. Any person with concerns or complaints about the conduct of this study should contact the Research Officer who is nominated to receive complaints from research participants. You should contact them on 02 9926 4590 and quote [*HREC project number*].

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Westmead Hospital, Royal North Shore Hospital, St Vincent's Hospital & Royal Prince Alfred Hospital

CONSENT FORM

The Experience of survival following BMT in Sydney, Australia

1. I,.....
   of.....
   agree to participate as a subject in the study described in the participant information statement *attached to this form.*

2. I acknowledge that I have read the participant information statement, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

4. I understand that I can withdraw from the study at any time without prejudice to my relationship to Westmead Hospital, Royal North Shore Hospital, St Vincent's Hospital or Royal Prince Alfred Hospital.

5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

6. I understand that if I have any questions relating to my participation in this research, I may contact Gemma Dyer on telephone 0459 805 603, who will be happy to answer them.

7. I acknowledge receipt of a copy of this Consent Form and the Participant Information Statement.

Complaints may be directed to *[insert local details]*

Signature of subject **Please PRINT name** **Date**

_____

Signature of investigator **Please PRINT name** **Date**

_____

[Institutional letterhead]

Westmead Hospital, Royal North Shore Hospital, St Vincent's Hospital and Royal Prince Alfred Hospital

The Experience of survival following BMT in Sydney, Australia

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with Royal North Shore Hospital or St Vincent's Hospital.

Signature Date

Please PRINT Name

The section for Revocation of Consent should be forwarded to Gemma Dyer, Royal North Shore Hospital, Haematology Department, Level 4, Pacific Highway, St Leonards, NSW 2065+

Blood and Marrow Transplant Network NSW

The Sydney Post-BMT study

A collaborative study conducted by the BMT Network of NSW including the bone marrow transplant units at Westmead Hospital, St Vincents Hospital, Royal North Shore Hospital and Royal Prince Alfred Hospital.

INSTRUCTIONS

- Use a black or blue biro
- Do not fold or bend this survey

- Cross the boxes like this:

In general, would you say your health is:
(Mark one only)

- Excellent ☐
- Very good ☐
- Good ☒
- Fair ☐
- Poor ☐

You would mark this one if you think your health is good.

- Print clearly in the boxes like this:

What is your postcode?
(PRINT clearly in the boxes) 2 3 0 8

- Correct mistakes like this:

When you go to a General Practitioner:
(Mark one on each line)

	Always	Most of the time	Sometimes	Rarely or never
Do you go to the same place?	☐	⊗	~~☒~~	☐

If you make a mistake, simply scribble it out and mark the correct answer with a circle.

This study is supported by the Agency for Clinical Innovation (ACI).

ACI NSW Agency for Clinical Innovation

The Sydney Post-BMT study

Survey No.:

We are interested in finding out about your experiences of life after having a Bone Marrow Transplant (BMT). We would like to know about the complications of BMT that have affected you most and also what lifestyle choices you have made. Your answers will remain strictly confidential.

DEMOGRAPHICS : Please tell us a little bit about you;

1. Date of birth: / /
2. Transplant date: / /
3. Postcode:
4. Ethnicity:
5. Gender: ☒ Male ☒ Female
6. Education: ☒ Some high school ☒ Completed high school ☒ Trade qualifications/diploma ☒ Some university ☒ Completed university

MEDICAL COMPLICATIONS : We know that BMT patients can experience many complications after treatment. We are particularly interested in finding out if any medical problems, including Graft vs Host Disease (GvHD) and other chronic conditions, have affected your health.

7. Have you ever been diagnosed with chronic Graft versus Host Disease (GvHD)? ☒ Yes ☒ No

If yes, please indicate which parts of your body have been affected by GVHD below (mark all that apply).

8. Skin ☒	9. Eyes ☒	10. Lungs ☒	11. Mouth ☒
12. Liver ☒	13. Stomach or intestines ☒	14. Nails ☒	15. Vagina ☒
16. Penis ☒	17. Muscles/joints ☒	18. Other organ ☒	19. Not sure ☒

Since your BMT have you ever been diagnosed with any of the following?

	NO	YES
20. An underactive thyroid	☒	☒
21. An overactive thyroid	☒	☒
22. Osteopaenia/Osteoporosis	☒	☒
23. Avascular Necrosis (dead bone in your joints)	☒	☒
24. Any spinal/hip fracture	☒	☒
25. Cataracts	☒	☒
26. Diabetes	☒	☒
27. High blood pressure	☒	☒
28. High cholesterol	☒	☒
29. Iron overload (too much iron in your body)	☒	☒
30. Depression	☒	☒
31. Anxiety	☒	☒
32. Mouth Cancer	☒	☒
33. Recurrent colds	☒	☒
34. Skin Cancer	☒	☒ → If YES, what type was it?
39. Any other Cancer?	☒	☒

If YES, what type was it?
35. ☒ BCC 36. ☒ SCC
37. ☒ Melanoma 38. ☒ Don't know

40. If yes, please specify:

	NO	YES
41. Any other medical problems that we haven't mentioned?	☒	☒

42. If YES, please specify:

REFERRALS, TESTS & ASSESSMENTS & TIME : We are interested in finding out if you have undergone any tests for long term medical complications as well as who has been involved in your care following BMT.

Have you had any of the following tests or assessments since your BMT?

		NO	YES
43.	Heart scan (Gated Heart Pool Scan, Cardiac Echo or Heart Ultrasound)	☒	☒
44.	Lung Function Tests	☒	☒
45.	Bone Mineral Density Scan	☒	☒
46.	Thyroid examination (had your thyroid felt by a doctor or had a Thyroid Ultrasound/Scan)	☒	☒

Since your BMT have you been referred to any of the following specialists or services?

		NO	YES
47.	Ophthalmologist (Eye Specialist)	☒	☒
48.	Dermatologist (Skin Specialist)	☒	☒
49.	Cardiologist (Heart Specialist)	☒	☒
50.	Respiratory Doctor (Lung Specialist)	☒	☒
51.	Endocrinologist/Diabetes Doctor	☒	☒
52.	Neurologist (Brain and Nervous System Specialist)	☒	☒
53.	Gastroenterologist (Bowel Specialist)	☒	☒
54.	Hepatologist (Liver Specialist)	☒	☒
55.	Infectious Diseases Specialist	☒	☒
56.	Gynaecologist	☒	☒
57.	Fertility Specialist	☒	☒
58.	Nephrologist (Kidney Specialist)	☒	☒
59.	Urologist (Bladder Specialist)	☒	☒
60.	Rehabilitation Specialist	☒	☒
61.	ENT Doctor (Ears, Nose, Throat Specialist)	☒	☒
62.	Orthopaedic Doctor (Bone Specialist)	☒	☒
63.	Psychologist	☒	☒
64.	Psychiatrist	☒	☒
65.	Social Worker	☒	☒
66.	Occupational Therapist	☒	☒
67.	Dietician	☒	☒
68.	Physiotherapist	☒	☒
69.	Exercise Physiologist	☒	☒
70.	Any other specialist or service not mentioned	☒	☒

↳ **71.** If yes, please specify: _____

We are interested in finding out how much time (days) you are required to spend attending hospital/medical appointments/tests/assessments related to your BMT or complications from your BMT?

72. On average, how often do you attend a hospital or medical practice/facility: (please mark one option)

☒ More than once a week ☒ Once per week ☒ Once per month ☒ Once every 3 months

☒ Once every 6 months ☒ Yearly ☒ Less than yearly

73. Are you ever required to stay overnight close to the hospital/medical practice when you attend appointments/tests? ☒ Yes ☒ No

If yes, where do you stay:

		NO	YES
74.	Hospital accommodation	☒	☒
75.	Other subsidised accommodation (eg funded by the Leukaemia Foundation)	☒	☒
76.	You stay with friends or family	☒	☒
77.	You pay for private accommodation (eg Hotel/motel)	☒	☒

MEDICATIONS & TREATMENTS : BMT patients may need to take medications for many years after transplant. We would like to know about the medications that you are currently taking.

Please indicated which medications you are **currently** taking: (Please mark all that apply)

- **78.** Penicillin ☒
- **79.** Cyclosporine/Tacrolimus/Mycophenolate (Immune drug) ☒
- **80.** Any cholesterol lowering drug ☒
- **81.** Acyclovir/Valaciclovir (Antiviral drug) ☒
- **82.** Prednisolone ☒
- **83.** Any bone strengthening drug (eg Zometa) ☒
- **84.** Bactrim/Septrin ☒
- **85.** Calcium ☒
- **86.** Any blood pressure drug ☒
- **87.** Fluconazole/ Posaconazole/Itraconazole (Antifungal drug) ☒
- **88.** Vitamin D ☒
- **89.** A drug to reduce iron (eg Exjade) ☒
- **90.** Antidepressant ☒
- **91.** Anti-anxiety drug ☒
- **92.** Any sleeping tablet/sedative ☒
- **93.** Hormone replacement/Oral contraceptive pill ☒
- **94.** Other, please specify: (include over-the-counter medications) ☒

95. Do you take all the medication that you are prescribed and at the doses prescribed? ☒ Yes ☒ No

If not, why not (mark as many as apply)?

- **96.** Cost ☒
- **97.** Side effects ☒
- **98.** You don't feel they are necessary ☒
- **99.** Other, please specify: ☒

BMT patients also may need medical treatments for many years after transplant.
We would like to know about the treatments you are currently receiving.

Please indicate which treatments which you are **currently** receiving: (please tick all that apply)

- **100.** Venesection (blood removed) ☒
- **101.** Immunoglobulin infusion (eg Intragam) ☒
- **102.** PUVA (Ultraviolet Light Therapy) ☒
- **103.** ECP (Extracorporeal Photopheresis) ☒
- **104.** Other, please specify: ☒

ORAL & DENTAL HEALTH : BMT patients sometimes develop dental problems after their transplant.
We would like to know about your dental health.

105. Do you regularly go to the dentist? ☒ Yes ☒ No

106. If yes, date last attended: / /

107. How often do you attend? (times per year)

If no, why not (tick as many as apply):

- ☒ **108.** Time
- ☒ **109.** Cost
- ☒ **110.** You don't feel it's necessary
- ☒ **111.** It has not been advised by your treatment team
- ☒ **112.** Other, please specify:

Since your transplant, have you been diagnosed with the following?

		NO	YES
113.	Mouth ulcers	☒	☒
114.	Dry mouth	☒	☒
115.	Gum disease (Gingivitis)	☒	☒
116.	Tooth abscess	☒	☒
117.	Decaying teeth/Cavities	☒	☒
118.	Any other dental problem not mentioned:	☒	☒

119. If yes, please specify:

INFECTIONS : Infections are a major concern for BMT patients. We would like to know about your infection history.

Have you been diagnosed with any of the following since your transplant?

			NO	YES
120.	Hepatitis A		☒	☒
121.	Hepatitis B		☒	☒
122.	Hepatitis C		☒	☒
123.	Haemophilus Influenza type B		☒	☒
124.	Pneumococcal disease		☒	☒
125.	Meningococcus		☒	☒
126.	Varicella / Chicken pox		☒	☒
127.	Zoster (Herpes Zoster) / Shingles		☒	☒
128.	Influenza "flu"		☒	☒
129.	Measles		☒	☒
130.	Mumps		☒	☒
131.	Rubella		☒	☒
132.	Pertussis "whooping cough"		☒	☒
133.	Tuberculosis		☒	☒
134.	Pap smear abnormality/HPV infection (females)	☒ N/A	☒	☒
135.	Genital warts		☒	☒
136.	Fungal infection		☒	☒

If yes, please specify:

VACCINATIONS : Vaccinations are an effective way of preventing some infections. We would like to know about your vaccination status after your diagnosis and after your BMT.

After your diagnosis, but **before** your transplant, did you receive the following vaccinations?

			NO	YES
137.	Annual flu shot (Influenza)		☒	☒
138.	Pneumococcus		☒	☒
139.	Human Papillomavirus Vaccine (HPV) vaccine, otherwise known as cervical cancer vaccine (Gardasil or Cervarix)	☒ N/A	☒	☒

If yes, where did you receive this vaccine or these vaccines?

140. GP ☒ 141. Hospital ☒ 142. Community clinic ☒ 143. Other ☒

Was this location:

144. Urban ☒ 145. Rural ☒ 146. Remote ☒

After your transplant, did you receive the following vaccinations?

	UNSURE	NO	YES
147. Diphtheria, Tetanus, Pertussis	☒	☒	☒
148. Polio vaccine	☒	☒	☒
149. Haemophilus Influenza type B	☒	☒	☒
150. Hepatitis B	☒	☒	☒
151. Pneumococcus	☒	☒	☒
152. Influenza (flu shot)	☒	☒	☒
153. Meningococcus	☒	☒	☒
154. Measles, Mumps, Rubella (MMR)	☒	☒	☒
155. Varicella (Shingles)	☒	☒	☒
156. HPV	☒	☒	☒

If yes, where did you receive this vaccine or these vaccines?

157. GP ☒ **158.** Hospital ☒ **159.** Community clinic ☒ **160.** Other ☒

Was this location: **161.** Urban ☒ **162.** Rural ☒ **163.** Remote ☒

164. Did you receive a vaccination schedule?	☒ Unsure	☒ No	☒ Yes
165. Did your GP receive a vaccination schedule?	☒ Unsure	☒ No	☒ Yes
166. Do you have a personal record (book) of any vaccinations you received?	☒ N/A	☒ No	☒ Yes

COMPLEMENTARY THERAPIES : Complementary therapy use has increased over the years. We would like to know if this is something you have tried since having your BMT.

Have you tried, or do you use any of the following complementary therapies?

167. Nutrition and dietary approaches (eg macrobiotic diet) ☒ Yes ☒ No
↳ **168.** If yes, please specify:

169. Herbal supplements (eg Ginseng) ☒ Yes ☒ No
↳ **170.** If yes, please specify:

171. Vitamin therapies ☒ Yes ☒ No
↳ **172.** If yes, please specify:

173. Mind-body therapies (eg Meditation, hypnosis, spiritual healing) ☒ Yes ☒ No
↳ **174.** If yes, please specify:

175. Manipulative and body based therapies (eg Acupuncture, Chiropractic, massage, reflexology) ☒ Yes ☒ No
↳ **176.** If yes, please specify:

177. Traditional whole medicine systems (eg Traditional Chinese Medicine, Indian (Ayurvedic Medicine) ☒ Yes ☒ No
↳ **178.** If yes, please specify:

179. Energy Medicine (eg Reiki) ☒ Yes ☒ No
↳ **180.** If yes, please specify:

181. Homeopathy ☒ Yes ☒ No

182. Any other type not mentioned ☒ Yes ☒ No
↳ **183.** If yes, please specify:

CANCER SCREENING : We would like to know if you have had any cancer screening tests or checks since your BMT.

Since your transplant, please indicate if you have ever had the following:

184. Skin check ☒ No ☒ Yes → **185.** If yes, date last attended: / /

If not, why not? (Mark as many as apply) **186.** How often do you attend (times per year?)

☒ **187.** Time ☒ **189.** You don't feel it's necessary

☒ **188.** Cost ☒ **190.** It has not been advised by your treatment team

---

191. Bowel cancer check (eg stool/bowel motion check, colonoscopy &/or haemoccult blood test)

☒ No ☒ Yes → **192.** If yes, date last attended: / /

If not, why not? (Mark as many as apply) **193.** How often do you have this done? (each year, every 2 years, etc)

☒ **194.** Time ☒ **196.** You don't feel it's necessary

☒ **195.** Cost ☒ **197.** It has not been advised by your treatment team

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FOR WOMEN

198. Pap smear ☒ No ☒ Yes → **199.** If yes, date last attended: / /

If not, why not? (Mark as many as apply) **200.** How often do you have this done? (each year, every 2 years, etc)

☒ **201.** Time ☒ **202.** You don't feel it's necessary

☒ **203.** It has not been advised by your treatment team ☒ **204.** Cost

☒ **205.** I don't need it because I have had the HPV Vaccination

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206. Mammogram (Breast Screen) ☒ No ☒ Yes

If not, why not? (Mark as many as apply) **207.** If yes, date last attended: / /

☒ **210.** Time ☒ **212.** You don't feel it's necessary

☒ **211.** Cost

☒ **213.** It has not been advised by your treatment team

☒ Other

208. How often do you have this done? (each year, every 2 years, etc)

209. How old were you when you had your first mammogram?

FOR MEN **214.** Prostate check (eg blood test for PSA level or prostate check by a doctor (Digital Rectal Exam)

☒ No ☒ Yes → **215.** If yes, date last attended: / /

If not, why not? (Mark as many as apply) **216.** How often do you attend? (times per year)

☒ **217.** Time ☒ **219.** You don't feel it's necessary ☒ Other

☒ **218.** Cost ☒ **220.** It has not been advised by your treatment team

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TRAVEL HISTORY : Most people enjoy travel, but travelling overseas can pose some health risks depending on the countries visited. We would like to know about any international travel you have undertaken since your BMT and whether there were any risks to your health while you were away.

221. Have you travelled overseas since your transplant? ☒ Yes ☒ No

222. If yes, where have you travelled (including region) and what years did you travel overseas (please list all).

Have you avoided travel because of (please tick all that apply):

	NO	YES
223. Not interested in travel	☒	☒
224. Physical limitations	☒	☒
225. The risk of exposure to new infections	☒	☒
226. Costs of travel	☒	☒
227. Costs of travel insurance	☒	☒

	NO	YES
228. Did you take out travel insurance before you travelled?	☒	☒

If no, was this because (please tick all that apply):

	NO	YES
229. Unable to afford Insurance premium	☒	☒
230. No policy covering you for preexisting or existing conditions	☒	☒
231. You did not consider it necessary to take out travel insurance	☒	☒
232. Other	☒	☒

233. If yes, please specify:

Who did you seek information from about what vaccinations you needed before you travelled (tick as many as apply)?

234. GP ☒ 235. Transplant doctor ☒ 236. Travel clinic ☒ 237. Other ☒

238. Did not seek information ☒

239. Did you require any additional vaccines or medicines to prevent infection? ☒ Yes ☒ No

240. If yes, please specify:

Did you have any of the following problems while you were away? (Please tick all that apply)

241. Diarrhoea ☒ 242. Vomiting ☒ 243. Respiratory infection ☒

What kind of activities did you participate in whilst away? (Please tick all that apply)

244. Swimming ☒ 245. Caving/kayaking ☒ 246. Outdoor adventure type exercise etc ☒

247. No outdoor activities ☒

Where did you eat while away? (Please tick all that apply)

248. Restaurants ☒ 249. Street food ☒ 250. Friends/Family ☒

251. Prepared your own ☒ 252. All of the above ☒

What kind of water did you drink? (Please tick all that apply) 253. Bottled ☒ 254. Tap ☒ 255. River ☒ 256. Lake ☒

CLOSE PERSONAL CONTACTS : People who have had a transplant are at risk of infections – including from their family. School-aged children, in particular, often get infections and can pass them on easily. We are interested in finding out who you live with and what their vaccination status is.

257. Do you live with any children? ☒ No ☒ Yes → 258. If yes, what are their ages?

259. Have they been fully vaccinated? ☒ No ☒ Yes

260. Who else do you live with? What is your relationship to them?

261. Do the people you live with have the Influenza Vaccine (flu shot) every year? ☒ No ☒ Yes

262. Do you care for young children (in your occupation or as a personal carer eg. grandparent)? ☒ No ☒ Yes

LIFESTYLE : Lifestyle habits can have an impact on a person's health. We are interested in finding out about your lifestyle choices.

263. Do you smoke? ☒ No ☒ Yes → **264.** If yes, how many cigarettes per day? ☐

265. Do you drink alcohol? ☒ No ☒ Yes → **266.** If yes, how many standard drinks per week (on average)? ☐

267. Do you exercise or play sport? ☒ No ☒ Yes → **268.** If yes, how many times per week? ☐

→ **269.** How many minutes per session? ☐

270. Is your ability to exercise compromised in anyway by your BMT or by complications of your transplant? ☒ No ☒ Yes

271. If yes, how? ☐

272. Do you always/routinely use sun protection (eg sunscreen, hat, sunglasses, avoid being in the sun between 11am-3pm, wear shirts with long sleeves and a collar)? ☒ No ☒ Yes

DIET / NUTRITION : We are interested in finding out about your eating habits and any ongoing symptoms which may be affecting you.

273. What is your height (cm)? ☐ **274.** What is your weight (kg)? ☐

275. Do you feel like you are: ☒ Underweight ☒ Overweight ☒ Neither

276. Are you happy with your current weight? ☒ Yes ☒ No

Do you have any of following symptoms?

	NO	YES
277. Nausea	☒	☒
278. Vomiting	☒	☒
279. Constipation	☒	☒
280. Diarrhoea	☒	☒
281. Taste alterations	☒	☒
282. Smell alterations	☒	☒
283. Poor appetite	☒	☒
284. Are your eating habits back to normal since your BMT?	☒	☒
285. Do you find eating as enjoyable as before your transplant?	☒	☒
286. Have you made any significant changes to your eating habits since your BMT transplant? (eg: organic, vegetarian, avoiding specific foods, as a result of a new diagnosis of diabetes etc)	☒	☒

287. If yes, please describe changes you have made to your diet? ☐

	NO	YES
288. Do you take any nutritional supplements? (eg: Sustagen, Ensure, Fortisip, Twocal, Protein powder etc)	☒	☒
289. Did you have enteral nutrition (tube feeding) during your transplant?	☒	☒

If yes,

	NO	YES
290. Do you think that tube feeding was a beneficial part of your care?	☒	☒
291. Would you recommend it to others?	☒	☒

OCCUPATION – INFECTION RISK : Some occupations are associated with an increased risk of infection or injury. We would like to know if you are involved in certain occupations.

Do you fall within any of the following occupational groupings:	NO	YES
292. Gardener or landscaper	☒	☒
293. Plumber	☒	☒
294. Building or construction worker	☒	☒
295. Armed Forces/Police/ emergency services/ worker at correctional facility	☒	☒
296. Laboratory worker	☒	☒
297. Child care worker	☒	☒
298. Teacher	☒	☒
299. Health Care Worker	☒	☒
300. Agricultural worker/farmer	☒	☒

If you are involved in farming, what type of farming:	NO	YES
301. Livestock/ animal husbandry or poultry	☒	☒
302. Crops	☒	☒

OCCUPATION – WORK STATUS & FUNCTIONING : We are interested in finding out if there has been a change to your occupation or work status since your transplant.

303. What was your pre-transplant work status?

☒ Worked Full-time ☒ Worked Part-time ☒ Homemaker ☒ Casual
☒ Unemployed ☒ Unable to work because of poor health ☒ Retired

304. What is your post-transplant work status?

☒ Worked Full-time ☒ Worked Part-time ☒ Homemaker ☒ Casual
☒ Unemployed ☒ Unable to work because of poor health ☒ Retired

305. If you are retired was your retirement related to your health post-transplant? ☒ Yes ☒ No

306. If you are not retired and also not working is this due to your health post-transplant? ☒ Yes ☒ No

307. What was the nature of your pre-transplant work?

☒ Physical: please specify

☒ Non-physical: please specify

308. What is the nature of your post-transplant work?

☒ Physical: please specify

☒ Non-physical: please specify

309. What was your pre-transplant household annual income?

☒ <$20,000 ☒ $20,000 - $39,999 ☒ $40,000 - $59,999 ☒ $60,000 - $79,000
☒ $80,000 - $99,999 ☒ $100,000 - $200,000 ☒ >$200,000

310. What is your post-transplant household annual income?

☒ <$20,000 ☒ $20,000 - $39,999 ☒ $40,000 - $59,999 ☒ $60,000 - $79,000
☒ $80,000 - $99,999 ☒ $100,000 - $200,000 ☒ >$200,000

311. Have you attended a job interview since your transplant? ☒ No ☒ Yes

312. Did you disclose that you had had a BMT in your job interview? ☒ No ☒ Yes

313. Did you feel that being a BMT recipient was a factor in your: ☒ Being employed ☒ Not being employed

314. Have you had any occupational counselling regarding your legal rights? ☒ No ☒ Yes

If yes, where was this provided?

		NO	YES
315.	At work	☒	☒
316.	Your healthcare provider/BMT service	☒	☒
317.	Centrelink	☒	☒
318.	Other (eg.Leukaemia Foundation, Cancer Council)	☒	☒

319. Has your occupation/field of work changed since transplant? ☒ No ☒ Yes

If yes, why? You were unable to do previous work because of (please tick all that apply):

☒ 320. Physical limitations ☒ 321. Psychological/emotional limitations

☒ 322. Cognitive limitations

		NO	YES
323.	You were concerned about the risks to you in your workplace	☒	☒
324.	You were made redundant	☒	☒
325.	Your employer had concerns about their liability or about the risks to you	☒	☒
326.	Your employer felt that you were unable to do your job.	☒	☒
327.	Unsatisfactory redeployment/change in your work responsibilities	☒	☒
328.	Reallocation of hours/shifts	☒	☒
329.	Exhausted sick leave to attend appointments	☒	☒

330. Have you ever experienced job discrimination as a result of your health after transplant?

☒ No ☒ Yes

If yes, was this discrimination related to:

		NO	YES
331.	Job transfer	☒	☒
332.	Denial of promotion	☒	☒
333.	Difficulty finding employment	☒	☒
334.	Limitation on work responsibilities	☒	☒
335.	Workplace harassment	☒	☒
336.	Forced redundancy	☒	☒
337.	Other, please specify:	☒	☒

FERTILITY AND SEXUAL FUNCTION : Most BMT patients experience problems with fertility and many report having sexual difficulties or problems with intimacy after transplantation. We would like to know about any concerns you may have had.

Before your BMT, did you:

		NO	YES
338.	Bank sperm	☒	☒
339.	Bank embryos after a cycle of IVF	☒	☒
340.	Have ovarian tissue or eggs frozen	☒	☒

341. If not, why not? (Please tick one option)

☒ This was not offered to you ☒ You declined ☒ It was not an option for you because you were too sick or had other health problems

☒ You had completed your family

342. Other, please specify:

	NO	YES
343. Have you tried to have a baby since your transplant?	☒	☒
344. If yes, were you successful?	☒	☒

If you have had a baby since your transplant, did you use:	NO	YES
345. IVF	☒	☒
346. Donor sperm	☒	☒
347. Donor eggs	☒	☒
348. You did not require medical assistance (Your baby was conceived 'naturally')	☒	☒

FOR MEN

349. Have you resumed sexual activity since your BMT? ☒ Not sexually active ☒ No ☒ Yes

350. If yes, have you had any difficulties with sexual function since your BMT? ☒ No ☒ Yes

If yes, what type of sexual problems have you had?	NO	YES
351. Decreased enjoyment of sex	☒	☒
352. Difficulty getting or sustaining an erection	☒	☒
353. Pain with intercourse	☒	☒
354. Decreased sexual desire	☒	☒
355. Difficulties with your partner regarding the issue of sex	☒	☒
356. Other, please specify:	☒	☒

FOR WOMEN

357. Have you resumed sexual activity since your BMT? ☒ Not sexually active ☒ No ☒ Yes

358. If yes, have you had any difficulties with sexual function since your BMT? ☒ No ☒ Yes

If yes, what type of sexual problems have you had?	NO	YES
359. Decreased enjoyment of sex	☒	☒
360. Pain with intercourse	☒	☒
361. Decreased sexual desire	☒	☒
362. Difficulties with arousal	☒	☒
363. Difficulties with your partner regarding the issue of sex	☒	☒
364. Other, please specify:	☒	☒

Apart from sexual problems, have you had any of the following genital problems since your BMT? (Tick as many as apply):	NO	YES
365. Vaginal dryness	☒	☒
366. Narrowing of the vagina	☒	☒
367. Vaginal irritation or soreness not related to sex	☒	☒
368. Vaginal bleeding	☒	☒
369. Recurrent vaginal infections	☒	☒
370. Recurrent thrush	☒	☒
371. Bladder infections/cystitis	☒	☒
372. Lower back pain	☒	☒
373. Other, please specify:	☒	☒
374. Were you still menstruating at the time of your BMT?	☒	☒

If yes,	NO	YES
375. Did your periods ever cease following BMT	☒	☒
376. If your periods stopped following BMT – did they later recommence?	☒	☒
377. If yes, were they regular?	☒	☒

378. If yes, how long after BMT did they recommence? _____ years _____ months

RELATIONSHIPS : BMT can have a significant impact on your life and the life of those around you. We are interested in any changes to your relationship after your BMT.

379. What is your relationship status **now**?

☒ Single ☒ Married ☒ De facto ☒ Divorced ☒ Separated

380. Since your transplant has there been a change in your relationship status? ☒ No ☒ Yes

381. If yes, how? Prior to your transplant were you:

☒ Single ☒ Married ☒ De facto ☒ Divorced ☒ Separated

LONG TERM FOLLOW UP CARE : We are interested in your views on how you would like your BMT long term follow up care delivered.

If given the choice, **who** would you prefer was primarily responsible for your BMT long term follow up care?

		NO	YES
382.	GP	☒	☒
383.	Local Haematologist	☒	☒
384.	Transplant Doctor/Transplant Centre	☒	☒

If given the choice, **where** would you prefer to have your BMT long term follow up care?

		NO	YES
385.	At your GP	☒	☒
386.	With your local Haematologist	☒	☒
387.	At the Transplant Centre (hospital) where your transplant was done	☒	☒
388.	At a local 'Satellite Clinic' run by your transplant centre and staffed by transplant staff from the hospital where your transplant was done?	☒	☒
389.	At your local hospital/clinic using telemedicine (a virtual consultant with the team from your transplant centre)	☒	☒

SOCIAL, OCCUPATIONAL ATTITUDES, PHYSICAL & PSYCHOLOGICAL CONCERNS : The table below includes a list of statements that other people with your illness have said are important. Please mark one number per line to indicate your response to each question.

		NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A BIT	VERY MUCH
390.	My income is a lot less now than it was prior to having a BMT	☒	☒	☒	☒	☒
391.	Since my transplant I have trouble remembering where I put things, like my keys or my wallet	☒	☒	☒	☒	☒
392.	Since my transplant, I have trouble paying attention when people are talking to me	☒	☒	☒	☒	☒
393.	My disease and treatment had a major financial impact on me and my family	☒	☒	☒	☒	☒
394.	Since my transplant I have to use written lists so I don't forget things	☒	☒	☒	☒	☒
395.	Since my transplant I have trouble forming thoughts	☒	☒	☒	☒	☒
396.	I have had to downsize my career since my transplant	☒	☒	☒	☒	☒
397.	Since my transplant I have trouble remembering new information, like phone numbers	☒	☒	☒	☒	☒
398.	Since my transplant it's hard for me to find the words to say what I mean in conversations with others	☒	☒	☒	☒	☒
399.	Since my transplant my thinking is slower	☒	☒	☒	☒	☒
400.	Since my transplant I have had trouble concentrating	☒	☒	☒	☒	☒
401.	My medical expenses are overwhelming	☒	☒	☒	☒	☒

Listed below are a number of statements concerning cancer patients' beliefs about having had cancer. In thinking about the past week, please indicate how much you agree or disagree with each statement: Strongly Agree, Agree, Not Certain, Disagree, or Strongly Disagree. [Please circle the number of your answer.]

		STRONGLY AGREE	AGREE	NOT CERTAIN	DIS-AGREE	STRONGLY DIS-AGREE
402.	Because cancer is unpredictable, I feel I cannot plan for the future.	☒	☒	☒	☒	☒
403.	I will probably have a relapse in the next 5 years.	☒	☒	☒	☒	☒
404.	My fear of having my cancer coming back gets in the way of my enjoying life.	☒	☒	☒	☒	☒
405.	I am afraid of my cancer coming back.	☒	☒	☒	☒	☒
406.	I am certain that I have been cured of cancer	☒	☒	☒	☒	☒

POSSIBLE AREAS OF GROWTH AND CHANGE : Please mark one box per line to indicate for each of the statements below the degree to which this change occurred in your life as a result of having a bone marrow transplant. Please using the following scale:

0 = I did not experience this change as a result of my crisis
1 = I experienced this change to a very small degree
2 = a small degree
3 = a moderate degree
4 = a great degree
5 = a very great degree as a result of my crisis

		0	1	2	3	4	5
407.	My priorities about what is important in life	☒	☒	☒	☒	☒	☒
408.	An appreciation for the value of my own life	☒	☒	☒	☒	☒	☒
409.	I developed new interests	☒	☒	☒	☒	☒	☒
410.	A feeling of self-reliance	☒	☒	☒	☒	☒	☒
411.	A better understanding of spiritual matters	☒	☒	☒	☒	☒	☒
412.	Knowing that I can count on people in times of trouble	☒	☒	☒	☒	☒	☒
413.	I established a new path for my life	☒	☒	☒	☒	☒	☒
414.	A sense of closeness with others	☒	☒	☒	☒	☒	☒
415.	A willingness to express my emotions	☒	☒	☒	☒	☒	☒
416.	Knowing I can handle difficulties	☒	☒	☒	☒	☒	☒
417.	I'm able to do better things with my life	☒	☒	☒	☒	☒	☒
418.	Being able to accept the way things work out	☒	☒	☒	☒	☒	☒
419.	Appreciating each day	☒	☒	☒	☒	☒	☒
420.	New opportunities are available which wouldn't have been otherwise	☒	☒	☒	☒	☒	☒
421.	Having compassion for others	☒	☒	☒	☒	☒	☒
422.	Putting effort into my relationships	☒	☒	☒	☒	☒	☒
423.	I'm more likely to try to change things which need changing	☒	☒	☒	☒	☒	☒
424.	I have a stronger religious faith	☒	☒	☒	☒	☒	☒
425.	I discovered that I am stronger than I thought I was	☒	☒	☒	☒	☒	☒
426.	I learned a great deal about how wonderful people are	☒	☒	☒	☒	☒	☒
427.	I accept needing others	☒	☒	☒	☒	☒	☒

Please read each statement and mark the box 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statements.

The rating scale is as follows:

0 = Did not apply to me at all
1 = Applied to me to some degree, or some of the time
2 = Applied to me to a considerable degree, or a good part of time
3 = Applied to me very much, or most of the time

		0	1	2	3
428.	I found it hard to wind down	☒	☒	☒	☒
429.	I was aware of dryness of my mouth	☒	☒	☒	☒
430.	I couldn't seem to experience any positive feeling at all	☒	☒	☒	☒
431.	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	☒	☒	☒	☒
432.	I found it difficult to work up the initiative to do things	☒	☒	☒	☒
433.	I tended to over-react to situations	☒	☒	☒	☒
434.	I experienced trembling (eg, in the hands)	☒	☒	☒	☒
435.	I felt that I was using a lot of nervous energy	☒	☒	☒	☒
436.	I was worried about situations in which I might panic and make a fool of myself	☒	☒	☒	☒
437.	I felt that I had nothing to look forward to	☒	☒	☒	☒
438.	I found myself getting agitated	☒	☒	☒	☒
439.	I found it difficult to relax	☒	☒	☒	☒
440.	I felt down-hearted and blue	☒	☒	☒	☒
441.	I was intolerant of anything that kept me from getting on with what I was doing	☒	☒	☒	☒
442.	I felt I was close to panic	☒	☒	☒	☒
443.	I was unable to become enthusiastic about anything	☒	☒	☒	☒
444.	I felt I wasn't worth much as a person	☒	☒	☒	☒
445.	I felt that I was rather touchy	☒	☒	☒	☒
446.	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	☒	☒	☒	☒
447.	I felt scared without any good reason	☒	☒	☒	☒
448.	I felt that life was meaningless	☒	☒	☒	☒

449. We are interested in hearing about what matters to you. What would you say are the **3 things** that have had the most impact on your quality of life since your transplant (or that cause you the most distress)?

i.

ii.

iii.

FACT-**BMT**(Version 4)

Below is a list of statements that other people with your illness have said are important.
Please mark one box per line to indicate your response as it applies to the <u>past 7 days</u>.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	☒	☒	☒	☒	☒
GP2	I have nausea	☒	☒	☒	☒	☒
GP3	Because of my physical condition, I have trouble meeting the needs of my family	☒	☒	☒	☒	☒
GP4	I have pain	☒	☒	☒	☒	☒
GP5	I am bothered by side effects of treatment	☒	☒	☒	☒	☒
GP6	I feel ill	☒	☒	☒	☒	☒
GP7	I am forced to spend time in bed	☒	☒	☒	☒	☒

SOCIAL/FAMILY WELL-BEING						
GS1	I feel close to my friends	☒	☒	☒	☒	☒
GS2	I get emotional support from my family	☒	☒	☒	☒	☒
GS3	I get support from my friends	☒	☒	☒	☒	☒
GS4	My family has accepted my illness	☒	☒	☒	☒	☒
GS5	I am satisfied with family communication about my illness	☒	☒	☒	☒	☒
GS6	I feel close to my partner (or the person who is my main support)	☒	☒	☒	☒	☒

Q1 Regardless of your current level of sexual activity, please answer the following question.

If you prefer not to answer it, mark this box: ☒
and go to the next question.

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS7	I am satisfied with my sex life	☒	☒	☒	☒	☒

Please mark one box per line to indicate your response as it applies to the <u>past 7 days</u>.

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	☒	☒	☒	☒	☒
GE2	I am satisfied with how I am coping with my illness	☒	☒	☒	☒	☒
GE3	I am losing hope in the fight against my illness	☒	☒	☒	☒	☒
GE4	I feel nervous	☒	☒	☒	☒	☒
GE5	I worry about dying	☒	☒	☒	☒	☒
GE6	I worry that my condition will get worse	☒	☒	☒	☒	☒

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	☒	☒	☒	☒	☒
GF2	My work (include work at home) is fulfilling	☒	☒	☒	☒	☒
GF3	I am able to enjoy life	☒	☒	☒	☒	☒
GF4	I have accepted my illness	☒	☒	☒	☒	☒
GF5	I am sleeping well	☒	☒	☒	☒	☒
GF6	I am enjoying the things I usually do for fun	☒	☒	☒	☒	☒
GF7	I am content with the quality of my life right now	☒	☒	☒	☒	☒

Please mark one box per line to indicate your response as it applies to the <u>past 7 days</u>.

ADDITIONAL CONCERNS		Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	☒	☒	☒	☒	☒
BMT2	I feel distant from other people	☒	☒	☒	☒	☒
BMT3	I worry that the transplant will not work	☒	☒	☒	☒	☒
BMT4	The effects of treatment are worse than I had imagined	☒	☒	☒	☒	☒
C6	I have a good appetite	☒	☒	☒	☒	☒
C7	I like the appearance of my body	☒	☒	☒	☒	☒
BMT5	I am able to get around by myself	☒	☒	☒	☒	☒
BMT6	I get tired easily	☒	☒	☒	☒	☒
BL4	I am interested in sex	☒	☒	☒	☒	☒
BMT7	I have concerns about my ability to have children	☒	☒	☒	☒	☒
BMT8	I have confidence in my nurse(s)	☒	☒	☒	☒	☒
BMT9	I regret having the bone marrow transplant	☒	☒	☒	☒	☒
BMT10	I can remember things	☒	☒	☒	☒	☒
Br1	I am able to concentrate	☒	☒	☒	☒	☒
BMT11	I have frequent colds/infections	☒	☒	☒	☒	☒
BMT12	My eyesight is blurry	☒	☒	☒	☒	☒
BMT13	I am bothered by a change in the way food tastes	☒	☒	☒	☒	☒
BMT14	I have tremors	☒	☒	☒	☒	☒
B1	I have been short of breath	☒	☒	☒	☒	☒
BMT15	I am bothered by skin problems (e.g. rash, itching)	☒	☒	☒	☒	☒
BMT16	I have trouble with my bowels	☒	☒	☒	☒	☒
BMT17	My illness is a personal hardship for my close family members	☒	☒	☒	☒	☒
BMT18	The cost of my treatment is a burdern on me or my family	☒	☒	☒	☒	☒

CHRONIC GRAFT VERSUS HOST DISEASE

If you have **ever** been diagnosed with chronic GvHD, **please complete all the questions that follow**.

If you have **never** been diagnosed with chronic GvHD, **then you have no more questions to answer**.

FORM B

Chronic**GVHD****Activity**Assessment – Patient Self Report Form B

SYMPTOMS

Please rate how severe the following symptoms have been in the last seven days. Please mark the box below from '0' (symptom has not been present) to '10' (the symptom was as bad as you can imagine it could be) for each item.

	Not present 0	1	2	3	4	5	6	7	8	9	As bad as you can imagine 10
Your **skin itching** AT ITS WORST?	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Your **mouth dryness** AT ITS WORST?	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Your **mouth pain** AT ITS WORST?	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒
Your **mouth sensitivity** AT ITS WORST?	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒

EYES

What is your main complaint with regard to your eyes?

Please rate how severe is this eye symptom, between '0' (not at all severe) and '10' (most severe)

0	1	2	3	4	5	6	7	8	9	10
☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒

VULVOVAGINAL SYMPTOMS (FEMALES ONLY)

Do you have any burning, pain or discomfort in the area of your vagina, vulva or labia?
OR
Do you have any discomfort or pain with sexual intercourse?

- ☒ Yes
- ☒ No
- ☒ Not applicable

PATIENT GLOBAL RATINGS

1. Overall, do you think that your chronic graft host disease is mild, moderate or severe?

- ☒ None
- ☒ Mild
- ☒ Moderate
- ☒ Severe

2. Please mark the box indicating how severe your chronic graft versus host disease symptoms are, where '0' is cGVHD symptoms that are not at all severe and '10' is the most severe chronic GVHD symptoms possible.

0	1	2	3	4	5	6	7	8	9	10
☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒

3. Compared to a month ago, overall would you say that your cGVHD symptoms are:

- ☒ +3 Very much better
- ☒ +2 Moderately better
- ☒ +1 A little better
- ☒ 0 About the same
- ☒ –1 A little worse
- ☒ –2 Moderately worse
- ☒ –3 Very much worse

LeeChronicGVHDSymptom scale

By marking one box per line, please indicate how much you have been bothered by the following problems in the past month.

		Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN						
1	Abnormal skin colour	☒	☒	☒	☒	☒
2	Rashes	☒	☒	☒	☒	☒
3	Thickened skin	☒	☒	☒	☒	☒
4	Sores on skin	☒	☒	☒	☒	☒
5	Itchy skin	☒	☒	☒	☒	☒
EYES AND MOUTH						
6	Dry eyes	☒	☒	☒	☒	☒
7	Need to use eye drops frequently	☒	☒	☒	☒	☒
8	Difficulty seeing clearly	☒	☒	☒	☒	☒
9	Need to avoid certain foods due to mouth pain	☒	☒	☒	☒	☒
10	Ulcers in mouth	☒	☒	☒	☒	☒
11	Receiving nutrition from an intravenous line or feeding tube	☒	☒	☒	☒	☒
BREATHING						
12	Frequent cough	☒	☒	☒	☒	☒
13	Coloured sputum	☒	☒	☒	☒	☒
14	Shortness of breath with exercise	☒	☒	☒	☒	☒
15	Shortness of breath at rest	☒	☒	☒	☒	☒
16	Need to use oxygen	☒	☒	☒	☒	☒
EATING AND DIGESTION						
17	Difficulty swallowing solid foods	☒	☒	☒	☒	☒
18	Difficulty swallowing liquids	☒	☒	☒	☒	☒
19	Vomiting	☒	☒	☒	☒	☒
20	Weight loss	☒	☒	☒	☒	☒
MUSCLES AND JOINTS						
21	Joint and muscle aches	☒	☒	☒	☒	☒
22	Limited joint movement	☒	☒	☒	☒	☒
23	Muscle cramps	☒	☒	☒	☒	☒
24	Weak muscles	☒	☒	☒	☒	☒
ENERGY						
25	Loss of energy	☒	☒	☒	☒	☒
26	Need to sleep/take more naps	☒	☒	☒	☒	☒
27	Fevers	☒	☒	☒	☒	☒
MENTAL AND EMOTIONAL						
28	Depression	☒	☒	☒	☒	☒
29	Anxiety	☒	☒	☒	☒	☒
30	Difficulty sleeping	☒	☒	☒	☒	☒

This is the end of the survey. Thank you for your time.

Blood and Marrow Transplant Network NSW

Survey No.:

ACI NSW Agency for Clinical Innovation

SydneyPost-BMT Clinical data form

Date of BMT: / /

Diagnosis:

- ☒ AML
- ☒ ALL
- ☒ CML
- ☒ CLL
- ☒ SAA
- ☒ NHL
- ☒ HL
- ☒ MM
- ☒ MDS/ Myeloproliferative disorder
- ☒ Other

Date of diagnosis: / /

Prognostic Group:

- ☒ Low risk
- ☒ Intermediate risk
- ☒ High risk

Stage of disease at BMT:

- ☒ CR1
- ☒ CR2
- ☒ >CR2
- ☒ Refractory
- ☒ Chronic Phase
- ☒ Accelerated Phase
- ☒ Blast crisis
- ☒ PR
- ☒ Other

Donor type:

- ☒ Sibling donor
- ☒ Haploidentical donor
- ☒ Matched Unrelated Donor
- ☒ Mis-matched Unrelated Donor

Stem Cell Source:

- ☒ Bone Marrow
- ☒ Peripheral Blood
- ☒ Cord Blood

Transplant conditioning:

Myeloablative:

- ☒ Bu/Cy
- ☒ Cy/TBI
- ☒ Bu/Flu
- ☒ Cy/ATGAM
- ☒ Cy/Flu/ATGAM
- ☒ Bu/Flu/Thymoglobuline/TBI
- ☒ Etop/TBI

Reduced Intensity:

- ☒ Flu/Cy
- ☒ Flu/Cy/TBI
- ☒ Flu/Mel
- ☒ FLAMSA
- ☒ Flu/BCNU/Mel/ATG
- ☒ Flu/TBI
- ☒ Other

GvHD Prophylaxis:

- ☒ CSA+ MTX
- ☒ CSA+Pred+MTX
- ☒ CSA+Pred+MMF
- ☒ Pred+MTX
- ☒ Tacro+MTX
- ☒ Cy+Tacro+MMF
- ☒ MTX+MMF
- ☒ Other

T-Cell Depletion?

- ☒ Yes → If YES:
  - ☒ ATGAM/ATG (Fresenius)/Thymoglobulin
  - ☒ Alemtuzumab (Campath)
  - ☒ Other
- ☒ No