Immunosuppression and malignancy in end stage kidney disease

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DECLARATION

The work in this thesis is the result of original research and has not been submitted for a higher degree at any other university or institution.

Angela C Webster Date

AUTHOR'S CONTRIBUTION

The work presented in this thesis has been carried out by the author under the supervision of Associate Professor Jonathan Craig, School of Public Health, and co-supervision of Clinical Professor Jeremy Chapman, Westmead Hospital and Associate Professor Judy Simpson, School of Public Health.

The author planned the research, designed the component studies, submitted ethics committee applications, assembled, managed and analysed the data, interpreted results, drafted and revised the manuscripts for submission to peer-reviewed journals, and wrote and compiled this thesis.

The data analysed in chapters 6 and 7 of this thesis were provided by the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), who supplied a raw dataset of variables specified by the author for all patients who commenced renal replacement therapy (RRT) in Australia or New Zealand from 1963-2004.

Chapter 6 involved data linkage of ANZDATA data with those of the Central Cancer Registry in New South Wales (NSW), which at the time of linkage was managed and operated by The Cancer Council NSW under contract to the NSW Department of Health. The author was based at the Cancer Epidemiology Research Unit at the Cancer Council NSW for the duration of this study.

Comparative data for the general population for chapter 7 were obtained from the website of the National Cancer Statistics Clearing House at the Australian Institute of Health and Welfare.

Further details of the author's and co-author's contribution to the publications presented in chapters 2 to 7 are documented at the beginning of each chapter.

The work presented in appendix 1 represents a published editorial which is separate to, but derived from this thesis. This editorial was co-written with my supervisor Clinical Professor Jeremy Chapman with the equal contribution of both of us.

The report presented in appendix 6 was published as a chapter of the 27th annual report (2004) of the Australian and New Zealand Dialysis and Transplant Registry and is primarily the work of the author. This work was the prelude to the studies presented in chapters 6 and 7.

ETHICAL CLEARANCE

The studies presented in chapters 2 –5 did not require ethical clearance.

The Australia and New Zealand Dialysis and Transplant Registry approved release and use of data for the analyses presented in chapters 6 and 7. The interpretation of these data is the responsibility of the author and should in no way be seen as an official policy or interpretation of the Australia and New Zealand Dialysis and Transplant Registry.

The study described in chapter 6 was also approved by the Cancer Institute of NSW Ethics Committee, the Cancer Council NSW Ethics Committee and the Human Research Ethics Committee at the University of Sydney.

ABSTRACT

Introduction

Kidney transplantation confers both survival and quality of life advantages over dialysis for most people with end-stage kidney disease (ESKD). The mortality rate on dialysis is 10-15% per year, compared with 2-4% per year post-transplantation.

Short-term graft survival is related to control of the acute rejection process, requiring on-going immunosuppression. Most current immunosuppressive algorithms include one of the calcineurin inhibitors (CNI: cyclosporin or tacrolimus), an anti-metabolite (azathioprine or mycophenolate) and corticosteroids, with or without antibody induction agents (Ab) given briefly peri-transplantation. Despite this approach, between 15-35% of recipients undergo treatment for an episode of acute rejection (AR) within one year of transplantation.

Transplantation is not without risk, and relative mortality rates for kidney recipients after the first post-transplant year remain 4-6 times that of the general population. Longer-term transplant and recipient survival are related to control of chronic allograft nephropathy (rooted in the interplay of AR, non-immunological factors, and the chronic nephrotoxicity of CNI) and limitation of the complications of chronic ESKD and long-term immunosuppression: cardiovascular disease, cancer and infection, which are responsible for 22%, 39% and 21% of deaths respectively.

This thesis is presented as published works on the theme of immunosuppression and cancer after kidney transplantation. The work presented in the first chapters of this thesis has striven to identify, evaluate, synthesise and distil the entirety of evidence available of new and established immunosuppressive drug agents through systematic review of randomised trial data, with particular emphasis on quantifying harms of treatment. The final chapters use inception cohort data from the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), which is first validated then used to explore the risk of cancer in more detail than was possible from trial data alone.

Interleukin 2 receptor antagonists

Interleukin-2 receptor antagonists (IL2Ra, commercially available as basiliximab and daclizumab) are humanised or chimeric IgG monoclonal antibodies to the

alpha subunit of the IL2 receptor present only on activated T lymphocytes, and the rationale for their use has been as induction agents peri-transplantation. Introduced in the mid-1990s, IL2Ra use has increased globally, and by 2003 38% of new kidney transplant recipients in the United States and 25% in Australasia received an IL2Ra. This study aimed to systematically identify and synthesise the evidence of effects of IL2Ra as an addition to standard therapy, or as an alternative to other induction agents.

We identified 117 reports from 38 randomised trials involving 4893 participants. Where IL2Ra were compared with placebo (17 trials; 2786 patients), graft loss was not different at one (Relative Risk -RR 0.84; 0.64 to 1.10) or 3 years (RR 1.08; 0.71 to1.64). AR was reduced at 6 months (RR 0.66; 0.59 to 0.74) and at 1 year (RR 0.66; 0.59 to 0.74) but cytomegalovirus (CMV) disease (RR 0.82; CI 0.65 to 1.03) and malignancy (RR 0.67; 0.33 to1.36) were not different. Where IL2Ra were compared with other antibody therapy no significant differences in treatment effects were demonstrated, but IL2Ra had significantly fewer side effects.

Given a 40% risk of rejection, 7 patients would need treatment with IL2Ra in addition to standard therapy, to prevent 1 patient having rejection, with no definite improvement in graft or patient survival. There was no apparent difference between basiliximab and daclizumab.

Tacrolimus versus cyclosporin for primary immunosuppression

There are pronounced global differences in CNI use; 63% of new kidney transplant recipients in the USA but only 22% in Australia receive tacrolimus as part of the initial immunosuppressive regimen. The side effects of CNI differ: tacrolimus is associated more with diabetes and neurotoxicity, but less with hypertension and dyslipidaemia than cyclosporin, with uncertainty about equivalence of nephrotoxicity or how these relate to patient and graft survival, or impact on patient compliance and quality of life. This study aimed to systematically review and synthesise the positive and negative effects of tacrolimus and cyclosporin as initial therapy for renal transplant recipients.

We identified 123 reports from 30 randomised trials involving 4102 participants. At 6 months graft loss was reduced in tacrolimus-treated recipients (RR 0·56; 0·36 to 0·86), and this effect persisted for 3 years. The relative reduction in graft loss with tacrolimus diminished with higher levels of tacrolimus (P=0.04), but did not vary

with cyclosporin formulation (P=0.97) or cyclosporin level (P=0.38). At 1 year, tacrolimus patients suffered less AR (RR 0·69; 0·60 to 0·79), and less steroid-resistant AR (RR 0·49; 0·37 to 0·64), but more insulin-requiring diabetes (RR 1·86; 1·11 to 3·09), tremor, headache, diarrhoea, dyspepsia and vomiting. The relative excess in diabetes increased with higher levels of tacrolimus (P=0.003). Cyclosporin-treated recipients experienced significantly more constipation and cosmetic side-effects. We demonstrated no differences in infection or malignancy.

Treating 100 recipients with tacrolimus instead of cyclosporin for the 1st year post-transplantation avoids 12 suffering acute rejection and 2 losing their graft but causes an extra 5 to become insulin dependent diabetics, thus optimal drug choice may vary among patients.

Target of rapamycin inhibitors for primary immunosuppression

Target of rapamycin inhibitors (TOR-I) are among the newest immunosuppressive agents and have a novel mode of action but uncertain clinical role. Sirolimus is a macrocyclic lactone antibiotic and everolimus is a derivative of sirolimus. Both prevent DNA synthesis resulting in arrest of the cell cycle. Animal models suggested TOR-I would provide synergistic immunosuppression when combined with CNI, but early clinical studies demonstrated synergistic nephrotoxicity. Since then diverse trials have explored strategies that avoid this interaction and investigated other potential benefits. The aim of this study was to systematically identify and synthesise available evidence of sirolimus and everolimus when used in initial immunosuppressive regimens for kidney recipients.

We identified 142 reports from 33 randomised trials involving 7114 participants, with TOR-I evaluated in four different primary immunosuppressive algorithms: as replacement for CNI, as replacement for antimetabolites, in combination with CNI at low and high dose, and with variable dose of CNI. When TOR-I replaced CNI (8 trials, 750 participants), there was no difference in AR (RR 1.03; 0.74 to 1.44), but creatinine was lower (WMD -18.31 umol/l; -30.96 to -5.67), and bone marrow more suppressed (leucopoenia RR 2.02; 1.12 to 3.66, thrombocytopenia RR 6.97; 2.97 to 16.36, anaemia RR 1.67; 1.27 to 2.20). When TOR-I replaced antimetabolites (11 trials, 3966 participants), AR and CMV were reduced (RR 0.84; 0.71 to 0.99 and RR 0.49; 0.37 to 0.65) but hypercholesterolaemia was increased (RR 1.65; 1.32 to 2.06). When low was compared to high-dose TOR-I, with equal CNI dose

(10 trials, 3175 participants), AR was increased (RR 1.23; 1.06 to 1.43) but GFR higher (WMD 4.27 ml/min; 1.12 to 7.41). When low-dose TOR-I and standard-dose CNI were compared to higher-dose TOR-I and reduced CNI AR was reduced (RR 0.67; 0.52 to 0.88), but GFR also reduced (WMD -9.46 ml/min; -12.16 to -6.76). There was no significant difference in mortality, graft loss or malignancy risk demonstrated for TOR-I in any comparison.

Generally surrogate endpoints for graft survival favoured TOR-I (lower risk of acute rejection and higher GFR) and surrogate endpoints for patient outcomes were worsened by TOR-I (bone marrow suppression, lipid disturbance). Long-term hard-endpoint data from methodologically robust randomised trials are still needed.

Monoclonal and polyclonal antibody therapy for treating acute rejection

Strategies for treating AR include pulsed steroids, an antibody (Ab) preparation, the alteration of background immunosuppression, or combinations of these options. In 2002, in the USA 61.4% of patients with AR received steroids, 20.4% received Ab and 18.2% received both. The Ab available for AR are not new: horse and rabbit derived polyclonal antibodies (ATG and ALG) have been used for 35 years, and a mouse monoclonal antibody (muromonab-CD3) became available in the late 1980s. These preparations remove the functional T-cell population from circulation, producing powerful saturation immunosuppression which is useful for AR but which may be complicated by immediate toxicity and higher rates of infection and malignancy. The aim of this study was to systematically evaluate and synthesise all evidence available to clinicians for treating AR in kidney recipients.

We identified 49 reports from 21 randomised trials involving 1394 participants. Outcome measures were inconsistent and incompletely defined across trials. Fourteen trials (965 patients) compared therapies for 1st AR episodes (8 Ab versus steroid, 2 Ab versus another Ab, 4 other comparisons). In treating first rejection, Ab was better than steroid in reversing AR (RR 0.57; CI 0.38 to 0.87) and preventing graft loss (RR 0.74; CI 0.58 to 0.95) but there was no difference in preventing subsequent rejection (RR 0.67; CI 0.43 to 1.04) or death (RR 1.16; CI 0.57 to 2.33) at 1 year. Seven trials (422 patients) investigated Ab treatment of steroid-resistant rejection (4 Ab vs another Ab, 1 different doses Ab, 1 different formulation Ab, 2 other comparisons). There was no benefit of muromonab-CD3

over ATG or ALG in reversing rejection (RR 1.32; CI 0.33 to 5.28), preventing subsequent rejection (RR 0.99; CI 0.61 to 1.59), graft loss (RR 1.80; CI 0.29 to 11.23) or death (RR 0.39; CI 0.09 to 1.65).

Given the clinical problem caused by AR, comparable data are sparse, and clinically important differences in outcomes between widely used interventions have not been excluded. Standardised reproducible outcome criteria are needed.

Validity of cancer data in an end stage kidney disease registry

Registries vary in whether the data they collect are given voluntarily or as a requirement of law, the completeness of population coverage, the breadth of data collected and whether data are assembled directly or indirectly through linkage to other databases. Data quality is crucial but difficult to measure objectively. Formal audit of ANZDATA cancer records has not previously taken place. The aim of this study was to assess agreement of records of incident cancer diagnoses held in ANZDATA (voluntary reporting system) with those reported under statute to the New South Wales (NSW) state Central Cancer Registry (CCR), to explore the strengths and weaknesses of both reporting systems, and to measure the impact of any disagreement on results of cancer analyses.

From 1980-2001, 9453 residents received dialysis or transplantation in NSW. Records from ANZDATA registrants were linked to CCR using probabilistic matching and agreement between registries for patients with 1 or more cancers, all cancers and site-specific cancer was estimated using the kappa-statistic (κ). ANZDATA recorded 867 cancers in 779 (8.2%) registrants; CCR 867 cancers in 788 (8.3%), with κ =0.76. ANZDATA had sensitivity 77.3% (CI 74.2 to 80.2), specificity 98.1% (CI 97.7 to 98.3) if CCR records were regarded as the reference standard. Agreement was similar for diagnoses whilst receiving dialysis (κ =0.78) or after transplantation (κ =0.79), but varied by cancer type. Melanoma (κ =0.61) and myeloma (κ =0.47) were less good; lymphoma (κ =0.80), leukaemia (κ =0.86) and breast cancer (κ =0.85) were very good. Artefact accounted for 20.8% non-concordance but error and misclassification did occur in both registries. Cancer risk did not differ in any important way whether estimated using ANZDATA or CCR records.

Quality of cancer records in ANZDATA are high, differences largely explicable, and seem unlikely to alter results of analyses.

Risk of cancer after kidney transplantation

Existing data on the magnitude of excess risk of cancer across different kidney recipient groups are sparse. Quantifying an individual transplant candidate's cancer risk informs both pre-transplant counselling, treatment decisions and has implications for monitoring, screening and follow-up after transplantation. The aims of this study were firstly to establish the risk of cancer in the post-transplant population compared to that experienced by the general population, and secondly to quantify how excess risk varied within the transplanted population, seeking to establish meaningful absolute risk estimates for post-transplant cancer based on unalterable recipient characteristics known *a priori* at the time of transplantation.

15,183 residents of Australia and New Zealand had a transplant between 1963 and 2004, and were followed for a median of 7.2 years (130,186 person-years), with 1642 (10.8%) developing cancer. Overall, kidney recipients had 3 times the cancer risk, with risk inversely related to age (Standardised Incidence Ratio of 15 to 30 in children reducing to 2 in people > 65 years). Female recipients aged 25 - 29 had rates of cancer (779.2/100,000) equivalent to women aged 55 - 59 from the general population. The risk pattern of lymphoma, colorectal and breast cancer was similar to the overall age trend, melanoma showed less variability across ages and prostate cancer showed no risk increase. Within the transplanted population cancer risk was affected by age differently for each sex (P=0.007), and was elevated for recipients with prior non-skin malignancy (Hazard Ratio: HR 1.40; 1.03 to 1.89), of white race (HR 1.36; 1.12 to 1.89), but reduced for those with diabetic ESKD (HR 0.67; 0.50 to 0.89)

Rates of cancer in kidney recipients were similar to non-transplanted people 20 - 30 years older, but risk differed across patient groups. Men aged 45 - 54 at transplantation with graft function at 10 years had a risk of cancer that varied from 1 in 13 (non-white, diabetic ESKD, no prior cancer) to 1 in 5 (white, prior cancer, ESKD from other causes).

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I would like to acknowledge the help and support of my Supervisors. Jonathan Craig has encouraged me consistently from the germination of ideas through to the final draft of this thesis and onwards, ever propelling me forwards. His effort and energy are an inspiration. Jeremy Chapman was the catalyst in giving me a job, bringing me to Australia and engineering opportunity. His extensive knowledge and careful advice have guided me throughout my time here, and I hope will continue to do so. Judy Simpson provided clarity: she understood where I wanted to go and showed me the way through the statistical mire. My other co-authors fed my enthusiasm and were a joy to work with. I hope this thesis is only the beginning of continued alliance.

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PUBLICATIONS ARISING FROM THIS THESIS

I present this thesis for examination as a 'thesis containing published work'. Most of the chapters presented in this thesis have been published in peer reviewed medical journals; the remainder have been submitted for publication.

Chapter 2 **Webster AC**, Playford EG, Higgins G, Chapman JR, Craig JC. Interleukin 2 receptor antagonists for renal transplant recipients: a meta-analysis of randomized trials. *Transplantation* 2004 Jan 27;77(2):166-76.

And in extended form:

Webster AC, Playford EG, Higgins G, Chapman JR, Craig J. Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database Syst Rev* 2004;(1):CD003897.

Chapter 3 **Webster AC**, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *Br Med J* 2005; 331(7520):810.

And in extended form:

Webster A, Woodroffe R, Taylor R, Chapman J, Craig J. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2005;(4):CD003961.

Chapter 4 **Webster AC**, Lee VWS, Chapman JR, Craig JC. Target of rapamicin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients; a systematic review and meta-analysis of randomised trials. *Transplantation* 2006 May 15; [in press]

And in extended form:

Webster AC, Lee VW, Chapman JR, Craig JC. Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary

immunosuppression in kidney transplant recipients. *Cochrane Database Syst Rev* 2006;(2): [in press]

Chapter 5 **Webster AC**, Pankhurst T, Rinaldi F, Chapman JR, Craig JC. Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients; a systematic review of randomised trial data. *Transplantation* 2006 Apr 15; [in press]

And in extended form:

Webster A, Pankhurst T, Rinaldi F, Chapman JR, Craig JC. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. *Cochrane Database Syst Rev* 2006;(2): [in press]

Chapter 6 **Webster AC**, Supramaniam R, O'Connell DL , Chapman JR , Craig JC. Validity of registry data: agreement between cancer records in an end stage kidney disease registry (voluntary reporting) and a cancer register (statutory reporting). Submitted March 2006 *J Am Soc Nephrol*

Chapter 7 **Webster AC,** Craig JC, Simpson JM, Jones MP, Chapman JR Risk of cancer after kidney transplantation: an inception cohort study of 15,183 kidney transplant recipients. Submitted March 2006 *JAMA*

Other related publications and reports are presented as appendices

Appendix 1 Chapman JR, **Webster AC**. Cancer after renal transplantation: the next challenge. *Am J Transplant* 2004; 4(6):841-842.

Appendix 6 Chapman JR, **Webster AC**. Cancer. ANZDATA Registry Report 2004. In: Excel L, McDonald S, editors. *27th annual report*. Adelaide, South Australia: Australia and New Zealand Dialysis and Transplant Registry (http://www.anzdata.org.au), 2005: 100-106.