Universitat Autònoma de Barcelona

QUALITY OF LIFE IN HEMATOPOIETIC CELL TRANSPLANTATION

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Facultat de Medicina

Programa de Doctorat en Psiquiatria i Psicologia Mèdica

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TESI DOCTORAL

Doctoranda: Anna Barata Badiella

Directors de Tesi: Dra. Heather Jim, Prof. Jordi Sierra Gil, Dr. Rodrigo Martino Bofarull

Tutor: Prof. Enric Àlvarez Martínez

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A Hans,

A Gerhard,

Por compartir este viaje

que es vivir

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ABBREVIATIONS

GvHD: Graft-versus-Host Disease

HCT: Hematopoietic Cell Transplantation

MTX: Methotrexate

PRO: Patient Reported Outcome

QoL: Quality of Life

RCT: Randomized Control Trial

SIR: Sirolimus

TAC: Tacrolimus

TPH: Trasplantament de Progenitors Hematopoètics

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PROLOGUE

The present thesis assesses quality of life, depression, and coping strategies, and unmet needs for psychosocial care, among allogeneic recipients and their caregivers. The thesis is presented in a compendium of publications format and is based on five manuscripts published in four indexed and international journals with impact factors. The manuscripts are as follows:

First Manuscript

1. Barata A, Wood WA, Choi SW, Jim HS. Unmet Needs For Psychosocial Care In Hematologic Malignancies and Hematopoietic Cell Transplant. Current Hematologic Malignancy Reports. 2016 Aug;11(4):280-7.

Second manuscript

2. Jim H, Barata A, Small BJ, Jacobsen PB, Pidala, J. Quality Of Life Associated With Sirolimus For Prevention Of Graft-Versus-Host Disease: Results From A Randomized Trial. Haematologica. 2014 Mar; 99 (3):548-53

Third manuscript

3. Barata A, González B, Sutton S, Small, BJ, Jacobsen, PB, Jim H. Coping Strategies Modify Risk of Depression Associated with Hematopoietic Cell Transplant Symptomatology. Journal of Health Psychology. 2016 Apr 22. pii: 1359105316642004.

Manuscript Addendum 1

4. Jim HS, Quinn GP, Gwede CK, Cases MG, Barata A, Cessna J, Christie J, González L, Koskan A, Pidala J. Patient Education In Allogeneic Hematopoietic Cell Transplant: What Patients Wish They Had Known About Quality Of Life. Bone Marrow Transplant. 2014 Feb; 49 (2): 299-303

Manuscript Addendum 2

5. Jim HS, Quinn GP, Barata A, Cases M, Cessna J, González B, Koskan A, Montiel Ishino F, Pidala J. Caregivers' Quality Of Life After Blood And Marrow Transplantation: A Qualitative Study. Bone Marrow Transplant. 2014 Sep; 49 (9):1234-6

1. SUMMARY

Allogeneic hematopoietic cell transplantation (HCT) is the primary curative option for some hematological cancers but is associated with significant physical and psychological morbidity. The aim of this thesis is to assess quality of life (QoL), depression, coping strategies, and unmet needs for psychosocial care among allogeneic recipients and their caregivers. Participants were adult allogeneic recipients who received an HCT at the Moffitt Cancer Center (Tampa, United States) and their caregivers. Qualitative and quantitative methodology were used. Five papers contribute to the current thesis. In the first study, we found significant unmet needs for psychosocial care among patients diagnosed with hematological malignancies, particularly allogeneic survivors. In the second paper, results showed that fatigue and nausea were associated with receipt of sirolimus (SIR) for graft-versus-host disease (GvHD) prophylaxis and contributed to diminished QoL during the first year post-HCT. In the third study, we found that adaptive coping mitigated the relationship between HCT symptoms and depression. In the fourth work focused on patient education about post-HCT QoL, we observed that HCT patients reported feeling well prepared to deal with the acute transplant phase, but unprepared to deal with the late onset of late effects and chronic GvHD. Similarly, the fifth study showed that caregivers also reported significant unmet needs for information on late effects as well as unmet needs for emotional support. In conclusion, results of this thesis highlight the emotional and physical burden associated with allogeneic HCT and the significant unmet needs for psychosocial care among this population. Future studies should assess and develop interventions aimed at improving patient education, patient and physician communication, symptom management, and coping with the side effects of HCT.

1.1. Resum

El trasplantament al·logènic de progenitors hematopoètics (TPH) és la principal opció curativa per diverses neoplàsies hematològiques tot i que comporta una morbiditat física i psicològica significativa. L'objectiu de la tesi és avaluar la qualitat de vida, la depressió, les estratègies d'afrontament de problemes i les necessitats psicosocials en receptors de TPH al·logènic i els seus cuidadors. Els participants són receptors adults de TPH al·logènic que havien rebut un TPH en el Moffitt Cancer Center (Tampa, Estats Units) i els seus cuidadors. Els resultats s'han analitzat mitjançant metodologia qualitativa i quantitativa. La tesi es basa en cinc articles. En el primer estudi vam observar que els pacients diagnosticats d'hemopatia maligna, i especialment els supervivents de TPH al·logènic, tenen necessitats psicosocials significatives. Els resultats del segon estudi mostren que la fatiga i les nàusees associades a la profilaxis de la malaltia de l'empelt contra l'hoste amb sirolimus contribueixen a disminuir la qualitat de vida durant el primer any post-TPH. En el tercer estudi vam observar que les estratègies d'afrontament adaptatives mitiguen la relació entre els símptomes associats al TPH i la depressió. En el quart treball, que avalua l'educació sobre la qualitat de vida post-TPH, vàrem trobar que els receptors de TPH al·logènic estan ben preparats per afrontar la fase aguda del TPH, però no els efectes tardans o la malaltia del l'empelt contra l'hoste crònica. De manera similar, el cinquè estudi mostra que els cuidadors dels receptors de TPH necessiten més informació sobre els efectes tardans del TPH al·logènic, així com suport emocional. En conclusió, els resultats d'aquesta tesi destaquen la càrrega física i emocional associada al TPH al·logènic i les significatives necessitats psicosocials d'aquesta població. Futurs estudis han d'avaluar i desenvolupar intervencions dirigides a millorar l'educació del pacient, la comunicació metge pacient, el maneig dels símptomes relacionats amb el TPH, i l'afrontament dels efectes secundaris del TPH.

2. INTRODUCTION

2.1. Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is considered the primary curative option for several hematological diseases [1]. Allogeneic HCT is the standard of care for patients diagnosed with high risk leukemia, high risk myelodysplastic syndromes, severe aplastic anemia, T-cell lymphomas and lymphoblastic B-cell non-Hodgkin lymphomas [2-5]. Since the first experimental HCTs in the 1950s [6, 7], advances in transplant methodology and supportive care have resulted in an increasing number of HCTs performed worldwide and significantly improved outcomes [2, 4, 5]. For example, the introduction of less toxic conditioning regimens has enabled older patients and those with comorbidities to receive an HCT [8]. Advances in human leukocyte antigen matching have facilitated the use of allogeneic transplant in patients without a related donor [9]. The use of peripheral blood allowed faster cell engraftment when compared to bone marrow [10]. In addition, advances in supportive care, such as more effective antimicrobial agents, have resulted in reduced infectious complications [11]. As a result, recent reports indicate that survivorship rates are increasing [2, 4] and now more than 80% of patients surviving the first two years are likely to be alive at 10 years post-HCT [12]. Nonetheless, the risk of transplant-related mortality in related transplants is 13% and 15% for patients undergoing transplant in first and second complete remission, respectively [13]. This risk is much higher for patients undergoing unrelated HCT; patients in first complete remission face a mortality risk of 31%, whereas patients in second complete remission have a mortality risk of 36% [13]. In addition, HCT-survivors face significantly early and long-term HCT-related morbidity which negatively impairs their physical, psychological, social and work functioning [14-16]. Thus, HCT is a prolonged and aggressive treatment, which begins with a psychological and physical arduous hospitalization [17] and is followed by a lengthy and complex period of recovery and survivorship [18].

2.2. Hospitalization

Hospitalization for allogeneic HCT lasts approximately 20 to 30 days. Initial days are characterized by adjustment to hospitalization and uncertainty and fear regarding the procedure and its outcome. As a result, a significant proportion of patients report psychological symptoms during this period: 6 to 15% of patients report symptoms of depression [14, 19], 22% symptoms of anxiety [14], and 10% adjustment disorders [20]. Screening and treatment of depressive symptoms is essential as depression has been associated to worse transplant outcomes. For example, depression before transplant predicts slower white blood cell recovery [21], post-transplant depression [19], and worse adherence to post-transplant medication and self-care regimens [22]. Of note, coping strategies such as avoidance [23-26] and acceptance/resignation [23] have been associated with worse anxiety and depression at pre-HCT indicating a subgroup of patients who might be at a higher risk to develop more severe psychological symptoms after transplant. At the time of transplant caregivers also report significant levels of depression, anxiety, and stress [27, 28], which are higher than population norms [28].

During first days of hospitalization patients receive the conditioning regimen, in which high dose chemotherapy, with or without total body irradiation, is administered. The aim of the conditioning regimen is to eliminate the underlying disease and suppress the patient's immune functioning to prevent the rejection of the transplanted graft. Conditioning regimens in allogeneic HCT are generally classified as myeloablative or reduced intensity. Myeloablative regimens are intended to eradicate the disease by means of cytotoxic therapy. However due to its intensity, myeloablative regimens are restricted to younger patients and those without comorbidities. In contrast, reduced intensity regimens are aimed to suppress host hemopoiesis via immunomediated effects, which act against underlying malignancies. These regimens are

better tolerated by older patients and those with comorbidities. Of note, conditioning regimens entail significant side effects, such as mucositis (gastrointestinal mucosa injury which can cause intense pain, preclude oral intake and require narcotic treatment), anorexia, diarrhea, nausea and vomiting, among others [29]. These side effects cause changes in body appearance and negatively affect survivors' wellbeing and QoL [30]. In addition, due to the severe immunosuppression attained with the conditioning regimen, patients are hospitalized in protective environment rooms and are required to follow maximum hygiene, low microbial diet and close monitoring of infectious complications. Visits from relatives and friends are also restricted and they are often required to wear protective clothing such as masks and gowns. The characteristics of the HCT hospitalization contribute to patients feeling isolated, which might worsen psychological wellbeing [31].

2.2.1. Early complications

Once the conditioning regimen is finished, patients receive the infusion of hematopoietic cells from a donor. The best suitable donor is a related sibling, but this option is only feasible for 30% of patients [32]. Alternative donor sources are: a) unrelated donors, b) haploidentical related donors, such as parents, siblings or children, and c) umbilical cord blood stem cells [33]. After the infusion of hematopoietic cells, patients can experience early complications, such as graft failure, pulmonary failure, sinusoidal obstructive syndrome, infections [29], and worse psychological wellbeing. Symptoms of depression tend to increase during this period; clinically-significant depressive symptomatology has been reported in 38% of recipients at day 8 post-HCT [14]. In addition, 12 to 19% of survivors report symptoms of anxiety [14, 20], and 15% adjustment disorders [20]. Of note, similar to pre-transplant depression, depression during hospitalization is associated with longer hospital stay [20] and increased risk of mortality [34]. Depression, anger, and uncertainty during hospitalization tends to be lower in patients who use adaptive cognitive coping, whereas the use of avoidance coping has been associated to

increased anxiety [24].

In addition to the abovementioned physical and psychological symptoms, allogeneic recipients are at risk of developing acute GvHD. Acute GvHD is a severe inflammatory complication of allogeneic HCT affecting the skin, the liver and the gastrointestinal tract [35, 36]. It may also affect the endothelium, the lungs, and the hematopoietic system [36]. Acute GvHD is a significant cause of morbidity and mortality [36-38] with current treatments leading to incomplete response in many cases [39]. However, the impact that acute GvHD has on patient-reported outcomes (PROs), such as QoL, has been overlooked in research [40].

2.3. Early survivorship

Once discharged, patients and caregivers must stay close to the transplant center during the first 100 days. Patients and caregivers who do not live near the transplant center must stay in temporary housing. At this time, caregivers usually assume the patient's care, which includes performing basic medical procedures such as giving medications and injections, frequent visits to the transplant center, and following strict rules regarding hygiene and diet. Patients may require rehospitalizations due to fever or HCT-related complications such as acute GvHD. Although this is a critical period for patients and caregivers, few studies have addressed their wellbeing during the early survivorship period. Existing data suggest that 13 to 43% of patients report symptoms of depression [19, 41] and 24% symptoms of post-traumatic stress disorder [41]. Avoidance coping has been associated with post-traumatic symptoms at 6 months post-HCT [42].

Chronic GvHD manifests 90 days after transplant or later in 40% to 80% of allogeneic survivors. Most studies indicate that almost 50% of patients surviving more than one year will develop chronic GvHD [43-45]. Chronic GvHD is characterized by immune dysregulation, immunodeficiency, impaired end-organ function and decreased survival [46]. It usually affects the mouth and the skin, but may also involve the gastrointestinal tract, the eyes, the liver, the

lungs, the musculoskeletal system, and genitalia [47]. Chronic GvHD is the most common late complication and cause of mortality among allogeneic recipients [48-50]. Its severity is significantly associated with impaired psychological functioning [51], diminished QoL [18, 52-54], activity limitations [54], and impaired social [55], role, and financial wellbeing [16, 55]. Active chronic GvHD has been associated with a twofold risk of distress [56]. Although some studies suggest that once chronic GvHD is resolved QoL returns to levels comparable to patients who never had it [16, 57], other studies have found that impairment in QoL persists beyond resolution of chronic GvHD [58]. There is a need to also include patient-reported measures of GvHD and other symptomatology into clinical trials. PROs can provide important information to guide clinical decisions, particularly when differences in survival between regimens are not evident.

2.4. Late survivorship

Late survivorship is characterized by late effects and life-threating conditions, which are especially prevalent among patients with chronic GvHD [18, 54, 59]. Chronic GvHD may result in 4 to 11-fold risk of developing additional morbidities such as diabetes, lung disease, coronary artery disease, stroke, ocular complications leading to significant visual impairment, and osteonecrosis requiring joint replacement [18, 59]. Allogeneic survivors without chronic GvHD may also develop these late effects, although at a lower rate [60]. Consequently, HCT recipients are at higher risk of developing medical complications when compared to other cancer survivors and the general population, with these differences lasting 10 years post-HCT [12, 18, 59, 61]. The cumulative incidence of non-malignant late effects at 5 years post-HCT among allogeneic survivors is 79% [60]. Some of these late effects contribute to non-relapse mortality, such as secondary cancers, infections, GvHD, and organ-specific complications. Other late effects such as osteonecrosis and xerostomia are not associated with increased risk of mortality [50], but significantly compromise the patient' QoL [60].

Psychological concerns are common in late survivorship, perhaps due in part to the multiple morbidities that can occur during this time. Psychological functioning tends to improve by one year post-HCT [62, 63], yet a subgroup of patients continue to experience emotional distress. For example, 26 to 28% of allogeneic survivors report depressive symptoms at one-year post-HCT [64, 65] and 7 to 15% of survivors experience moderate to severe depressive symptoms between the first and the fifth year post-HCT [16, 66]. After ten years post-HCT, 9 to 20% of survivors report depressive symptoms [15, 56] and 25% of survivors use antidepressant or anti-anxiety medication, twice the rate observed in non-transplant controls [67]. Depression during survivorship has been associated to slower physical and psychological recovery [16, 66], higher mortality [68] and increased suicidal risk [18]. Of note, HCT survivors face a 2.12 increase risk of death due to suicide when compared with the general population [69]. Fear of relapse, sexual dysfunction, sleep disorders, neurocognitive effects, fatigue, infertility, difficulties reassuming previous family and social roles, and job and financial insecurity are also significant during this period [66, 67, 70]. In addition, available data suggests that caregivers' psychological wellbeing is more impaired than that of patients an average of 13 years post- transplant [71].

The abovementioned physical and psychological challenges of HCT patients emphasize the need to optimize supportive care to this population [72, 73]. Needs not addressed by means of standard care are classified as unmet needs [74], and can generally be defined as encompassing domains of physical functioning, psychological functioning, activities of daily living, information, spirituality, sexuality and finances [74]. Whereas previous literature has largely described physical unmet needs, psychosocial unmet needs have received less attention.

In summary, allogeneic HCT is one of the most complex, lengthy, and aggressive treatments for cancer. It entails a significant mortality and morbidity, among which GvHD, late effects, and psychological issues are prevalent. While a growing literature has described patient-reported QoL after transplant, many studies have been characterized by methodological limitations, including mixed samples of autologous and allogeneic recipients, small sample sizes, and high

rates of attrition. Moreover, results have been generally reported as means and standard deviations, which is difficult to communicate to patients [75]. Due to the unique needs of the allogeneic population and the multiple advances performed in the HCT field it is necessary to identify and address treatment and patient-related variables placing survivors at a higher risk of worse wellbeing. In parallel, there is a need to study patient-related variables which could protect or mitigate the risk of worse psychosocial and QoL outcomes, such as specific coping strategies. Addressing these topics by means of well-designed studies that overcome the abovementioned limitations has the potential to optimize educational programs, individualize intervention approaches, and in turn, improve HCT outcomes.

3. OBJECTIVES AND HYPOTHESIS

3.1. Objectives

Main objective

The present thesis assesses HCT patients' unmet needs for psychosocial care as well as QoL, depression, and coping strategies among allogeneic recipients and their caregivers.

Specific objectives

- To describe unmet needs for psychosocial care as well as interventions to address these needs among patients diagnosed with hematological malignancies, particularly among those who received an allogeneic HCT.
- To describe patient-reported QoL through Day 360 in a randomized control trial (RCT) comparing two arms of GvHD prophylaxis regimens: SIR/tacrolimus (TAC) versus TAC/methotrexate (MTX).
- To describe the incidence and relationship between depression, HCT-related symptomatology, and coping strategies among allogeneic patients at day 90 post-HCT.
- To examine the extent to which coping modifies the risk of depression associated with HCT-related symptomatology.
- To qualitatively assess patient's perspectives on education regarding post-HCT QoL: what patients remembered from the education received pre-HCT, how they describe their QoL during the post-HCT, and how the transplant team could better prepare future candidates for life after HCT.
- To qualitatively assess QoL of caregivers of allogeneic recipients, as well as their perceptions of patients' QoL.

3.2. Hypothesis

- It was expected that a review of existing literature would reveal significant unmet needs among HCT patients
- The SIR/TAC arm will be associated with a more rapid recovery of QoL over time when compared to the MTX/TAC arm.
- HCT-related symptom severity will be significantly associated with depression.
- Maladaptive coping will predict greater depression among patients with severe HCT-related symptomatology.
- It was expected that patients and their caregivers would report the desire for more information about post-HCT QOL

Results will contribute to efforts to reduce HCT-related morbidity. First, elucidating the impact that GvHD prophylaxis regimens have on patients' QoL will inform clinical decision-making. Second, significant results indicating that coping strategies moderate the relationship between symptomatology and depression would suggest that intervention programs aimed at decreasing depressive symptoms should focus on coping strategies. Third, the identification of areas in which more support, counseling, and education efforts are needed will contribute to improved quality of care provided to HCT survivors and their caregivers.

4. RESULTS

4.1. First manuscript: Barata A, Wood WA, Choi SW, Jim HS. Unmet Needs For Psychosocial Care In Hematologic Malignancies and Hematopoietic Cell Transplant. Current Hematologic Malignancy Reports. 2016 Aug;11(4):280-7

4.2. Second manuscript: Jim H, Barata A, Small BJ, Jacobsen PB, Pidala J. Quality Of Life Associated With Sirolimus For Prevention Of Graft-Versus-Host Disease: Results From A Randomized Trial. Hematologica. 2014 Mar; 99 (3):548-53

4.3. Third Manuscript. Barata A, González B, Sutton S, Small BJ, Jacobsen PB, Jim H. Coping Strategies Modify Risk of Depression Associated with Hematopoietic Cell Transplant Symptomatology. Journal of Health Psychology. 2016 Apr 22. pii: 1359105316642004. [

4.4. Manuscript Addendum 1: Jim HS, Quinn GP, Gwede CK, Cases M, Barata A, Cessna J, Christie, González L, Koskan A, Pidala J. Patient Education In Allogeneic Hematopoietic Cell Transplant: What Patients Wish They Had Known About Quality Of Life. Bone Marrow Transplant. 2014 Feb; 49 (2): 299-303

4.5. Manuscript Addendum 2: Jim HS, Quinn GP, Barata A, Cases M, Cessna J, González B, Koskan A, Montiel-Ishino F, Pidala J. Caregivers' Quality Of Life After Blood And Marrow Transplantation: A Qualitative Study. Bone Marrow Transplant. 2014 Sep; 49 (9):1234-6

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HEALTH ECONOMICS (N KHERA, SECTION EDITOR)

Unmet Needs for Psychosocial Care in Hematologic Malignancies and Hematopoietic Cell Transplant

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Abstract Individuals diagnosed with hematologic malignancies experience significant unmet psychological, physical, informational, financial, and spiritual needs. The goal of the current review is to summarize and highlight recent research focused on these issues in the diagnosis and treatment periods and beyond. The review also describes the needs of adolescent and young adult (AYA) and pediatric patients. While a large body of research has reported on unmet needs among adult hematologic cancer patients, there is far less data regarding the challenges confronted by AYA and pediatric populations. Available data suggests that among all age groups, hematopoietic cell transplantation (HCT) is a risk factor for greater unmet needs. Recommendations for screening and evidence-based interventions to prevent or ameliorate unmet needs are provided. Future research is needed to develop additional evidence-based psychosocial interventions with a focus on hematologic cancer.

Keywords Hematologic neoplasms · Health services needs and demand · Hematopoietic stem cell transplantation · Child · Adolescent · Quality of life

This article is part of the Topical Collection on *Health Economics*

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Introduction

Hematologic malignancies are a diverse group of diseases that are optimally treated with a variety of regimens including chemotherapy, targeted therapies, and hematopoietic cell transplantation (HCT). Advances in treatment and supportive care have resulted in increases in survival, resulting in a significant population of survivors who may be struggling to cope with the aftermath of their disease and treatment. Increased awareness of the unmet needs of hematologic cancer patients has resulted in a sizable literature documenting the pervasive effects of a hematologic cancer diagnosis on patients' lives, although less work has evaluated interventions to meet patients' needs. The goal of the current review is to summarize and highlight recent observational and intervention research focused on unmet needs among patients with hematologic malignancies. Unmet needs are defined broadly as problems requiring assistance that may occur in one or more life domains including psychological, physical, informational, financial, and spiritual domains. The review will primarily describe unmet needs among adult hematologic cancer patients, with additional sections devoted to the needs of adolescent and young adult (AYA) and pediatric patients.

Psychological Needs

Overall, the burden of unmet psychological needs is very high among adult hematologic cancer patients, with 51 % of patients reporting at least one unmet need [1•] and 25 % reporting seven or more [2]. Across studies, the most common unmet needs are psychological in nature, including depression, anxiety, fear of cancer recurrence, and cognitive problems [1•, 2, 3]. There is evidence to suggest that psychological unmet needs such as depression and anxiety decrease over

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time among hematologic cancer patients on treatment [4]. However, unmet needs appear to be relatively stable following treatment completion [5, 6]. Rates of significant depression range from 13 to 27 % in HCT survivors [5, 7, 8], while significant anxiety is estimated to occur in 14 to 27 % [7, 8] and significant fear of progression in 23 to 29 % [6, 8]. Estimates of posttraumatic stress disorder after HCT range from 15 to 28 % [8, 9]. Less data are available regarding hematologic cancer patients receiving other treatment modalities, although it has been reported that 17 % of patients diagnosed with acute leukemia and 37 % of patients treated with a tyrosine kinase inhibitor (TKI) experienced significant depression [10, 11]. High levels of unmet psychological needs may be due to underdiagnosis and undertreatment of depression and anxiety. A recent study reported that of allogeneic HCT recipients reporting distress, only 39 % were taking antidepressant or anxiolytic medications and 22 % were receiving psychotherapy [8]. Similar findings were observed in patients with newly diagnosed or recently relapsed leukemia; among patients expressing significant worry and sadness, only 13 % received psychiatric or psychological support within 1 month [12].

Data suggest that psychological unmet needs are associated with a variety of negative outcomes among hematologic cancer patients. For example, depression is associated with worse quality of life and reduced social functioning, although not with return to work, after hematologic cancer [13, 14]. Among HCT recipients, depression is associated with nonadherence to the post-HCT regimen, increased hospital length of stay, greater mortality, and increased suicidal ideation [15–17], although evidence is conflicting [18].

Although the burden of unmet psychological needs is high, there is evidence to suggest that routine screening can detect distress among hematologic cancer patients and is associated with greater patient and provider satisfaction with care [7, 19, 20]. Relatively few studies have examined pharmacologic or psychosocial interventions to reduce distress among hematologic cancer patients. Nevertheless, there is evidence that telephone-based cognitive-behavioral therapy can reduce depression, distress, and posttraumatic stress symptomatology in patients previously treated with HCT [21]. In contrast, a study of an Internet-based coping intervention in HCT recipients found no effects on psychological functioning [22], perhaps due to the importance of the therapeutic relationship in this population [23].

Physical Needs

Physical unmet needs are frequently endorsed by hematologic cancer patients, including fatigue, impaired physical functioning, and cognitive changes [1•]. Patients have described these physical changes as "devastating," "demoralizing," and "difficult to accept" in terms of their impact on quality of life [24, 25]. A recent study found that 18 % of long-term survivors of hematologic malignancy reported significant fatigue [26]. Fatigue has also been reported in 50 % of patients treated with TKIs [27] and 42 % in hematologic cancer survivors previously treated with HCT [5]. In addition to its negative effects on quality of life, fatigue is associated with a reduced likelihood of returning to work after hematologic cancer diagnosis [14]. Among HCT recipients, physical functioning has been shown to drop precipitously following transplant, then return to baseline levels by 6 months post-HCT and remain relatively stable thereafter [28]. Among long-term HCT survivors, 11 % reported impaired physical functioning; risk factors for impairment included younger age, higher body mass index, no or part-time work, more comorbid diseases, autologous transplantation, and chronic graft-versus-host disease [29]. While little data are available regarding cognitive changes in hematologic cancer patients treated with modalities other than HCT, a meta-analysis of HCT recipients found no significant change from pretransplant to posttransplant [30]. However, because patients had been treated with induction chemotherapy prior to the pre-HCT assessment, the extent of cognitive impairment relative to pretreatment was not able to be determined.

Exercise may help to ameliorate some unmet physical needs among hematologic cancer patients. Meta-analyses of randomized controlled trials of exercise for HCT recipients have reported beneficial effects on self-reported fatigue, physical functioning, cognitive functioning, emotional functioning, and global quality of life in addition to objectively measured cardiorespiratory fitness and muscle strength [31, 32]. In contrast, although no studies have been conducted specifically in hematologic cancer patients, pharmacologic management of cancer-related fatigue or cognitive impairment with modafinil, methylphenidate, or donepezil have reported little to no improvement with significant side effects [33–35]. Consequently, physical therapy or a rehabilitation program should be considered first for patients who report significant fatigue, physical impairment, or cognitive problems.

Informational Needs

Informational needs are high among hematologic cancer patients. Recent studies have indicated that 82 % of patients wanted to have all available information and be involved in decision-making [36], while 66 % needed information communicated in a way they could understand, and 62 % needed up-to-date information [3]. In order of importance, needs included information on treatment, disease, diagnostic test results, physical functioning, and psychosocial functioning [36]. Patients with the highest needs for information were those who were younger and those who had lower socioeconomic

status, greater comorbidity, and/or worse quality of life [36]. Among HCT recipients, a recent qualitative study found that many felt well-prepared for the acute transplant period but wanted more information regarding late effects and posttransplant quality of life [25]. A qualitative analysis of physician-patient communication found that while physicians talked at length with patients about prognostic information and treatment options, they rarely checked for patient understanding of the presented information [37]. Therefore, there may be a significant gap between the information communicated by clinicians and what is understood by patients. Unmet informational needs are important to address because satisfaction with information has been found to be associated with less distress and greater adherence to imatinib among hematologic cancer patients [38, 39].

Technology offers the opportunity to enhance patient-provider communication in the context of high clinic workflow. For example, an electronic patient portal entitled "BMT Roadmap" has been created to provide patient-specific laboratory and medication information from the electronic health record to caregivers of pediatric HCT patients during hospitalization [40]. A similar project has been undertaken for adult allogeneic HCT recipients [41]. In addition, an e-tool has been developed for patients with non-Hodgkin's lymphoma to provide personalized patient disease and treatment information as well as general disease information [42]. An Internet-based program to improve awareness of post-HCT survivorship care has also been developed and is currently being evaluated in a randomized trial [43]. While most of these initiatives have currently undergone only pilot testing, they provide promising avenues for future patient education efforts.

Financial Needs

There is increasing recognition of the financial toxicity of cancer treatment. Financial toxicity is especially relevant to hematologic cancer patients, many of whom undergo long and costly therapies such as HCT, with side effects that may prevent patients and caregivers from returning to work. Financial toxicity is widespread. For example, 36 % of patients with multiple myeloma reported that they requested financial assistance during treatment, 46 % used savings to pay for treatment, and 21 % borrowed money to pay for medications [44]. Among patients receiving TKIs, higher copayment costs are associated with reduced adherence to treatment [45]. Among HCT patients, 73 % reported that they had been hurt financially by their illness and 47 % reported significant financial burden such as a decrease in household income by at least 50 %, selling/mortgaging their home, or withdrawing money from their retirement accounts [46]. HCT patients also report bankruptcy, loss of a business, and divorce due to financial stress [47]. Among patients returning to work after HCT, job insecurity, discrimination, and delayed career goals have occurred [48]. Financial insecurity can significantly affect adherence to medical regimens; 19 % of HCT recipients reported cutting back or not purchasing prescription medication, 21 % reported not making an physician appointment or having a medical test performed, and 28 % reported deferring use of a medical service [46]. Of note, all patients who provided insurance information in this study reported being insured [46], suggesting that insurance does not prevent financial toxicity. Lower socioeconomic status is associated with a variety of negative outcomes among HCT patients, including decreased overall survival and increased treatment-related mortality [49]. Consequently, greater patient education, screening, and counseling are needed regarding the financial consequences of HCT and other hematologic cancer treatments.

Spiritual Needs

The physical and emotional adversity of cancer diagnosis and treatment can cause patients to question fundamental assumptions about their religious or spiritual beliefs and the meaning of their lives [50]. Nevertheless, patients often report that cancer has deepened their religious or spiritual beliefs [51]. Research regarding spiritual needs in the context of hematologic cancer has focused primarily on HCT recipients. A recent study found that spiritual faith increased after transplant, while patients' sense of meaning and peace decreased during the acute transplant period and returned to pretransplant levels by 6 months post-HCT [52]. Greater spiritual well-being among HCT recipients is consistently associated with better quality of life, reduced symptomatology, and less depression and anxiety [52, 53]. In contrast, one study has found that spiritual absence among HCT recipients is associated with lower overall survival [54]. These data point to the importance of considering spirituality as part of care of the whole cancer patient. Although intervention studies in hematologic cancer patients are lacking, a randomized controlled trial of group therapy to increase meaning in life in advanced cancer patients resulted in improvements in quality of life, physical symptom distress, depression, hopelessness, and desire for hastened death compared to supportive group therapy [55]. Consequently, efforts to enhance patients' meaning in life, regardless of their religious or spiritual orientation, may provide broad benefits across multiple domains.

Needs of Adolescent and Young Adult Patients

AYA patients, defined as those age 15–39 at diagnosis, experience unique needs and challenges related to quality of cancer care; physical health; peer and family relationships;

educational attainment and employment; financial independence; concerns regarding dating, marriage, and fertility; body image; and health behaviors [56, 57]. Much of the data regarding AYA cancer patients come from large studies of patients with hematologic malignancies or solid tumors. Regarding quality of cancer care, survival improvements due to treatment advances in AYA patients have lagged behind those observed in pediatric and adult patients. Lack of survival gains may be due in part to low AYA participation in clinical trials and a lack of awareness among community cancer physicians regarding specialized AYA treatment protocols [58]. A recent study observed that optimal treatment was received by only 56 % of acute lymphoblastic leukemia patients, 58 % of Hodgkin's lymphoma patients, and 73 % of non-Hodgkin's lymphoma patients [58]. These data suggest that more work is needed to ensure that AYA patients receive appropriate care.

Following treatment completion, AYA cancer patients report worse quality of life as well as greater symptomatology such as fatigue, insomnia, constipation, and cognitive impairment [59, 60]. Moreover, rates of frailty in AYA and pediatric cancer survivors, including low muscle mass, self-reported exhaustion, slow walking speed, and weakness are similar to that of adults aged 65 and older [61]. Physical deficits may interfere with social functioning; among participants in the Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) study, patients reporting a high symptom burden were more likely to report the desire to talk to their family and friends about the cancer experience and meet peers diagnosed with cancer [62].

Work and educational attainment can be a problem for AYA cancer patients as well. While 72 % of cancer survivors in the AYA HOPE study returned to work or school after cancer treatment, 50 % of full-time workers/students reported problems in these areas [63]. Regarding financial unmet needs, AYA cancer patients tend to have more lost productivity, greater healthcare expenditures, and increased likelihood of financial problems than patients diagnosed at older ages [64, 65].

Fertility preservation is also a significant concern for this population. Among patients of reproductive age treated with HCT, 22 % reported trying to conceive and only 10 % reported success [66]. Although fertility concerns may not be present at the time of diagnosis, they may arise during or after treatment and negatively impact patients' psychological well-being [67]. Recommendations regarding fertility preservation after HCT have recently been published to provide guidance to clinicians on this important issue [68••].

Psychological morbidity in AYA patients is high. The AYA HOPE study found that 41 % of AYA cancer patients reported an unmet need for psychological counseling 12 months after diagnosis [69]. Studies of AYA hematologic cancer patients have found that 69 % report fear of recurrence, 46 % demonstrate symptoms of posttraumatic stress, 28 % met criteria for depression, and 23 % met criteria for anxiety [70, 71]. No differences in psychological morbidity were observed between patients on treatment compared to early survivors [70]. Interestingly, providers' perceptions of patients' psychological morbidity was not related to patients' own perceptions [70], suggesting that better patient-provider communication is necessary.

Psychological interventions for AYAs must take into account multiple competing demands for their time such as school, work, and family [72]. Use of technology such as the Internet, smartphone apps, and social media may help to reach AYA patients. Resources currently available include blogs, Twitter, and Facebook to help AYAs learn about health topics and connect with other AYA cancer patients [73••], although their efficacy has not been evaluated. Randomized trials of psychosocial interventions for AYA cancer patients with hematologic or solid tumors have generally yielded nonsignificant results, suggesting that more impactful interventions are needed [74]. Recent national workshops focused on AYA cancer survivors have called for additional research on supportive care intervention studies to assist AYAs with their psychological, physical, occupational, financial, and social unmet needs [75, 76••].

Pediatric Unmet Needs

Research regarding the unmet needs of pediatric hematologic cancer patients is sparse, particularly those treated with modalities other than HCT. Cancer survivors diagnosed during childhood tend to report better quality of life than those diagnosed during adolescence or young adulthood [77]. Nevertheless, psychological distress, impaired physical functioning, cognitive dysfunction, behavioral issues, and financial hardship frequently occur during treatment and many years thereafter. Rates of clinically significant depression or anxiety range from 6 to15 % during treatment among pediatric patients with hematologic cancer or solid tumors [78–80]. Among pediatric HCT recipients, psychological morbidity is significantly higher, with 30 % of patients meeting criteria for an anxiety disorder prior to transplant and 10 % meeting criteria for depression [80]. Among long-term childhood cancer survivors with mixed cancer types, 7 % met criteria for clinically significant anxiety or depression, although 48–54 % expressed concerns about emotional functioning or unmet psychosocial needs [79, 81, 82]. Survivors diagnosed with leukemia report significantly greater levels of depression and anxiety than their siblings [83]. Among survivors treated with HCT, rates of depression and post-traumatic stress disorder are significantly higher than siblings [84, 85]. Few psychosocial interventions have been developed specifically for pediatric cancer patients during treatment or in the survivorship period [86, 87], although several studies have demonstrated the feasibility of screening for distress and other unmet needs in this population [88, 89] and national guidelines currently

recommend annual screening of childhood and AYA cancer survivors for psychosocial distress [90••].

Physical functioning is a significant concern among pediatric hematologic cancer patients. Patients often contend with fatigue, nausea, and pain during treatment [91]. Although these symptoms tend to decrease over time [91], fatigue may become chronic among survivors [92]. Among long-term survivors of acute myelogenous leukemia (AML), 50 % reported chronic health conditions and 16 % reported severe or life-threatening health problems [93]. Rates of chronic health conditions and severe or life-threatening conditions are significantly higher among pediatric cancer survivors treated with HCT than other therapy modalities [94]. Childhood leukemia or lymphoma survivors are more likely than their siblings to report physical limitations; clinical risk factors include central nervous system irradiation and chemotherapy [83]. Thus, greater attention is needed to preventing and ameliorating late effects of childhood cancer treatment.

Cognitive impairment secondary to pediatric cancer and its treatment is a significant concern and may result in behavioral issues and decreased or delayed educational attainment and workforce participation. Greater than 20 % of childhood cancer survivors reported cognitive problems and 43 % reported concerns about their cognitive functioning [81, 95]. A study of functional neuroimaging in survivors of childhood acute lymphocytic leukemia (ALL) reported deficits in working memory despite significant compensatory activation in areas underlying working memory [96]. Cognitive impairment is also evident among patients treated with HCT, especially those who were younger than five at the time of transplant and those who received total body irradiation [97]. Regarding behavioral issues, failure in school performance, restricted group activity, and less social relations were observed in children with ALL treated with chemotherapy compared to healthy children, although healthy children displayed more social problems, attention problems, and oppositional and aggressive behavior [98]. In contrast, studies of adolescent survivors of childhood cancer have reported that those diagnosed with leukemia reported greater attention deficits, social skill deficits, and antisocial behavior relative to siblings [83, 99]. Regarding educational attainment, it has been reported that survivors of AML are less likely to complete college and more likely to be unemployed compared to their siblings [93, 100]. In light of evidence suggesting cognitive, behavioral, and educational deficits, it is currently recommended that pediatric and AYA cancer survivors complete neurocognitive evaluation at the transition to long-term follow-up and as needed thereafter for impaired educational or vocational progress [90••].

Financial hardship is also a concern for pediatric hematologic cancer patients and may adversely impact family well-being [101]. Among pediatric HCT recipients, 38 % of insured families experienced material hardship such as food, housing or energy insecurity in the year after their child's transplant [47]. Lower socioeconomic status is associated with increased mortality among pediatric leukemia patients [102]. Children with ALL living in high-poverty areas have been shown to experience significantly higher incidence of relapse, resulting in decreased overall survival and event-free survival [103]. Although data are sparse regarding the long-term effects of childhood cancer on survivors' finances, data suggest that survivors are more likely to receive supplemental security income and social security disability insurance compared to individuals without cancer [104]. Thus, childhood cancer may have a long-term negative impact on the financial well-being of survivors. Indeed, screening for material hardship, such as food, energy, and housing insecurity, should also be considered throughout the trajectory of health care [105].

Challenges in Addressing Unmet Needs

While there has been an increased awareness of the importance of treating the whole cancer patient, significant challenges remain in addressing patients' unmet needs. One challenge is improving patient-physician communication to ensure that the treatment team is aware of patients' needs. Screening guidelines and tools (e.g., the Distress Thermometer) have been developed but are still underutilized [106]. A second challenge is allocating enough staff time to help manage patient needs [107], particularly because reimbursement for these services is suboptimal. There are also relatively few evidence-based interventions for distress in hematologic cancer patients, particularly those treated with HCT and pediatric and AYA patients. More research is clearly required to fill these gaps. Following cancer treatment, fragmentation of care between the oncologist, primary care physician, and other specialists may contribute to overlooked needs. Survivorship clinics may help to remedy this problem moving forward. In sum, additional effort is needed in both research and clinical care to ensure patients receive adequate support during diagnosis, treatment, and beyond.

Conclusion

Hematologic cancer patients experience significant unmet needs in the psychological, physical, informational, financial, and spiritual domains. AYA and pediatric patients experience psychological and physical challenges as well as unique difficulties reaching developmental milestones in terms of cognition, behavior, social and romantic relationships, and educational and vocational attainment. Although a large body of literature has documented the needs of adult hematologic cancer patients, far less data have been amassed regarding AYA and pediatric patients. Thus, additional observational studies

are needed to better understand the challenges of hematologic cancer diagnosis and treatment during childhood, adolescence, and young adulthood. In addition, randomized clinical trials of psychosocial interventions to address the unmet needs of hematologic cancer patients, regardless of age, are almost completely lacking. A concerted effort must be made to develop evidence-based interventions for depression, anxiety, posttraumatic stress disorder, fatigue, pain, cognitive impairment, and other concerns that will potentially be elicited from increased efforts to screen for unmet needs in this population. Similar efforts are required to prevent and treat late effects that can cause physical limitations and reduced quality of life. Additional progress on these fronts will help to ensure better quality of life for the many current and future hematologic cancer patients.

Compliance with Ethical Standards

Conflict of Interest Anna Barata, William A. Wood, Sung Won Choi, and Heather S.L. Jim each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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4.2. Second Manuscript

Quality Of Life Associated With Sirolimus For Prevention Of Graft-Versus-Host Disease: Results From A Randomized Trial.

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Quality of life associated with sirolimus for prevention of graft-*versus*-host disease: results from a randomized trial

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ABSTRACT

Several studies have examined sirolimus-based immune suppression for the prevention of graft-*versus*-host disease after allogeneic hematopoietic cell transplantation, but little is known regarding its effects on quality of life. The current study reports on changes in quality of life to Day 360 in a randomized phase II trial of sirolimus and tacrolimus *versus* methotrexate and tacrolimus. Quality of life was assessed prior to transplant and on Days 30, 90, 180, 270, and 360 with the Functional Assessment of Cancer Therapy – Bone Marrow Transplant Trial Outcome Index. Random effects models examined the effects of study arm on change in Trial Outcome Index scores from Day 30 to 360, controlling for base-line Trial Outcome Index. The sirolimus/tacrolimus arm (n=37) showed less improvement in Trial Outcome Index scores over time compared to the methotrexate/tacrolimus arm (n=34) (P=0.02). Patients receiving sirolimus and tacrolimus were more likely to endorse nausea and a lack of energy over time ($PS \leq 0.01$). These data suggest that sirolimus-based immune suppression is associated with less improvement in quality of life in the first year post-transplant compared to methotrexate/tacrolimus. Quality of life differences may be due to increased fatigue and nausea in patients treated with sirolimus. These findings should be considered in the clinical management of patients treated with sirolimus. (*Clinicaltrials.gov identifier:00803010*).

Introduction

Graft-*versus*-host disease (GVHD) is a common and debilitating complication of allogeneic hematopoietic cell transplantation (HCT). Severe and treatment-unresponsive acute GVHD, as well as moderate-severe chronic GVHD, are associated with increased mortality.[1-3] In addition, acute and chronic GVHD are associated with significant morbidity and reduced quality of life (QOL) across multiple individual domains and overall QOL.[4-9,10,11] While acute and chronic GVHD may themselves contribute to reduced QOL, greater infectious complications, hospitalizations, and treatment with immunosuppressive medications may also result in lower QOL.[7] Interestingly, the effects of acute and chronic GVHD on QOL appear to be independent from one another, suggesting that patients diagnosed with both acute and chronic GVHD have worse QOL than patients diagnosed with either alone.[7]

As the current standard prophylaxis regimen including a calcineurin inhibitor and methotrexate (MTX) inadequately prevents acute and chronic GVHD, investigators have explored alternative approaches. One of the most extensively studied has been the combination of sirolimus (SIR) and calcineurin inhibitors (including cyclosporine and tacrolimus). An initial study found that a regimen of SIR, tacrolimus (TAC), and MTX was associated with low incidence of grade III-IV acute GVHD.[12] In contrast, two additional studies of SIR administered with MTX and a calcineurin inhibitor reported greater acute GVHD and serious toxicity.[13] Additional single center phase II trials and retrospective analyses have reported encouraging outcomes utilizing SIR/TAC.[14-17] Importantly, differences in included patients, transplantation characteristics, and intensity and duration of immune suppression exposure between these trials may have impacted the observed results. We recently reported results of a randomized clinical trial (*Clinicaltrials.gov identifier:00803010*) indicating that SIR/TAC resulted in significantly less grade II-IV acute and moderate-severe chronic GHVD compared to MTX/TAC.[18] Of note, this study investigated whether prolonged (one year post-HCT) administration of SIR would decrease risk for chronic GVHD. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) phase III randomized trial 0402 recently reported reduced grade III-IV acute GVHD but greater incidence of chronic GVHD in patients receiving SIR/TAC compared to MTX/TAC.[19]Across multiple studies, SIR/TAC appears to confer several benefits, i.e. reduction in severity of mucositis,[20] improvement in time to engraftment, reduction in GVHD, as well as increased risks, i.e. hepatic veno-occlusive disease,[21] and thrombotic microangiopathy.[22]

While these clinical results suggest competing risks and benefits associated with SIR/TAC, data on patient-reported quality of life (QOL) are needed. Significantly greater improvement in QOL after HCT among patients treated with SIR/TAC would provide further justification for its use over other regimens. While we previously reported QOL outcomes through Day 90 in our phase II trial,[18] we are not

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aware of other published QOL data from patients treated with SIR/TAC. Although patients randomized to the SIR/TAC arm reported worse pre-HCT QOL compared to patients in the MTX/TAC arm, at 30 and 90 days post-HCT, there were differences in QOL between study arms.[18] The current study builds on our previous work by describing QOL outcomes through Day 360. It was hypothesized that patients in the SIR/TAC arm would show greater improvements in QOL over time compared to patients in the MTX/TAC arm.

Methods

Patients

Patients were recruited as part of a randomized phase II study comparing sirolimus and tacrolimus (SIR/TAC) to methotrexate and tacrolimus (MTX/TAC) for prevention of GVHD. The study was approved by the University of South Florida Institutional Review Board. Study methodology has been described previously.[18] All patients provided written informed consent.

Table 1. Sociodemographic and clinical characteristics of the sample.

	MTX/TAC (n=34)	SIR/TAC (n=37)	P
Age: median (range)	49 (23-69)	49 (25-68)	0.19
Gender: n., % male	21 (62%)	28 (76%)	0.31
Ethnicity: n., % non-Hispanic	25 (74%)	33 (89%)	0.16
Race: n., % Caucasian	31 (91%)	34 (94%)	0.95
Marital status: n., % married	28 (82%)	30 (81%)	1.00
Education: n., % college grad	15 (44%)	20 (56%)	0.47
Annual household income: n., % $40,000 or greater	18 (67%)	19 (66%)	1.00
Diagnosis: n. (%)			0.10
Acute lymphoblastic leukemia	9 (26%)	5 (14%)	
Acute myelogenous leukemia	8 (24%)	15 (41%)	
Chronic lymphocytic leukemia	3 (9%)	3 (8%)	
Chronic myelogenous leukemia	0 (0%)	2 (5%)	
Myelodysplastic syndrome	7 (21%)	2 (5%)	
Multiple myeloma	2 (6%)	6 (16%)	
Myeloproliferative neoplasm	2 (6%)	0 (0%)	
Non-Hodgkin lymphoma	3 (9%)	4 (11%)	
Donor: n. (%)			0.92
Matched sibling donor	17 (50%)	17 (46%)	
Matched unrelated donor	17 (50%)	20 (54%)	
Conditioning regimen: n. (%)			0.26
Flu/Bu	28 (82%)	26 (70%)	
Pento/Bu	4 (12%)	4 (11%)	
Flu/Mel	2 (6%)	7 (19%)	
Maximum aGVHD grade: n. (%)			<0.01
0	2 (6%)	11 (30%)	
1	2 (6%)	10 (27%)	
2	27 (79%)	11 (30%)	
3	3 (9%)	4 (11%)	
4	0 (0%)	1 (3%)	
Maximum cGVHD grade: n. (%)			<0.01
0	9 (26%)	17 (46%)	
1	1 (3%)	10 (27%)	
2	10 (29%)	5 (14%)	
3	8 (24%)	1 (3%)	

Maximum grade of cGHVD not reported for 10 patients due to death. SIR: sirolimus; TAC: tacrolimus; MTX: methotrexate; Flu: fludarabine; Bu: busulfan; pento: pentostatin; Mel: melphalan; aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease; college grad: college graduate.

Study design

Briefly, all patients received peripheral blood mobilized grafts from sibling or unrelated donors matched at HLA-A, B, C, and DRB1 by high resolution typing. Randomization was stratified for age (i.e. >50 *vs.* <50 years) and donor source (i.e. sibling *vs.* unrelated). TAC was administered from Day -3 at 0.02 mg/kg/day and was then transitioned to oral formulation before hospital discharge. Serum TAC target was 5-15 ng/mL in the MTX arm and 3-7 ng/mL in the SIR arm. Patients without evidence of acute GVHD and not on systemic glucocorticoids were eligible for TAC taper at Day 50 following HCT. SIR was administered as a 9 mg oral loading dose on Day -1, followed by maintenance to target 5-14 ng/mL through at least one year post-HCT. MTX was administered on Day +1 at 15 mg/m^2, then 10 mg/m^2 on Days 3, 6 and 11. Beyond these requirements, the taper schedule for TAC, SIR, systemic glucocorticoids, and other immune suppressive agents was directed by physician judgment.

Data collection and evaluation

Self-reported socio-demographic characteristics were assessed prior to transplant. Clinical characteristics were collected prospectively as standard data elements in the parent clinical trial. QOL was assessed prior to transplant and at Days 30, 90, 180, 270 and 360 with the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT).[23] The FACT-BMT is a 47-item measure with reliability and validity in HCT patients.[23,24] It yields a total score as well as subscales assessing physical well-being (PWB), functional well-being (FWB), social/family well-being (SWB), emotional well-being (EWB), and BMT-specific concerns (BMTS). A Trial Outcome Index (TOI) is calculated by summing the PWB, FWB, and BMTS subscales. TOI was selected as the QOL outcome of interest due to its sensitivity to GVHD.[7,25] Higher scores indicate better QOL. As in previous research,[26,27] a difference of 5-9 points on the TOI was considered clinically meaningful.

Statistical analysis plan

The initial analysis plan was to conduct random effects models to examine change in QOL by study arm over the six QOL assessment points (i.e. baseline, Days 30, 90, 180, 270, 360). Random effects models are a special application of regression analysis used to estimate trajectories in QOL. Random effects models were selected because they allow for analysis of multiple within-person assessment points using all available data. Results yield intercepts and beta weights similar to standard regression models. Because groups did not display equivalent QOL at baseline,[18] the analysis plan was revised to examine the trajectory of QOL over the five post-HCT assessment points (i.e. Days 30, 90, 180, 270, and 360), controlling for pre-HCT QOL. Consequently, the results presented here examine the effect of study arm on post-HCT change in QOL independent of base-line QOL.

Results

Participants

Seventy-four patients were randomized 1:1 to SIR/TAC *versus* MTX/TAC. Three participants did not provide enough QOL data to calculate trajectories, resulting in 71 participants who contributed data to the current analyses. Socio-demographic and clinical characteristics of the sample are displayed in Table 1.

QOL by study arm

BMT-TOI scores were normally distributed; no outliers

were evident. Analyses examining the effects of study arm on post-HCT change in TOI are shown in Table 2 and Figure 1. Results indicate that TOI increased significantly over time in both study arms ($P<0.01$). There was also a significant effect of study arm over time indicating that the SIR/TAC arm showed smaller improvements in TOI than the MTX/TAC arm ($P=0.02$). Study arm significantly predicted TOI at Day 360 such that scores in the SIR/TAC group were a mean of 7.17 points lower than the MTX/TAC group ($P=0.03$).

To explore the contribution of potential clinical differences between study arms on changes in TOI scores (i.e. acute GVHD, chronic GVHD, HGB), *post hoc* analyses were conducted including these variables as controls. These variables were selected because they were measured potential clinical confounds of group differences in QOL, even though the SIR group demonstrated lower incidence of acute and chronic GVHD[18] and GVHD is associated with worse QOL.[7,25] Results are shown in Table 3. Similar to the previous analyses, results indicated that TOI increased significantly over time in both study arms ($P<0.001$). Significant differences in study arms at Day 360 and over time persisted; the SIR/TAC group demonstrated less improvement in TOI over time when controlling for potential clinical cofounds ($P<0.01$) and reported TOI scores 9.54 points lower at Day 360 ($P<0.01$).

To explore the effects of study arm on specific domains of QOL, *post hoc* analyses were conducted examining the subscales that comprise TOI (i.e. PWB, FWB, BMTS) as outcomes. Study arm was a significant predictor of PWB at Day 360 ($P=0.02$) and across time ($P=0.02$) controlling for base-line PWB, such that the SIR/TAC arm reported worse physical well-being at Day 360 and across time. The effects of study arm and study arm by time on FWB were non-significant ($P>0.05$), controlling for base-line FWB. Similarly, the effects of study arm and study arm by time on BMTS were non-significant, controlling for base-line BMTS ($P>0.05$). Additional post hoc analyses were conducted to explore the effects of study arm on the seven items comprising the PWB subscale. Controlling for base-line responses to these items, a significant difference between study arms at Day 360 was found on item 1 (i.e. "I have a lack of energy"), with the SIR/TAC arm endorsing greater symptom severity ($P<0.01$). Significant differ-

Table 2. Changes in FACT-BMT Trial Outcome Index (TOI) by study arm.

Predictor	Regression coefficient (SE)	*t*	Interpretation
Intercept	38.82 (7.53)	5.16**	TOI at Day 360 adjusted for other predictors in the model was significantly different from 0 irrespective of study arm.
Time	0.04 (0.01)	6.41**	TOI significantly improved over time irrespective of study arm
Pre-HCT TOI	0.52 (0.10)	5.17**	Pre-HCT TOI significantly predicted change in TOI after HCT
Study arm	-7.17 (3.37)	-2.13*	At Day 360, average TOI scores in the TAC/MTX group were significantly higher than SIR/TAC
Study arm by time	-.02 (0.01)	-2.27*	The TAC/MTX group showed significantly greater improvement in TOI over time than SIR/TAC

*Results of random effects (i.e. regression-based) models are shown. MTX/TAC group membership was coded as 0 in analyses, while SIR/TAC group membership was coded as 1. Time is measured in days from Day 360. HCT: hematopoietic cell transplant. Regression coefficients indicate the magnitude of relationship between the predictor variable and TOI after adjusting for other variables in the model. For example, the intercept indicates the overall mean TOI score across both groups at Day 360 after apportioning out the effects due to time, pre-HCT TOI, study arm, and study arm by time. As another example, the regression coefficient for study arm indicates that the mean TOI score in the SIR/TAC group at Day 360 was 7.17 points lower than that of the MTX/TAC group after adjusting for the other variables in the model. *P<0.05; **P<0.01.*

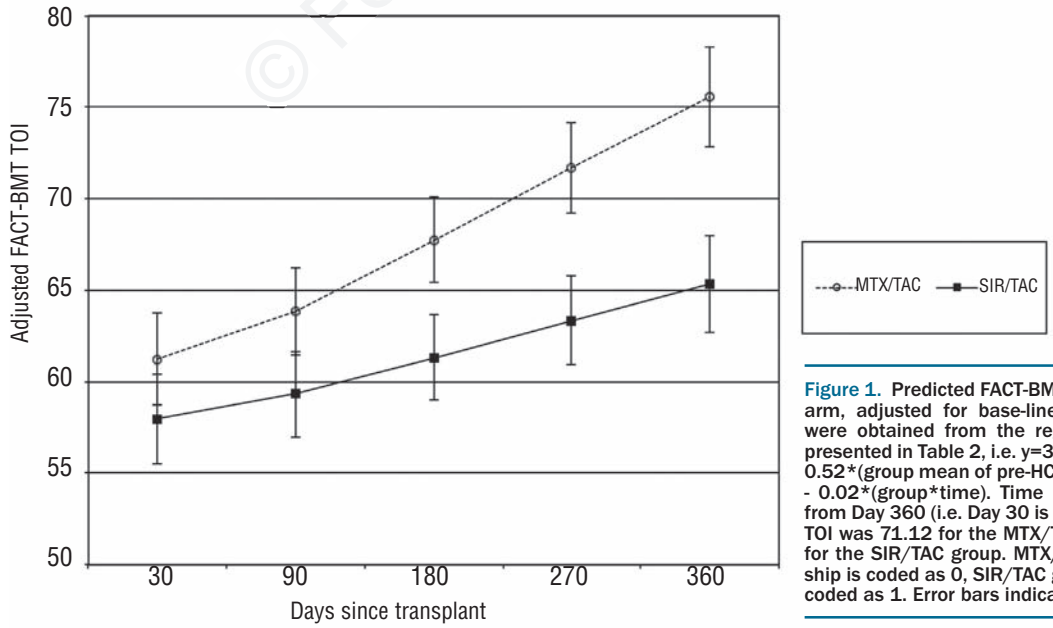

Figure 1. Predicted FACT-BMT TOI scores by study arm, adjusted for base-line TOI scores. Values were obtained from the regression coefficients presented in Table 2, i.e. y=38.82 + 0.04*(time) + 0.52*(group mean of pre-HCT TOI) – 7.17*(group) - 0.02*(group*time). Time is measured in days from Day 360 (i.e. Day 30 is -330). Mean pre-HCT TOI was 71.12 for the MTX/TAC group and 65.22 for the SIR/TAC group. MTX/TAC group membership is coded as 0, SIR/TAC group membership is coded as 1. Error bars indicate standard errors.

ences between study arms over time were observed on item 1 (P<0.01) and item 2 (i.e. "I have nausea") (P=0.01), with the SIR/TAC arm reporting less improvement in these symptoms over time. Study arm differences on these items remained significant when controlling for acute GVHD, chronic GVHD, and HGB (P<0.01).

Discussion

The present study examined QOL outcomes in a randomized clinical trial of SIR/TAC compared to MTX/TAC for the prevention of GVHD. Patients randomized to the SIR/TAC arm received SIR for at least one year post-HCT, while patients randomized to the MTX/TAC arm received MTX on Days +1, 3, 6, and 11. In both arms, TAC taper was started on Day 50 for patients who were free of acute GVHD and off systemic glucocorticoid therapy. Contrary to our hypothesis, the SIR/TAC arm demonstrated less improvement in QOL in the year post-HCT. By one year post-HCT, adjusted FACT-BMT TOI scores in the SIR/TAC arm were 7 points lower than the MTX/TAC arm. To put this finding into context, a difference of 5-9 points on the TOI is considered clinically meaningful in other cancer populations.[26,27] Thus, results from the current study suggest that administration of SIR as opposed to MTX for prevention of GVHD is associated with clinically significant, inferior recovery of QOL.

Reduced QOL associated with SIR is not explained by differences in base-line QOL, anemia, or severity of GVHD. Although the SIR/TAC arm also reported worse pre-HCT QOL, base-line differences were controlled in all statistical analyses, indicating that findings were not due to better initial QOL. Analyses controlling for HGB did not attenuate the relationship between study arm and QOL, indicating that anemia did not significantly contribute to study arm differences. QOL differences were also not attributable to differences in acute or chronic GVHD. Patients treated with SIR/TAC demonstrated a significantly lower incidence of grade II-IV acute GVHD and severe chronic GVHD than patients treated with MTX/TAC.[18] Based on these findings and the robust association between severity of chronic GVHD and reduced QOL,[7,25,28] it would be expected that reduced severity of chronic GVHD in the SIR/TAC arm would be associated with better, not worse, QOL. Analyses controlling for the effects of GVHD (Table 3) show that more severe chronic GVHD was associated with worse QOL at Day 360 and less improvement in QOL over time. Controlling for acute and chronic GVHD strengthened the relationship between study arm and QOL. These findings indicate that reductions in QOL associated with SIR were strong enough to overcome any beneficial effects of SIR on QOL due to reduced GVHD severity.

Reduced QOL associated with SIR is also not explained by potential differences in immunosuppressive medication usage between study arms. There was no difference in the proportion of living patients treated with prednisone, systemic glucocorticoids, or budesonide between study arms.[18] The incidence of TAC discontinuation by 30 months also did not differ between study arms.[18] Fewer patients in the SIR/TAC arm were treated with beclomethasone for acute GVHD to week 14, which suggests that reduced QOL in the SIR/TAC arm was not due to potential beclomethasone-associated side-effects.[18] Infrequent and heterogeneous use of second-line immune suppressive agents (i.e. those used beyond initial trial-mandated prophylaxis and steroid therapy to treat established acute and chronic GVHD) such as mycophenolate mofetil, infliximab, rituximab, and extra-corporeal photopheresis (ECP), precluded statistical comparisons for these agents across study groups. However, severity of acute and chronic GVHD can be considered a proxy for the extent of required immunosuppressive therapy. As noted

Table 3. Changes in FACT-BMT Trial Outcome Index (TOI) by study arm controlling for potential clinical confounds.

Parameter	Regression coefficient (SE)	*t*	Interpretation
Intercept	47.04 (8.31)	5.66**	TOI at Day 360 adjusted for other predictors in the model was significantly different from 0 irrespective of study arm
Time	0.06 (0.01)	4.98**	TOI significantly improved over time irrespective of study arm
Pre-HCT TOI	0.50 (0.10)	5.14**	Pre-HCT TOI significantly predicted change in TOI after HCT
aGVHD	-3.05 (1.77)	-1.72	aGVHD did not significantly predict TOI at Day 360
aGVHD by time	-.01 (0.01)	-1.59	aGVHD did not significantly predict change in TOI over time
cGVHD	-4.22 (1.51)	-2.79**	cGVHD significantly predicted TOI at Day 360
cGVHD by time	-0.04 (0.01)	-3.02**	cGVHD significantly predicted change in TOI over time
HGB	2.08 (1.42)	1.46	HGB did not significantly predict TOI at Day 360
HGB by time	0.00 (0.01)	0.14	HGB did not significantly predict change in TOI over time
Study arm	-9.54 (3.62)	-2.71**	At Day 360, average TOI scores in the TAC/MTX group were significantly higher than SIR/TAC
Study arm by time	-0.03 (0.01)	-2.96**	The TAC/MTX group showed significantly more improvement in TOI over time than SIR/TAC

*Results of random effects (i.e. regression-based) models are shown. Intercept indicates TOI scores across both study arms at Day 360 after apportioning out the effects due to other variables in the model. aGVHD indicates the effect of maximum grade of acute GVHD by Day 360. cGVHD indicates the effect of maximum grade of chronic GHVD by Day 360. HGB indicates the effect of hemoglobin level by Day 360. Study arm indicates difference in TOI by study arm at Day 360. MTX/TAC group membership was coded as 0 in analyses, while SIR/TAC group membership was coded as 1. Time is measured in days from Day 360. All regression coefficients are adjusted for the other variables in the model. For example, the regression coefficient for cGHVD indicates that an increase in severity of chronic GHVD by one stage resulted in a decrease in TOI of 4.22 points at 360 days after adjusting for other variables in the model. HCT: hematopoietic cell transplant. *P<0.05, **P<0.01.*

above, controlling for acute and chronic GVHD resulted in stronger associations between study arm and QOL, indicating that immunosuppressive therapy was likely not the cause of study arm differences in QOL.

Exploratory *post hoc* analyses indicated that QOL differences were due at least in part to more severe fatigue and nausea in the SIR/TAC arm. These findings are consistent with previous reports of fatigue and nausea as side-effects of SIR.[29-31] Notably, no statistically significant study arm differences in QOL were evident at Day 30 and 90. QOL instead began to diverge after 90 days when patients in the MTX/TAC arm were no longer being treated with MTX but patients in the SIR/TAC arm were still receiving SIR. Although the current protocol mandated SIR use through one year, while previous studies have discontinued SIR at earlier time points (commonly aiming to discontinue by 180 days post-HCT).[12-16] our findings suggest that QOL differences may be relevant to both regimens. Unfortunately, no QOL data have been reported from these other trials that have utilized SIR/TAC for GVHD prophylaxis.

Despite inferior recovery in QOL found in the current study, SIR/TAC is associated with a variety of clinical benefits including reduced severity of acute and chronic GVHD, shorter time to engraftment, and reduced severity of mucositis.[14,15,18,20] Consequently, we believe that the benefits of SIR/TAC outweigh reductions in QOL. However, our data support the need for greater attention to QOL in SIR-treated patients. Patients treated with SIR may benefit from proactive management of fatigue and nausea to increase QOL. Several studies have shown that moderate exercise (i.e. 75-80% of maximal heart rate) is associated with decreased fatigue and improved QOL among HCT patients.[32-36] Inpatient, home-based, and outpatient rehabilitation programs have all shown beneficial effects. Incorporation of exercise and behavioral methods for improving QOL into the treatment program could offset the inferior QOL recovery observed in patients treated with SIR/TAC, and should be explored further.

The current study is characterized by several strengths, including a randomized design and assessment of QOL at uniform times from transplant with a well-validated measure. Nevertheless, study limitations should be noted: the sample of 71 participants was relatively small and QOL was not equivalent between study arms at baseline. Although base-line QOL differences were controlled in analyses, there may have been one or more unmeasured variables that differed between arms and contributed to changes in QOL over time. It may also be possible that participants in the MTX/TAC study arm had unusually high QOL. FACT-BMT TOI scores in the MTX/TAC group were slightly higher than those reported previously in allogeneic HCT recipients,[7] although they were within a standard deviation. Also, we cannot determine whether inferior QOL is the result of intentionally prolonged administration of SIR itself, or if similar results would be observed with prolonged administration of other immune suppressive agents. In addition, patients' overall perception of their QOL results from an integration of multiple factors after transplant (e.g. ongoing or resolved graft *vs.* host disease, multiple immune suppressive agents, other medications, anemia, various organ dysfunction, diminished cardiopulmonary fitness, sleep disturbance, changes in mood, changes in relationships, ability, and personal and professional roles, etc.). While we have controlled for several relevant factors in the reported analyses, it is not possible to definitively implicate sirolimus alone in the observed results.

In summary, findings from the current study indicate that prolonged administration of SIR after HCT is associated with inferior QOL through one year post-HCT, despite reduction in significant chronic GVHD. This finding highlights a disparity between clinician and patient perception of benefit, and suggests the importance of inclusion of patient-reported outcomes in GVHD prevention trials. These data should be factored into counseling of prospective HCT patients who will be treated with this regimen, and post-HCT exercise and behavioral interventions to improve QOL should be explored in this setting to improve recovery in QOL.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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4.3. Third Manuscript

Coping Strategies Modify Risk of Depression Associated with Hematopoietic Cell Transplant Symptomatology.

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Coping strategies modify risk of depression associated with hematopoietic cell transplant symptomatology

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Abstract

To determine whether coping strategies modify the risk of depression among allogeneic recipients experiencing post-transplant-related symptomatology, 105 participants (mean age = 52 years, 42% female) completed questionnaires 90 days post-transplant. A total of 28 percent reported depressive symptoms. Univariate correlations indicated that depression was associated with greater transplant-related symptomatology and avoidance, acceptance/resignation, and emotional discharge coping. Depression was negatively associated with problem-solving coping. Moderator analyses indicated that transplant-related symptomatology was significantly associated with depression among patients who frequently used maladaptive coping and rarely used adaptive coping. These data suggest that transplant-related symptomatology, combined with maladaptive coping, place patients at risk of depression.

Keywords

cancer, coping, depression, hematopoietic stem cell transplantation, oncology

Allogeneic hematopoietic cell transplantation (HCT) improves long-term survival rates among patients diagnosed with malignant hematologic diseases (Pasquini and Wang, 2011). Allogeneic HCT is increasingly performed worldwide, resulting in a large number of survivors for whom HCT-related morbidities are an important outcome. Morbidities among HCT recipients are common due to high-dose chemotherapy, opportunistic infections, and acute and chronic graft-versus-host disease (GVHD). Morbidities can affect multiple organs and be life-threatening; the cardiovascular, gastrointestinal, musculoskeletal, and auditory or visual systems are particularly vulnerable (Sun et al., 2013). Consequently, patients often report a high degree of HCT-related symptomatology which is associated with reduced quality of life (Bevans et al., 2008; Cohen et al., 2012) and worse mental health

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(Bevans et al., 2008). For example, 12–29 percent of HCT recipients report posttraumatic stress disorder (El-Jawahri et al., 2015b; Hefner et al., 2014), 13–20 percent anxiety (El-Jawahri et al., 2015a; Pillay et al., 2015), and 6–44 percent depression (Artherholt et al., 2014; El-Jawahri et al., 2015a, 2015b; Pillay et al., 2015).

Depression is a cause for concern among HCT recipients due to its association with adverse health outcomes. For example, pre-transplant depression prospectively predicted slower white blood cell recovery in the first 3 weeks after transplant (McGregor et al., 2012), while post-transplant depression has been found to be associated with non-adherence to treatment (Mumby et al., 2011), increased hospital length of stay (Prieto et al., 2002), and greater mortality (Loberiza et al., 2002; Prieto et al., 2002). Moreover, HCT recipients with depression are 13 times more likely to report suicidal ideation as recipients without depression (Sun et al., 2013).

An important question is the extent to which risk of depression is modifiable among HCT recipients, such as through adaptive patient coping. Coping can be defined as dynamic cognitive and behavioral efforts to manage stress (Lazarus and Folkman, 1984). Coping strategies can be broadly conceptualized as adaptive (e.g. engaging with the problem in a constructive manner) or maladaptive (e.g. evading the problem or blaming others) (Moos, 1993; Wenzel et al., 2002). To our knowledge, only three studies have examined coping and depression in HCT recipients. They suggest that prior to HCT, problem solving was associated with less depression, while acceptance/resignation and avoidant coping were associated with greater depression (Fife et al., 2000; Rodrigue et al., 1993; Wells et al., 2009). However, coping was not associated with depression at 2 weeks or at 6-months post-HCT (Fife et al., 2000; Wells et al., 2009). All three studies included both allogeneic and autologous HCT recipients; thus, differences in recovery post-HCT based on transplant type (e.g. GVHD) may have obscured relationships between coping and depression. In summary, existing data suggest that HCT recipients who cope with maladaptive coping strategies rather than adaptive coping strategies may be at higher risk for depression; however, the degree to which these relationships persist beyond the pre-HCT period remains to be clarified.

The goal of this study was to examine the relationship between HCT-related symptomatology, coping, and depression in a sample of allogeneic HCT recipients. Moreover, we sought to examine the extent to which coping modifies risk of depression associated with HCT-related symptom severity. Significant results would suggest that depression risk may be mutable among patients experiencing HCT-related symptoms, perhaps via intervention to improve coping skills. We hypothesized that (1) severity of HCT-related symptomatology would be significantly associated with depression, (2) adaptive coping strategies would be associated with less depression and maladaptive coping would be associated with more depression, and (3) risk of depression associated with HCT-related symptom severity would be greatest in patients who exhibited poor coping.

Methods

Participants

Participants were recruited as part of a larger study of quality of life in allogeneic HCT recipients. Eligible patients were at least 18 years old, were diagnosed with hematologic cancer, were scheduled to receive allogeneic HCT with peripheral blood stem cells at Moffitt Cancer Center, had no history of cerebrovascular accident or head trauma with loss of consciousness, had completed 6 or more years of formal education, were able to speak and read standard English, and signed the written informed consent. The study was approved by the University of South Florida Institutional Review Board.

Procedures

Potential participants were identified using clinical information systems in consultation with the

attending physician. Participants were approached at an outpatient visit approximately 1 month prior to transplant. Eligible patients who wished to participate signed informed consent prior to participation and completed baseline demographic information at this time. Participants were contacted again 90 days after transplant to complete follow-up questionnaires regarding HCT-related symptomatology, depression, and coping. Participants for the current analyses were recruited between December 2010 and January 2013. At the time the analyses were conducted, 217 patients were approached, 34 refused (e.g. not interested, overwhelmed or no reason given), 183 signed consent, and 105 had data at baseline and 90 days post-HCT.

Measures

Demographic and clinical data. Self-reported sociodemographic characteristics were assessed prior to transplant (i.e. age, gender, race, ethnicity, marital status, education, and annual household income). A medical record review was performed at study entry in order to obtain clinical information (i.e. cancer type and date of HCT).

HCT-related symptomatology. The 30-item HCT Symptom Scale (Lee et al., 2002) assesses self-reported severity of HCT symptomatology across multiple organ systems in the previous month. Items are evaluated on a five-point Likert scale, (0 = not at all, 4 = extremely), with higher scores indicating more severe symptoms. The scale yields a total score and subscales for seven categories of symptomatology: skin, eyes and mouth, lung, digestive, muscles and joints, energy, and psychological symptoms. A modified version of the total summary score was used in the current analyses; this version did not include the psychological symptoms subscale to avoid inflated relationships with coping and depression. The scale has excellent reliability and validity (Lee et al., 2002).

Coping. Coping was assessed using the 48-item Coping Response Inventory (CRI) (Moos, 1993). Items are assessed on a four-point Likert scale (0 = not at all, 3 = fairly often). The scale yields eight subscales: Logical Analysis, Positive Reappraisal, Seeking Guidance, Problem Solving, Cognitive Avoidance, Acceptance/Resignation, Seeking Alternative Rewards, and Emotional Discharge. Subscale scores range from 0 to 18 with higher scores indicating more frequent use of the strategy. The CRI has demonstrated reliability and validity (Moos, 1993) and has previously been used in HCT recipients (Jacobsen et al., 2002; Wells et al., 2009).

Depression. Depression was assessed using the 20-item Center for Epidemiological Studies—Depression Scale (CES-D) (Radloff, 1977). Items assess the frequency of depressive symptoms in the past week according to a four-point scale (0 = rarely or none of the time, 3 = most or all of the time). A total score is obtained by summing item responses. Scores range from 0 to 60 with higher scores indicating greater depressive symptomatology. A score of 16 or higher indicates clinically significant depressive symptomatology (Radloff, 1977). The CES-D is commonly used for assessing depression in patients with cancer due to the absence of items related to cancer-related physical symptoms that could overlap with depression (e.g. weight loss, appetite, fatigue, and health concerns) (Andrykowski, 1994). The CES-D has high internal consistency (Radloff, 1977) and validity in cancer populations (Hann et al., 1999).

Statistical analyses

Means and frequencies were calculated to describe sample sociodemographic and clinical characteristics. Spearman's correlations were performed to assess the magnitude of univariate relationships among depression, HCT-related symptomatology, and coping strategies. Linear regression analyses were conducted to examine the relationship between HCT-related symptomatology and depressive symptomatology. Because younger age and female gender have been found to be risk factors for depression in

HCT recipients (Kuehner, 2003), these variables were identified *a priori* as covariates to be included in multivariate analyses. Analyses examining coping strategies as moderators of the relationship between HCT-related symptomatology and depression were conducted using bootstrapping (Hayes and Matthes, 2009). Interactions significant at $p < .05$ were decomposed using the Johnson–Neyman technique to plot changes in beta weights regressing depression on HCT-related symptomatology at various levels of the coping strategy examined.

Results

A total of 105 participants contributed data to the current analyses. Sample demographic and clinical descriptives are reported in Table 1. At 90 days post-HCT, 30 (28%) patients met criteria for clinically significant depressive symptoms. Self-reported HCT symptomatology at this time was widespread. A total of 88 (83%) patients reported symptoms of the skin, 73 (71%) eye or mouth symptoms, 65 (62%) pulmonary symptoms, 43 (41%) digestive symptoms, 86 (82%) muscle and joint symptoms, and 91 (87%) reported reduced energy.

Frequency of coping strategy use and correlations between coping, HCT-related symptomatology, and depression are shown in Table 2. Problem-solving coping was associated with significantly less depressive symptomatology ($p = .04$), while avoidance, acceptance/resignation, and emotional discharge were associated with greater depressive symptomatology (p values < .002). HCT-related symptomatology was not associated with any coping strategy (ps > .13) but was significantly associated with depressive symptomatology ($p < .0001$). The relationship between HCT-related symptomatology and depressive symptomatology remained significant in regression analyses controlling for age and gender (see Table 3).

Moderation analyses indicated that coping significantly modified the risk of depression associated with HCT-related symptomatology (see Table 4). Specifically, the relationship between HCT-related symptomatology and depression was stronger among patients who frequently used maladaptative coping strategies (i.e. cognitive avoidance and emotional discharge) and rarely used adaptive coping strategies (i.e. positive reappraisal and problem solving) (p values < .05). The relationship between HCT-related symptomatology and depression was not modified by patients' use of logical analysis, seeking guidance and support, acceptance or resignation, or seeking alternative rewards (p values > .11). Figure 1 shows the risk of depression associated with HCT-related symptomatology according to the use of the four coping strategies found significant in the moderation analyses.

Table 1. Demographic and clinical characteristics of the sample ($n = 105$).

Age: mean, SD	51.85	12.90
Gender: *n*, % female	44	42
Ethnicity: *n*, % non-Hispanic	98	93
Race: *n*, % Caucasian	90	86
Marital status: *n*, % married	70	67
Education: *n*, % college graduate	44	42
Annual household income: *n*, % US$ 40,000 or greater	56	53
Diagnosis: *n*, %		
AML	32	30
MDS	20	19
NHL	17	16
ALL	13	12
CLL	8	8
CML	7	7
MM	4	4
MPD	2	2
Other leukemia	2	2
Mean (SD) CES-D score	12.03	8.70
Mean (SD) HCT Symptom Scale score[a]	15.40	10.89

ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; CES-D: Center for Epidemiological Studies—Depression Scale CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPD: myeloproliferative syndrome; NHL: non-Hodgkin lymphoma; SD: standard deviation;.
[a]HCT Symptom Scale score calculated as a mean of all subscales except mental distress.

Table 2. Frequency of use of coping strategies and correlations with HCT-related symptomatology and depression.

Coping strategy	Definition (Moos, 1993)	Any use, *n* (%)	Use "sometimes" or "fairly often," *n* (%)	Correlation: HCT-related symptomatology, *r*	Correlation: depression, *r*
Logical analysis	Cognitive attempts to prepare mentally for a stressor	102 (97)	26 (25)	0.09	0.11
Positive reappraisal	Cognitive attempts to construe and restructure a problem in a positive way while accepting the reality	103 (98)	63 (60)	0.00	−0.05
Seeking guidance and support	Behavioral attempts to seek information, guidance, and support	103 (98)	35 (33)	0.05	0.04
Problem solving	Behavioral attempts to take action to deal directly with the problem	104 (99)	54 (51)	−0.13	− .20*
Cognitive avoidance	Cognitive attempts to avoid thinking realistically	99 (94)	14 (13)	0.08	0.37**
Acceptance/ resignation	Cognitive attempts to react to the problem by resigning oneself to it	99 (94)	14 (13)	0.15	0.31**
Seeking alternative rewards	Behavioral attempts to get involved in substitute activities and create new sources of satisfaction	100 (95)	12 (11)	−0.03	− .11
Emotional discharge	Behavioral attempts to reduce tension by expressing negative feelings	92 (88)	1 (1)	0.13	0.32**

*$p < .05$; **$p < .01$.

Conclusion

This study examined relationships among self-reported HCT symptomatology, depressive symptoms, and coping strategies in hematologic cancer patients treated with allogeneic HCT. Hypotheses were largely confirmed. Greater depressive symptomatology was associated with greater HCT-related symptomatology, less use of use of problem-solving coping, and greater use of avoidance, acceptance/resignation, and emotional discharge coping. Coping moderated the risk of depression associated with HCT-related symptomatology such that patients with greater HCT-related symptomatology who used more maladaptive coping strategies (i.e. cognitive avoidance and emotional discharge) and less adaptive strategies

Table 3. Linear regression analyses examining the effects of HCT-related symptomatology on depressive symptomatology controlling for age and gender.

	Statistics by predictor	
	b	*t*
Age	−0.26	−3.22**
Gender (female)	−0.01	−0.12
HCT-related symptomatology	0.51	6.25**

**$p < .01$.

Table 4. Results of analyses examining coping strategies as moderators of the relationship between HCT-related symptomatology and depression.

	Statistics by predictor	
	b	*t*
Moderator: logical analysis		
Age	−0.18	−3.39**
Gender (female)	−0.65	−0.45
HCT-related symptomatology	0.62	4.18***
Logical analysis	0.47	1.55
Interaction HCT-related symptomatology × logical analysis	−0.02	−1.61
Moderator: positive reappraisal		
Age	−0.19	−3.29**
Gender (female)	−0.52	−0.36
HCT-related symptomatology	0.74	4.25***
Positive reappraisal	0.45	1.53
Interaction HCT-related symptomatology × positive reappraisal	−0.03	−2.06*
Moderator: seeking guidance		
Age	−0.18	−3.34**
Gender (female)	−0.43	−0.29
HCT-related symptomatology	0.52	4.23***
Seeking guidance and support	0.26	0.84
Interaction HCT-related symptomatology × seeking guidance and support	−0.01	−1.13
Moderator: problem solving		
Age	−0.16	−2.92**
Gender (female)	−0.13	−0.09
HCT-related symptomatology	0.87	3.84***
Problem solving	0.27	0.79
Interaction HCT-related symptomatology × problem solving	−0.04	−2.18*
Moderator: cognitive avoidance		
Age	−0.12	−2.34*
Gender (female)	−0.95	−0.72
HCT-related symptomatology	0.02	0.10
Cognitive avoidance	−0.01	−0.03
Interaction HCT-related symptomatology × cognitive avoidance	0.04	2.62*
Moderator: acceptance or resignation		
Age	−0.16	−2.91**
Gender (female)	−0.17	−0.12
HCT-related symptomatology	0.39	2.28*
Acceptance or resignation	0.38	1.23
Interaction HCT-related symptomatology × acceptance or resignation	−0.01	−0.06
Moderator: seeking alternative rewards		
Age	−0.17	−3.01**
Gender (female)	0.37	0.25
HCT-related symptomatology	0.37	3.27**
Seeking alternative rewards	−0.33	−0.99
Interaction HCT-related symptomatology × seeking alternative rewards	<0.01	0.35
Moderator: emotional discharge		
Age	−0.13	−2.42*
Gender (female)	−1.04	−0.76
HCT-related symptomatology	0.13	1.05
Emotional discharge	0.09	0.19
Interaction HCT-related symptomatology × emotional discharge	0.04	2.08*

*$p < .05$; *$p < .01$; ***$p < .001$.

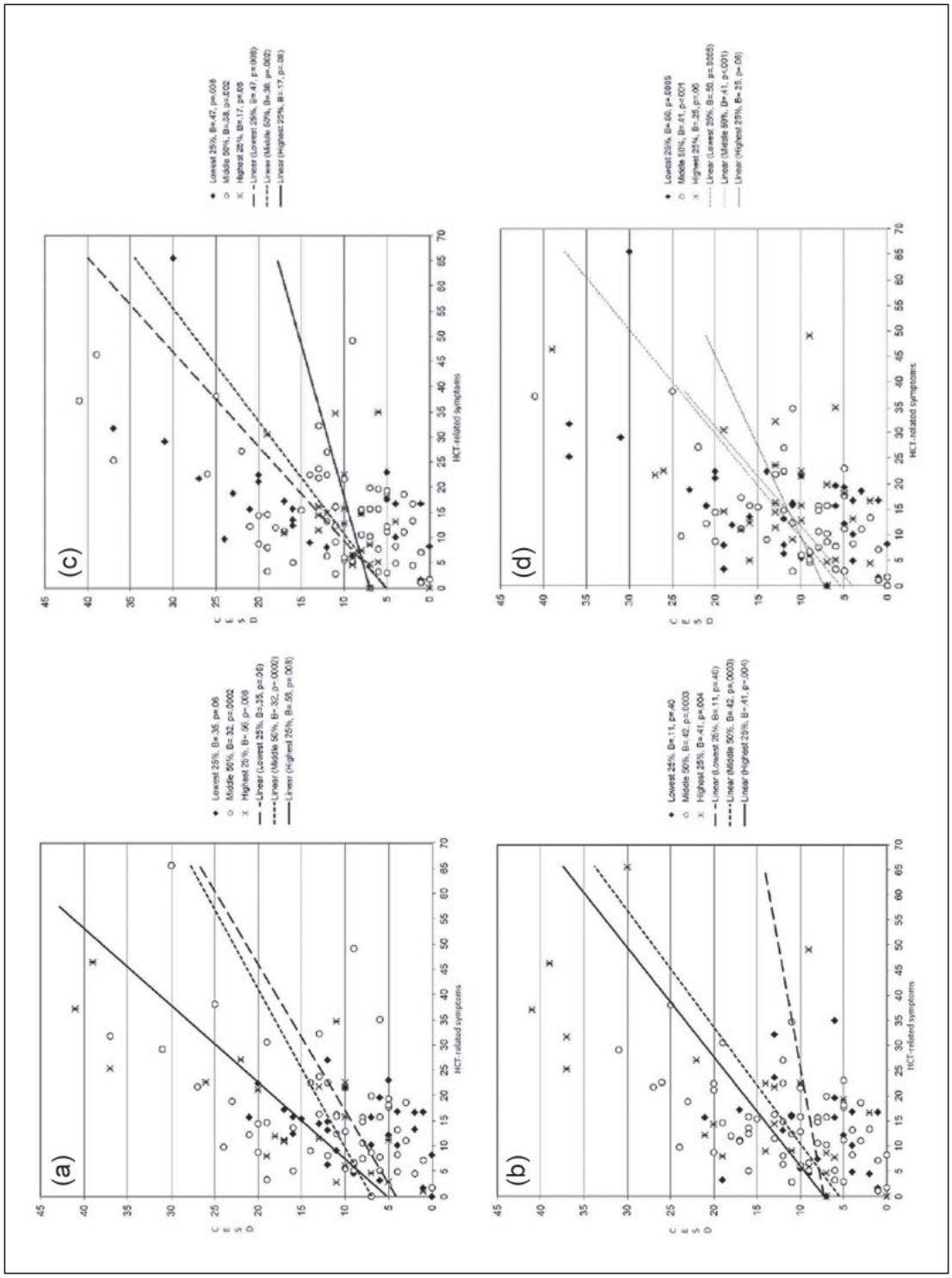

Figure 1. Associations between HCT-related symptomatology and depression at high, medium, and low levels of coping: (a) avoidance, (b) emotional discharge, (c) problem solving, and (d) positive reappraisal. As a guide to interpretation, relationships between HCT-related symptomatology and depression are shown for the 25 percent of the sample reporting the greatest use of the coping strategy (solid line, Xs), the 50 percent of the sample reporting moderate use of the symptom (short dashed line, Os), and the 25 percent of the sample reporting the least use of the coping strategy (long dashed line, diamonds). Beta weights and *p* values for the relationship between HCT-related symptomatology and depression within each group are provided in the legends.

(i.e. reappraisal and problem solving) were more likely to be depressed.

The significant relationship between HCT-related symptomatology and depressive symptomatology observed in this study is consistent with previous literature reporting that severity of HCT-related symptoms is a risk factor for depression (Lee et al., 2006; Mosher et al., 2011; Pidala et al., 2011; Syrjala et al., 2004). We observed significant relationships among post-HCT coping and depression, which has not been reported in previous studies (Rodrigue et al., 1993; Wells et al., 2009). In contrast to previous studies which analyzed data from mixed samples of autologous and allogeneic HCT recipients, this study focused exclusively on allogeneic HCT recipients. Greater homogeneity of our sample regarding treatment type may have enabled us to detect a signal that other studies missed. Interestingly, coping was not associated with HCT-related symptomatology, suggesting that patients do not cope with HCT-related symptoms in a consistent manner. This study adds significant new knowledge regarding coping as a moderator of the risk of depression associated with HCT-related symptomatology. Specifically, HCT recipients with good coping skills demonstrate psychological resilience even when experiencing greater HCT-related symptoms.

This study is characterized by several strengths, including a focus on allogeneic HCT recipients who face significant challenges post-transplant but for whom little about their coping is known. The study also used validated measures of coping, depression, and self-reported HCT-related symptomatology. In addition, participants were assessed at a uniform time since transplant when many were experiencing HCT-related morbidities. Nevertheless, study limitations should also be noted. The cross-sectional design of the study does not allow for determination of directionality of findings. For example, it may be that depression alters patients' coping repertoire such that they cope less adaptively after onset of depression. However, studies in other cancer populations have demonstrated that maladaptive coping strategies often precede depressive symptoms (Hack and Degner, 2004; Kraemer et al., 2011). In addition, the study was performed at a single site in the United States and included a sample of mainly white, Caucasian, married, and well-educated participants. Both of these factors may limit the generalizability of findings.

In conclusion, results highlight the fact that patients with poor coping skills are more vulnerable to depression when faced with HCT-related symptomatology. These patients may benefit from proactive clinical care to reduce or prevent depression when experiencing HCT-related symptoms, such as antidepressant medication or referral to a mental health professional. Future studies should examine whether interventions to improve coping skills reduce risk of depression among patients who cope poorly with HCT-related symptoms. Previous research in breast cancer patients has demonstrated benefits of group psychological interventions aimed at helping patients cope with their illness and treatment side effects (Andersen et al., 2004, 2008; Antoni, 2013; Antoni et al., 2006; Carver et al., 2005). These benefits include decreased symptoms of depression and anxiety, less intrusive thoughts, less social disruption, greater positive emotions, and better quality of life. Moreover, benefits persisted up to 13 years after treatment (Carver et al., 2005). Only two studies have aimed to adapt such interventions to the unique needs of HCT survivors. DuHamel et al. (2010) developed a 10-week telephone-delivered psychological intervention to address posttraumatic stress and social support in patients who were 1 to 3 years post-HCT (DuHamel et al., 2010). Participants receiving this intervention reported significant improvement in posttraumatic stress symptoms, distress, and depression relative to controls (DuHamel et al., 2010). Syrjala et al. (2011) reported on the development of an Internet-delivered intervention to address survivorship care needs in HCT survivors who were 3 to 18 years post-HCT; a large clinical trial is currently underway (Syrjala et al., 2011). Therefore, additional studies are needed to adapt psychosocial interventions for HCT

recipients. Such studies have the potential to significantly improve patient outcomes after HCT.

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4.4. Manuscript Addendum 1

Patient Education In Allogeneic Hematopoietic Cell Transplant: What Patients Wish They Had Known About Quality Of Life.

Jim HS, Quinn GP, Gwede CK, Cases MG, Barata A, Cessna J, Christie J, Gonzalez L, Koskan A, Pidala J.

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ORIGINAL ARTICLE

Patient education in allogeneic hematopoietic cell transplant: what patients wish they had known about quality of life

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Quality of life (QOL) is increasingly recognized as an important clinical outcome of hematopoietic cell transplantation (HCT), but patient education is often overlooked. The aim of the current qualitative study was to examine education regarding post-HCT QOL from the patient's perspective. Allogeneic HCT recipients participated in one of four focus groups. Participants were asked to recall what they had been told about post-HCT QOL as they were preparing for transplant, how their QOL differed from what they expected and how to educate future patients about post-HCT QOL. Verbatim transcripts were coded for both *a priori* and emergent themes using content analysis. A total of 24 patients participated (54% female, mean age 51, range 23–73 years). Participants frequently expressed the desire for additional education regarding post-HCT QOL, particularly late complications. They noted that late complications were often unexpected, had a profound impact on their QOL and threatened their ongoing sense of recovery. They emphasized that the timing, content and format of education regarding QOL should be flexible to meet their diverse needs. Findings from the current study draw attention to the importance of patient education regarding post-HCT QOL as well as additional QOL research designed with patient education in mind.

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Keywords: hematopoietic SCT; quality of life; patient education as topic

INTRODUCTION

There is growing recognition of the importance of quality of life (QOL) following hematopoietic cell transplant (HCT). Patients commonly cite QOL as one of their primary concerns.[1,2] QOL is increasingly assessed as a secondary end point in clinical trials as well as a main focus of observational research. Consequently, there is now a sizeable body of research, published or underway, comparing QOL in various treatment regimens and describing changes in QOL during the transplant process.[3–8]

Advances in knowledge regarding post-HCT QOL have the potential to facilitate better patient education about the potential risks and benefits of transplantation. Nevertheless, the extent to which QOL research has been incorporated into routine patient education is not clear. A major barrier is that studies often report means and standard deviations of commonly used QOL measures such as the Medical Outcomes Study Short Form 36 (SF-36), the Functional Assessment of Cancer Therapy-BMT scale (FACT-BMT) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30). The information provided by these measures is valuable to researchers but often non-intuitive to patients.[3] A few studies have presented QOL results in a format that is easier to understand, such as percent of participants who return to work or school, are able to climb a flight of stairs or rate their QOL as 'very good' or 'excellent'.[9–12] Nevertheless, studies that report these types of results are subject to bias because of high rates of attrition caused by morbidity and mortality. To our knowledge, only one study has quantified QOL in a way that is easy to understand and also accounted for attrition bias.[10] That study reported the percentage of HCT participants who survived with good outcome, survived with poor outcome, died or had missing data on a variety of QOL descriptors such as 'Life has returned to normal' and 'I have fully recovered from my transplant.' Additional innovative research efforts such as these are needed to improve patient education regarding post-HCT QOL.

In an effort to foster innovations in QOL research and patient education, we conducted a single-site, qualitative study of patients' perspectives on education regarding QOL after allogeneic HCT. Patients at this institution standardly receive pre-HCT education on the anticipated post-HCT course through counseling (provided by HCT physicians, nurses and social workers), printed educational materials and by targeted education of patients' caregivers. Allogeneic HCT recipients were recruited to participate in one of several face-to-face focus groups. We were interested in how patients recalled the pretransplant education they received regarding post-HCT QOL, how they described their QOL at various points in the transplant process and how their QOL differed from what they expected it to be. We also solicited recommendations from study participants regarding the optimal ways to educate future patients regarding post-HCT QOL. Thus, the aim of the study was not learning about post-HCT QOL *per se* but rather patient's perceptions of education regarding QOL. Although a variety of themes emerged from the groups, the current report focuses on content related to patient education. As the study was exploratory in nature, there were no *a priori* hypotheses.

MATERIALS AND METHODS

Participants

Following University of South Florida Institutional Review Board approval, potential participants were identified through a database maintained by

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the BMT Department at Moffitt Cancer Center. Eligible patients were allogeneic HCT recipients who had been transplanted 1–4 years previously, were without evidence of primary disease relapse, were able to speak and read English and were able to provide informed consent. Because participants were asked to travel to the Cancer Center to take part in an in-person focus group, recruitment focused on patients who lived in the greater Tampa Bay area. Participants were provided with a meal as compensation for their time.

Moderators' guide

A focus group guide was developed by the study investigators based on clinical experience and relevant literature. The guide consisted of 16 questions regarding patients' expectations and experiences of post-HCT QOL, which was defined for participants as encompassing physical, social, emotional and role functioning (see Table 1).[3,4] Questions and prompts were reviewed for accuracy by a transplant physician and pretested with HCT recipients.

Procedure

Participants attended one of four focus groups held in November 2011 and March 2012. Separate focus groups were held for male and female HCT recipients to facilitate open discussion of topics such as changes in sexuality and appearance. Groups ranged in size from four to six patients. Before the focus group, participants signed informed consent and completed a brief demographic questionnaire. Questionnaire items included date of birth, ethnicity, race, marital status, education and annual household income. Clinical information (i.e., cancer diagnosis, disease status, donor type and time since transplant) was obtained later from the BMT Department registry. Each focus group lasted approximately 90 min and was audio-recorded. A moderator, comoderator and research assistant were present for all focus groups. All moderators and assistants were gender concordant with the group and none had prior relationships or contact with the participants. Each moderator had previously received training from an experienced qualitative health researcher. Moderators were not affiliated with the transplant team and no members of the transplant team were present, although a transplant physician was available at the completion of each group to answer medical questions.

Table 1. Interview Guide Questions

Before transplant, what did the BMT team tell you to expect regarding your post-transplant quality of life?
Did you go to other sources to learn about quality of life after transplant?
What was your quality of life like during the first 100 days following transplant?
How did your quality of life in the first 100 days differ from what you expected going into transplant?
What is your quality of life like now?
How is your quality of life now differ from what you expected going into transplant?
When was the last time you felt like yourself?
At this point in your recovery, is this how you expected to feel? Did you expect to recover faster? Slower? Was your recovery about what you expected?
Are there things that you understand about your quality of life now that you wish your doctor would have told you prior to the transplant?
Would having this information have changed your decision to have a transplant?
If you had that information, would you have prepared for life after transplant differently? How?
When is the best time to discuss quality of life information?
What is the best way to share quality of life information?
What is the most important thing you have done to improve your quality of life after transplant?
If you met someone who was planning to have a transplant, what would you tell them to expect about post-transplant quality of life?
If you met someone who was planning to have a transplant, what advice would you give them about how to improve their quality of life after transplant?

Focus group audio files were professionally transcribed verbatim by a local transcriptionist with experience in qualitative health research. The transcripts were analyzed using a combination of content analysis via hand coding and crystallized immersion method whereby the researchers reviewed all the data and culled out those aspects most relevant to the objectives.[13] Content analysis of the transcripts provided common themes illustrating the informational needs and concerns about QOL. Eight investigators participated in the coding process. Codes were generated and refined using an iterative process that included the whole group. One pair of raters was then assigned to code each transcript. Members of the pair conducted coding independently, compared codes and resolved disagreements by consensus. The research team concluded that saturation had been reached (i.e., no new themes emerged) after the fourth focus group. After consensus was reached and a definition was created for each code, a member of the research team re-read the transcripts and, using the final code categories, entered the data into ATLAS.ti.[14] Validity was determined by peer debriefing in which the entire research team reviewed, validated and verified all interpretations and conclusions of the data (consensual validity).

RESULTS

Participants

A total of 24 HCT recipients participated in the focus groups. As shown in Table 2, participants were a median age of 53 (range 23–73 years). The majority was Caucasian, non-Hispanic, married, had not completed college and reported a current annual household income of $40 000 a year or less.

Sources of information regarding post-HCT QOL

Focus group participants were first asked to recall how they obtained information regarding post-HCT QOL. Representative participant quotes are presented in Table 3. Nearly all participants reported receiving information from the transplant team in the form of a book and/or orientation class, attendance at which was

Table 2. Sociodemographic and clinical characteristics of the sample

	n = *24*
Age: median (range)	53 (23–73)
Gender: *n* (%) male	12 (50)
Ethnicity: *n* (%) non-Hispanic	23 (95.8)
Race: n (%) Caucasian	23 (95.8)
Marital status: *n* (%) married	17 (70.8)
Education: *n* (%) college grad	8 (33.3)
Annual household income: *n* (%) $40 000 or more	9 (37.5)
Diagnosis: n (%)	
Acute myelogeneous leukemia	11 (46)
ALL	4 (17)
Non-Hodgkin's lymphoma	3 (13)
Myelodysplastic syndrome	2 (8)
Aplastic anemia	2 (8)
CLL	1 (4)
Chronic myelomonocytic leukemia	1 (4)
Disease Status: n (%)	
CR 1	10 (41.7)
CR 2	4 (16.7)
CR 3	1 (4.2)
PR	3 (12.5)
Hematologic improvement	1 (4.2)
No response/stable	3 (12.5)
Untreated	2 (8.3)
Donor: n (%)	
Unrelated	13 (54.1)
Related	10 (41.7)
Umbilical cord blood	1 (4.2)
Time since transplant in months: mean (range)	29.7 (12–71.2)

Table 3. Representative participant responses to focus group questions

Sources of Information regarding post-HCT QOL
'I did not want to read that book, I did not want to know, I just wanted to go into what I had to do and deal with the rest later.'
'Someone said, 'Don't look up bone marrow transplants on the computer… it's only going to scare you to death'… So I just do what I am told [by my physician] and stay off the computer.'
'I still read everything.'
'On the computer, my wife did most of [the research]. I mean, I did some of it but she really took care of everything.'
'My family had a lot of talk. It's like everybody became an instant doctor in their own minds… you know, start doing this, stop doing that… but I had to leave it up to my doctor and myself.'
Expectations regarding post-HCT quality of life
'I have to admit that [the transplant team] explained it pretty well, I knew it, I knew going in where it was, what might happen.'
'Well, I know [the transplant team] said some things about it to me, but I was more focused on what was going to happen during the transplant, because I wanted to get through the transplant, and I'd worry about what happens afterwards [later].'
'It's better than what I expected… I had a few bad days, I had the mouth sores and that was pretty much it.'
'It's like devastating things that aren't in the manual, you know, the chronic side effects are in the manual but the degree that they limit the things that you can do.'
What patients wished they had known
'I would like to see some practical tips added to the manual.'
'Let me know in my situation [how long it will be until I feel better]. Is it going to be five years? Is it going to be three years?... [First] it was six months, then it was one year, then it was after two years… they didn't tell me when I am going to actually be me, me again, because I am not me, and I know I am never going to be me, but I'd like to be close to me.'
'They tell you about graft versus host disease, but they don't really go into that much detail of what exactly that means and, you know, what it entails.'
When and How to Communicate QOL Information
'If you are going to have a transplant it would be nice to sit with a group of people who have been through it, so that you can hear the stories of what they have done, as long as they are wise enough to know you don't want to scare the bejesus out of somebody.'
'...that's what I am hoping will come out of this [study], is that you have support groups that would focus on key areas: neurological side effects, orthopedic side effects, you know, mental emotional side effects.'
'I don't like to go to groups like that because I may hear something that may happen to me and I am going to worry and I am thinking 'oh my God! What if that happens to me? Oh my God.' You know, I don't want to know that kind of stuff.'
QOL information and transplant decisions
'I still would have gone through with it; I don't think I had much of a choice.'
'I don't think I could have prepared any differently.'
'I am not sure I would have gone through [with it] if I knew [all of the side effects].'
'No, there is no way [I would have another transplant]… it is just brutal on your caregivers.'

required. Most of these participants recalled receiving specific information on side effects of the conditioning regimen, GVHD and dietary and other behavioral restrictions to prevent infection. Participants were divided on their responses to the information. Many indicated that they tried to avoid information about the transplant; many of these same participants also reported avoiding information from other sources. Other patients sought additional information about transplant outcomes from books, scientific articles, Internet searches and advice from patients who were farther along in the transplant process. Participants also mentioned the role of family and friends in locating and sharing information with them regarding transplant. This was helpful for some, as trust in a knowledgeable caregiver allowed them to focus on the transplant itself. For others, information from friends and family was intrusive and unwelcome.

Expectations regarding post-HCT QOL

Participants were asked to describe how their actual experience of post-HCT QOL differed from what they had expected before the transplant. Several patients reported that they were well-informed by the treatment team. Others did not recall any expectations regarding QOL after transplant. Still other participants indicated that their post-transplant experiences differed from what they had expected before transplant. A few participants reported relief that the transplant was not as bad as they expected. In contrast, others emphasized that they had expected gradual improvement after transplant and were surprised by late-onset or persistent side effects that compromised their daily functioning. Participants also reported that they felt unprepared for the 'ups and downs' of recovery. The late or persistent side effects most often described as distressing were avascular necrosis and joint replacement, peripheral neuropathy, edema, diabetes, fatigue, dry mouth, dry eyes, cataracts, weight gain and hair loss. Many patients reported being unaware that these side effects could occur, or if aware, surprised by their severity and duration. Participants reported that side effects such as these were distressing because they prevented return to activities of daily life, such as walking unaided, standing for extended periods of time, reading, watching television, participating in hobbies, driving a car and returning to work or school.

What patients wished they had known

In general, participants reported being well prepared for the acute transplant process. Although most patients described the first 100 days post transplant as 'rough' and 'horrible', many noted that the acute transplant unfolded as they had been told it would. There were very few suggestions for improving education regarding the acute transplant process. An exception noted by three participants was a better description of the transplant itself (i.e., the infusion of the blood product). Another participant suggested that education should include practical tips from nurses and other patients. The majority of suggestions for patient education focused on late

complications. Although participants acknowledged that there was a great deal of variability in patients' experiences of QOL after the acute transplant period, they wanted more information regarding what long-term side effects could happen, how severe they might be, how long they could persist and how they might affect their lives.

When and How to communicate QOL information

Nearly all participants agreed that talking to patients further along in the transplant process was an important adjunct to education by the transplant team. Some participants wanted to talk to patients one-on-one, whereas others preferred a support group, and still others wanted to attend a question-and-answer session moderated by a physician. In fact, many participants reported that they independently sought out HCT survivors before their transplant, which was helpful in dispelling some of their fears.

Although many participants focused on the importance of interacting with HCT survivors before the transplant, some indicated that they wanted regular contact with other survivors after the transplant. One suggestion was to match newly transplanted patients with a mentor or buddy who had been transplanted several months or years previously. Another popular suggestion was support groups that focused on specific side effects.

There was also enthusiasm about educating patients via the Internet. Some participants pointed out that a website would be easy to update, whereas others liked the flexibility of navigating only to areas of the website that were of interest to them. In contrast, there were mixed responses to the suggestion of print or audiovisual material. Some patients wanted a hard copy of information such as a book, whereas others worried that it would be similar to the education book they received before transplant. Regardless of the format of patient education, participants emphasized that it was important to present a range of different possible outcomes. Equally important to participants was the ability to control the amount and timing of information they received, because many were afraid of feeling overwhelmed or discouraged by too much negative information.

QOL information and transplant decisions

Participants were asked whether more QOL information would have changed their decision to have a transplant or plan differently for life after transplant. A large majority of patients indicated that additional information would not have changed their decision. A few participants reported that they would not have had the transplant or were uncertain. These participants reported that the experience had been too arduous for themselves or their caregivers. Some patients dreaded or planned to refuse a second transplant if it became necessary. Thus, patients reported that greater information about post-HCT QOL would not only be helpful in coping with long-term side effects but may also help with transplant decision-making as well.

DISCUSSION

The aim of the current study was to collect qualitative information from allogeneic HCT recipients regarding education about post-HCT QOL. As such, we conducted face-to-face focus groups of patients who responded to questions regarding their recollection of patient education regarding post-HCT QOL, their experience with post-HCT QOL, how their experience differed from what they expected and how we could better educate future patients. In general, we found that study participants were eager to share their experiences and suggestions for how to improve patient education.

A primary theme that emerged in all four focus groups was the importance of controlling information to manage anxiety regarding transplant. Study participants generally fell into two categories regarding their preference for information: monitors and blunters.[15,16] Monitors cope with anxiety by scanning for threatening information. They actively seek out detailed information regarding health risks as well as strategies for preventing or managing risks.[15] In the current study, patients who were monitors took an active role in seeking out information from multiple sources, primarily the transplant team, the Internet and other patients. In contrast, blunters cope with anxiety by actively avoiding potentially threatening information. They tend to find large amounts of detailed information to be stressful and try to block it out.[15] In the current study, blunters reported avoiding information provided by the transplant team, such as making the decision not to read educational materials. These comments suggest that, beyond information required for informed consent, educational material should be presented in a format that allows patients to select as much or as little information as they wish. For example, a website with a menu of topics could accommodate both monitors and blunters. It could also be a useful reference throughout the transplant process, as patients and caregivers could select topics most relevant to their current situation. Further, tailored health information often enhances the relevance of health messages and may improve patient engagement.[17–19]

A second major theme was concern about late complications of HCT and immunosuppressive therapy. Although patients reported that they had been educated regarding side effects such as GVHD, they described feeling unprepared for many of the other side effects such as neuropathy, diabetes, weight gain and avascular necrosis. Patients also reported feeling unprepared for the extent to which these side effects and GVHD could affect their lives. Many expressed feeling a loss of identity as they could no longer engage in many of the normal activities of daily living, such as driving, reading, walking and other hobbies. One of the most difficult aspects of chronic side effects was uncertainty regarding when and if their health would improve. For patients who expected a gradual return to normal life, the unpredictability of GVHD flares and other late complications was particularly upsetting. These findings are consistent with previous research suggesting that active chronic GVHD is associated with a twofold risk of distress.[20] Some would have decided against a transplant if they had known about its negative impact on their caregivers or their own QOL. Thus, patient education materials should provide extensive information describing chronic side effects. Information should describe the side effects, why they occur, the extent to which they could interfere with daily functioning and QOL, their chronicity and common treatment options. This information should be available to interested patients as they make decisions about transplant and also as part of long-term follow-up care.[21,22]

A third major theme that emerged in all of the focus groups was the desire to hear about QOL from other patients. Many participants expressed appreciation for the focus groups, which helped to normalize some of their experiences. Participants reported seeking out other HCT patients in the clinic waiting room, local HCT patient housing or online via Facebook. Although many expressed the desire to attend support groups, some described ambivalence about hearing overly negative or upsetting information. Nevertheless, the frequency with which other patients were mentioned as a desired source of information underscores the importance of including them in patient educational materials. A primary concern to educators is the accuracy of information patients provide to one another. Lay health educators trained by the transplant team are one option to address this issue. Another option is to incorporate patients' perspectives into print or audiovisual materials through quotations or video interviews. It was clear that participants wanted detailed, practical and genuine information from patients regarding their own experiences. Thus, information from other patients should be an integral and informative part of educational materials.

To our knowledge, this is the first study of patient education regarding post-HCT QOL. Strengths of the study include a sample of allogeneic recipients interviewed 1–4 years after HCT as well as use of rigorous qualitative research methodology. Study limitations should also be noted. The sample was relatively small and composed primarily of Caucasian and non-Hispanic participants. Thus, although saturation was reached with this sample, a more diverse sample of allogeneic HCT recipients may have yielded additional themes. The current study was conducted at one institution and findings may not generalize to other transplant centers with different educational practices. In addition, participants' responses were often based on retrospective recall, which may be inaccurate. These data are nonetheless valuable since the aim of the current study was to better understand patients' perceptions of their transplant rather than to garner accurate information regarding patient education practices.

In summary, the current study provides a great deal of information regarding post-HCT QOL that has not been captured to date by standardized instruments such as the SF-36, FACT-BMT or EORTC QLQ-C30. This information can be used clinically to develop better educational materials regarding post-HCT QOL. It also points to gaps in existing research. For example, literature is sparse regarding how long-term side effects such as avascular necrosis, joint replacement and peripheral neuropathy affect QOL in allogeneic HCT recipients. It underscores the importance of conducting QOL research that yields findings that are easily understandable to patients. Research on topics such as these may inform future interventions to educate patients and improve their QOL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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4.5.Manuscript Addendum 2

Caregivers' Quality Of Life After Blood And Marrow Transplantation: A Qualitative Study.

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Caregivers' Quality of Life after Blood and Marrow Transplantation: A Qualitative Study

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Keywords

Bone Marrow Transplantation; Hematopoietic Stem Cell Transplantation; Quality of Life; Caregivers

A sizable literature has documented the challenges of providing care to a family member with cancer, although fewer studies have reported on caregivers of allogeneic hematopoietic cell transplantation (HCT) recipients. Existing studies of HCT caregivers suggest that they are at risk for distress. For example, prior to HCT, caregivers report significantly higher levels of anxiety, traumatic stress, and insomnia than population norms (1, 2). Several years after transplant, risk of depression among spouses of HCT recipients is 3.5 times greater than that of similar peers (3). Spouses of HCT recipients also report less social support, greater marital dissatisfaction, greater loneliness, and less spiritual well-being than their peers (3). In qualitative interviews of HCT recipients and spouses, spouses were more likely than patients to report negative life changes as the result of transplant (4).

The goal of the current study was to qualitatively examine post-HCT quality of life from the caregiver's perspective. As part of a larger qualitative study of patient education regarding quality of life after allogeneic HCT, patients and caregivers were recruited from a single institution to participate in separate focus groups. At this institution, caregivers are required to attend a class regarding how to care for an allogeneic HCT recipient. Caregiver support groups are available as well. Results of the patient focus groups have been reported previously (5). Caregivers were asked about their quality of life and their perceptions of the patient's quality of life, with a focus on how the transplant team could better prepare future

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caregivers for life after transplant. As the study was exploratory in nature, there were no *a priori* hypotheses.

Caregivers were nominated by eligible patient participants (5). To be eligible, caregivers had to be able to speak and read English and provide informed consent. Caregivers attended one of four caregiver-only focus groups held in November 2011 and March 2012. Groups ranged in size from three to six caregivers. Details of study methodology have been described previously (5). Focus group questions are listed in Table 1.

A total of 16 caregivers participated in the focus groups. Participants had a median age of 55 (range 25-80). The majority was Caucasian (100%), non-Hispanic (88%), married (94%), had not completed college (62%), and reported a current annual household income of US$ 40,000 a year or more (79%). Representative quotes from caregivers are displayed in Table 2.

Nearly all participants agreed that providing care to a HCT recipient entailed significant physical and emotional demands. Several participants noted that caregiving required permanent life changes and a lifelong commitment to the patient. Social isolation was commonly reported and perceived to be detrimental for both the patient and caregiver. Many described constant vigilance about disinfecting their surroundings to prevent infection, sometimes far longer than required by the transplant team. Some caregivers reported a loss of identity as they no longer engaged in the activities they used to find meaningful. Although some caregivers reported significant emotional support from family and friends, others felt overlooked as loved ones' concerns were typically centered exclusively on the patient.

Caregivers reported feeling unprepared for the severity and duration of emotional and physical changes in the patient. They also expressed difficulty determining how much they should push patients to engage in activities the caregivers perceived to be beneficial (e.g., exercising, resuming previous hobbies). Nearly all caregivers reported that their relationship with the patient was significantly changed due to the transplant process. Some felt that the transplant brought them closer together while others perceived significant strain in the relationship.

Caregivers commonly voiced feelings of gratitude for the patient's survival in addition to insomnia, helplessness, guilt, fatigue, and fear about cancer recurrence. They also described high levels of anxiety at each outpatient follow-up appointment, which were temporarily assuaged by hearing the patient's blood counts. Although caregivers described significant negative emotions, few reported receiving psychosocial services.

In general, caregivers were reluctant to discuss ways in which they took care of themselves. Many reported guilt about focusing on their own needs. Prayer, use of social support, and focusing on one day at a time were the most commonly reported coping strategies. Use of web-based sharing systems such as blogging, email, or other social networking sites to inform family and friends of the patient's progress and receive support was also widely perceived to be helpful.

Caregivers reported being well-informed regarding physical symptoms patients were likely to experience during the acute transplant period, symptom management, and other requirements for daily care of an HCT recipient (e.g., flushing lines, precautions against infection). Caregivers wanted more information regarding how to cope with emotional and cognitive changes in the patient. It was suggested a mentoring program be created, in which names and phone numbers of experienced caregivers were provided to caregivers new to HCT.

In general, caregivers echoed many of the same themes as patients (5), including greater need for information regarding post-transplant morbidities such as graft-versus-host disease (GVHD). Caregivers also provided unique information about the patients' experiences, most notably observed changes in personality, difficulty handling stress, and cognitive impairment. Caregivers participating in the current study frequently expressed significant unmet needs for information and support. We are aware of only one previous study of an intervention for caregivers of allogeneic HCT recipients, which found that caregivers perceived emotional expression to be helpful in dealing with stress (6). Caregivers may also benefit from greater information regarding long-term morbidities, tools to help manage their own and the patient's emotional distress, and awareness of the importance of self-care and outside support (7). Studies among cancer patients suggest that this type of intervention can significantly reduce caregiver burden and improve quality of life (8). Although evidence-based caregiving interventions are currently lacking in HCT, caregivers should be directed towards resources available through cancer- and transplant-specific websites (e.g., National Marrow Donor Program, National Bone Marrow Transplant Link, Leukemia and Lymphoma Society).

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5. DISCUSSION

The studies included in the present thesis indicate that unmet needs for care in the physical, psychological, and informational domains are common among patients diagnosed with hematological malignancies, and particularly, among allogeneic recipients and their caregivers.

5.1. First manuscript

The aim of the first work of the thesis was to describe current unmet needs for psychosocial care as well as interventions to address them among patients diagnosed with hematological malignancies, and particularly, among allogeneic recipients. Results indicate significant current unmet needs in physical, psychological, informational, spiritual, and financial domains. These findings underscore current recommendations for patient-centered care [72, 76]. In this line, screening and preventive guidelines for HCT survivors recommend screening for psychosocial aspects 6-12 months post-HCT [77]. However, the efficacy of these guidelines have not been tested [78], and its application might be restricted to centers who have clinicians with expertise in managing post-transplant complications and to patients who receive care in these transplant centers [77]. The importance of individualizing patient care is the focus of the "Randomized Study of Individualized Care Plans for Hematopoietic Cell Transplant Survivors," performed by the Center for International Blood and Marrow Transplant Research, which assesses if personalized plans improve adherence to recommended healthcare indications and behaviors, as well as reduce HCT-related distress when compared to usual care. Unmet needs may also be due to different perceptions of patients' symptoms between clinicians and patients. Clinicians tend to underestimate patients' symptoms and overestimate their QoL [79], suggesting that difficulties in communication can lead to unmet needs for care. This aspect can be ameliorated by patient-reported symptom monitoring during clinical visits, which may facilitate screening and management of symptoms, and result in increased patient

and physician satisfaction [80, 81]. Finally, the current fragmented care to long-term survivors also presents barriers to addressing their specific needs. Due to distance from the transplant center, or patient or center preference, long-term survivors might not receive care at their transplant center. Instead, survivors might receive care from their primary hematologist-oncologist, primary care physician or other healthcare provider [77]. These professionals might not be aware of transplant and treatment-specific side effects, such as conditioning regimens, total body irradiation or immunosuppressants; as well as long-term transplant complications and potential drug interactions [77, 82]. Fragmentation of care can be overcome by long-term follow-up clinics integrated in transplant centers where HCT-specialized staff can properly screen, address and coordinate care [83]. HCT-survivors have expressed their preference to receive care in these clinics when compared to other approaches, such as "satellite centers" closer to their place of residence or telemedicine [84]. When access to transplant centers is not possible, coordination of transplant and non-transplant multidisciplinary clinicians is necessary [83] in order to properly address survivors' needs.

5.2. Second manuscript

The second study evaluated the impact that SIR/TAC and MTX/TAC prophylaxis regimens have on patient-reported QoL over the first year post-HCT. Because SIR/TAC was associated with significant reduction of grade II-IV acute GvHD and severe chronic GvHD when compared to MTX/TAC, it was hypothesized that the SIR/TAC group would report better QoL than the MTX/TAC group [85]. We analyzed the effect of study arm on changes on post-HCT QoL, controlling for pre-HCT QoL, anemia, and severity of GvHD. Contrary to the hypothesis, SIR/TAC was associated with inferior QoL relative to MTX/TAC with clinically significant differences in QoL observed at day 360. Post-hoc analyses revealed that SIR/TAC was

associated with fatigue and nausea, confirming previous findings of these side effects with SIR-based regimens [86, 87]. In addition to the clinical relevance of the findings, it is noteworthy that this study incorporated PROs for assessing the impact of GvHD prophylaxis regimens. Despite the National Institute of Health Conference of 2005 recommended including PROs in the assessment of GvHD [35], few studies routinely incorporate them. For example, a recent review of RCTs assessing the effects of mychophenolate mofetil and MTX for the prevention of acute GvHD found that none included QoL outcomes [40]. In contrast, the incorporation of PROs in this study highlighted the disparity between patients' and clinicians' perception of benefit, as better recovery of QoL was expected in patients receiving SIR/TAC due to reduced incidence of acute grade II-IV GvHD. Thus, results point to the importance of incorporating PROs in clinical trials as well as standard care. In addition, results have clear clinical implications, indicating that educational efforts should address SIR-related secondary effects when counseling patients who will be treated with this regimen.

5.3. Third manuscript

The third work of this thesis assessed the incidence and the relationship between HCT-related symptomatology, coping, and depression among allogeneic recipients at day 90 post-HCT. Clinically significant depressive symptoms were found in 28% of the sample, which is consistent with previous findings at this time of HCT [19, 88]. In addition, more than 80% of the sample reported HCT-related symptoms of the skin, muscles and joints, and reduced energy; whereas 41 to 71% developed eye, mouth, pulmonary and digestive symptoms. Results indicated that coping strategies were associated with post-HCT depression but not with HCT-symptoms. Specifically, problem solving was associated with less depressive symptomatology, whereas cognitive avoidance, resignation and emotional discharge were associated with more depressive symptoms. These findings are in line with previous [23-25] and more recent studies [89] showing that problem solving is associated with less depression,

whereas acceptance, resignation, and avoidant coping are associated with greater depression. Further analyses indicated that severe HCT-related symptoms were associated with greater depressive symptoms in the presence of more maladaptive coping and less adaptive coping. Adaptive coping attenuated the associated between HCT-related symptoms and depression. Thus, the combined impact of worse physical morbidity with poor coping may place patients at risk for greater depression. These results provide new knowledge, as the relationship of post-HCT coping and depression has not been previously assessed [23, 25]. Moreover, the study focused only on allogeneic patients in contrast to previous studies with samples of both autologous and allogeneic recipients [23, 25]. These results have clear clinical implications, as they describe a subgroup of patients –those with poor coping skills- who are more vulnerable to depression when experiencing HCT-related symptomatology, and another group of patients –those using adaptive skills- who are more resilient. In addition, results indicate that coping strategies should be considered for inclusion in psychological interventions aimed to decrease distress.

5.4. Fourth manuscript

The fourth work of this thesis assessed how well pre-transplant education prepared patients for life after HCT. Results indicated that participants did not understand the impact that chronic and long-term side effects would have on their QoL. This finding is important because previous literature has noted that participants tend not to recall information on HCT-risks and complications [90]. However, participants on this study recalled the education received, but noted the unpredictability of GvHD, which significantly undermined their physical and emotional recovery. Results are clinically meaningful, as discordance between pre-HCT expectations and post-HCT functional status is associated with psychological distress [91]. In the current study, while most participants indicated that they would have elected to have the transplant even if they had known more about deficits in post-HCT QoL, a subgroup of patients

expressed that they would have not gone through HCT if they knew the effects it had on their caregivers and on their own QoL. In order to meet the described informational needs, participants suggested that educational programs should address the HCT-related morbidity across the HCT continuum, emphasizing a flexible format, content and timing. Specifically, participants suggested that information should be presented in a format that allow patients selecting the amount and type of information they want, such us a website with a menu of topics. Second, participants requested more information about late complications and immunosuppressive therapy, which should be available as they make decisions about transplant and also as part of long-term follow-up care. In addition, participants expressed their desire to hear about QoL from other patients, which could be facilitated by health educators trained by the transplant team or through incorporating patients' perspectives into print or audiovisual material. To our knowledge this is the first study assessing education regarding post-HCT QoL and patients' recommendations to improve current education. This is noteworthy, as there are very few studies addressing interventions to improve post-HCT wellbeing [92], and to our knowledge, none is based on qualitative research in HCT recipients. Other strengths of the study are its qualitative design, which enabled us to describe the impact that late effects have on survivors' wellbeing, which is not extensively captured by the standardized quantitative instruments used previously. Moreover, results are provided in a way easy to understand to patients and caregivers, which will help further patients with HCT decision-making and guide them during the HCT recovery.

5.5. Fifth manuscript

The fifth study of this thesis qualitatively assessed post-HCT QoL from the caregivers' perspective. Results indicated that caregivers didn't realize how long they would be providing care to the patient, expecting that recovery would take place by one-year post-HCT. As in the fourth study of this thesis, caregivers reported not being prepared for late effects and the

relapsing-remitting nature of GvHD. In addition, caregivers requested support to deal with patients' cognitive, emotional and personality changes. These results are noteworthy, as previous research on caregivers is minimal. Moreover, as in the fourth study of this thesis, its qualitative design enabled us to draw attention to areas in which caregivers need more help, such as information and support, along with the detection of patients' clinical changes - personality, emotional and cognitive changes that might be overlooked during clinical visits.

Participants described caregiving as emotionally and physically demanding. They expressed high rates of insomnia, fatigue, fear of cancer recurrence, and isolation as described previously [14, 27]. However, caregivers reported feeling guilty about taking care of themselves or worried about leaving the patient alone. This is consistent with previous research indicating that caregivers are reluctant to attend their own needs in order to focus on patients' needs [93]. However, participants in our study described that a mentoring program with experienced caregivers could be helpful to them.

In addition, caregivers reported that the relationship with the patient changed over the course of HCT: in some cases, the HCT experience fostered a closer relationship whereas in others, it strained the relationship. Literature addressing this aspect of HCT is scare, although it has been described that there are no differences in rates of divorce, separation, and quality of the marital relationship between HCT survivors at 5- [94] and 10-years [67] post-HCT when compared with the general population. In addition to the clinical implications of this study, results help to fill in a gap in existing knowledge as interventions on HCT caregivers are scarce. However, available data suggest that problem solving and stress management-based interventions are effective in decreasing distress among HCT caregivers [95, 96].

In summary, the five studies of this thesis describe important unmet needs for care among allogeneic recipients and their caregivers. Thus, results highlight areas which could benefit from further improvement in order to optimize the HCT outcomes. A strength of this line of

research is the focus on allogeneic patients and their caregivers, overcoming limitations of previous studies which have included mixed samples of autologous and allogeneic patients [23-25, 89]. Moreover, the studies assessed patients at different times of HCT to describe the impact of transplant-related physical and psychological morbidity on survivors' QoL and wellbeing. In addition, main outcomes were assessed by means of validated measures of QoL, patient-reported HCT-symptoms, depression, coping strategies, and qualitative methodology. Moreover, manuscripts are based on rigorous methodology. The first manuscript extensively reviews unmet needs for psychosocial care and interventions to address them among patients diagnosed of hematological malignancies. The second study is based on a RCT assessing the effects of SIR/TAC versus MTX/TAC arms on QoL over one year. The third manuscript is based on a cross sectional design assessing allogeneic survivors at day 90 post-HCT, a critical period for this population. The fourth and fifth manuscripts are based on a qualitative design which enabled us to provide QoL results in terms easy to understand for patients, researchers and clinicians, also overcoming a previously reported limitation [97]. However, study limitations should also be noted. Sample sizes of the second, fourth and fifth manuscripts are relatively small. All clinical studies were performed at a single site in the United States and included mainly Caucasian, married and well-educated patients. This homogeneity could limit the generalization of the obtained findings.

Our results highlighted the negative impact that late effects, chronic GvHD and immunosuppressants have on patient- reported wellbeing. These results should be incorporated in further educational programs preparing patients and caregivers for transplant. PROs are increasingly receiving attention among researchers in the field of HCT, as they provide a broader picture of the impact that HCT has on a patient's life [98]. For example, an increasing number of clinical trials are including PROs, which will provide information that should be included in further counseling of patients who will be treated with these regimens. PROs are the aim of a current project entitled "Engaging Patients in Developing a Patient-

Centered HCT Research Agenda" performed by the Patient-Centered Outcomes Research Institute. This project assesses outcomes that matter most to patients and caregivers with the aim of providing evidence-based data that will contribute to make better-informed decisions. In addition to the abovementioned educational and research efforts, a recent review from a panel of experts in PROs have concluded the need to develop and assess a dose-intensity modulation intervention matching survivors' needs according to survivor's risk factors [78]. These interventions could focus on enhancing adaptive coping strategies, due to the significant role of coping strategies in modifying the risk of depression. A previous randomized trial of a cognitive-behavioral telephone intervention reported promising results in decreasing symptoms of depression and post-traumatic stress disorder, but included a mixed sample of HCT patients [92]. Additional interventions demonstrate promise in improving survivors' wellbeing. Exercise-based programs have resulted in decreased fatigue and improved QoL among allogeneic patients [87, 99]. Problem solving and stress management –based programs have been shown to reduce distress among caregivers of allogeneic patients [95, 96]. Studies assessing patients and clinicians communication on the HCT setting are scarce but highlight important deficiencies. For example, discussion of treatment options and information about side effects are underrepresented during consultations on the hematology setting [100]. In addition, physicians rarely assess patients' preferences for information, comprehension of the provided information, and role in decision making [101]. In contrast, it has been demonstrated that assessing patients' preferences and expectations as well as checking patients' understanding of the information helps to target patient' needs [102] and reinforces patient and physician communication [100, 101]. Technology-based applications have shown the potential to improve health-related information and coordination of care and reduce information overload during consultations [103]. For example, the "BMT Roadmap" is an information-technology based portal displaying patient-specific laboratory and medical information to caregivers of pediatric HCT patients during hospitalization [104, 105]. In

addition, interventions aimed at improving patient and physician communication have shown encouraging results in the oncology setting. A RCT assessing the effects of a training program aimed at improving physicians' communication skills according to patients' preferences for communication, significantly improved patients' emotional wellbeing and physicians' performance and confidence when communicating with patients [106]. In addition, another RCT found that skills trained in these programs were easily transferred into practice and resulted in patients reporting increased satisfaction with care when attended by a trained member [107]. Interventions such as these have the potential to improve QoL for large numbers of HCT patients and their caregivers.

In conclusion, allogeneic recipients, particularly those developing HCT-related symptoms, chronic GvHD, or side effects of immunosuppression, are at risk of worse psychological functioning and impaired QoL. In addition, these survivors and their caregivers report significant unmet needs for information and support. Additional education and psychosocial intervention programs should be developed in order to help them cope with the HCT and its morbidity, which can result in reduced psychological symptomatology and improved wellbeing. Survivors and caregivers wellbeing should be routinely assessed at clinical visits in order to evaluate potential unmet needs for care.

6. CONCLUSIONS

6.1. Conclusions

6.1.1. First manuscript

There exist significant unmet needs for psychosocial care among patients diagnosed with hematological malignancies, particularly among allogeneic patients. Main reported unmet psychosocial needs are related with the physical, psychological, informational, financial and spiritual domains.

6.1.2. Second manuscript

Patients treated with SIR/TAC for GvHD prophylaxis demonstrate inferior recovery in QoL post-HCT relative to patients treated with MTX/TAC despite reduced severity of acute and chronic GvHD. Side effects of fatigue and nausea associated with SIR are thought to contribute to these deficits.

6.1.3. Third manuscript

The incidence of HCT-related symptomatology and depression is high at day 90 post-HCT. Coping strategies modify the risk of depression associated to HCT-related symptom severity: patients facing greater HCT-related symptomatology report more depressive symptoms if they display maladaptive coping, such as cognitive avoidance and emotional discharge, and less adaptive coping, such as reappraisal and problem solving.

6.1.4. Fourth manuscript

Qualitative study methodology indicated that patients feel well-prepared to face the acute HCT phase but unprepared to cope with the late onset of late effects, chronic GvHD, and how they impair their daily functioning.

6.1.5. Fifth manuscript

A qualitative study of caregivers of allogeneic HCT patients reported an important psychological burden, as well as unmet needs for information about onset of late effects and support. Caregivers also described concerns about patients not described by patients themselves, such as cognitive impairments, personality changes and difficulty managing stress.

6.2. Conclusions

6.2.1. Primer manuscrit

Els pacients diagnosticats d'hemopatia maligna i especialment els receptors de TPH al·logènic tenen importants necessitats psicosocials, especialment físiques, psicològiques, informatives, financeres i espirituals.

6.2.2. Segon manuscrit

Els pacients que segueixen profilaxis de la malaltia de l'empelt contra l'hoste crònica amb SIR/TAC tenen una recuperació de la qualitat de vida més lenta en comparació amb els pacients tractats amb MTX/TAC; tot i que aquest segon règim està associat a una disminució significativa de la malaltia de l'empelt contra l'hoste aguda i crònica. Els efectes secundaris del SIR, tal i com la fatiga i la nàusea, contribuirien a aquests dèficits.

6.2.3. Tercer manuscrit

La incidència de la simptomatologia relacionada amb el TPH i la depressió és elevada en el dia 90 post-TPH. Les estratègies d'afrontament de problemes modifiquen el risc de depressió associat a la gravetat de la simptomatologia relacionada amb el TPH; els pacients que desenvolupen més simptomatologia relacionada amb el TPH refereixen més símptomes depressius si utilitzen estratègies desadaptatives, com ara l'evitació cognitiva i la descàrrega emocional; i menys estratègies adaptatives, com la reapreciació o la resolució de problemes.

6.2.4. Quart manuscrit

La metodologia qualitativa de l'estudi mostra que els pacients estan ben preparats per afrontar la fase aguda del TPH però menys preparats per afrontar els efectes tardans, la malaltia de l'empelt contra l'hoste crònica; i com aquesta morbiditat afecta la seva funcionalitat.

6.2.5. Cinquè manuscrit

Els resultats d'aquest estudi qualitatiu indiquen que els cuidadors de receptors de TPH al·logènic presenten una morbiditat psicològica significativa així com necessitats d'informació sobre els efectes tardans, i de suport emocional. A més, els cuidadors expliquen preocupacions sobre els pacients no descrites per ells mateixos, com ara l'afectació cognitiva, canvis de personalitat i dificultats per afrontar l'estrès.

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