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Psychosocial aspects of hematopoietic stem cell transplantation

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Abstract

Hematopoietic stem cell transplantation (HSCT) has become a conventional and potentially curative treatment for various hematological diseases. As more sophisticated procedures have been developed and mortality rates have decreased, attention has shifted to the psychosocial challenges associated with transplantation. The psychosocial difficulties accompanying transplantation are addressed in the context of both quality of life (QOL) and psychopathological research. Among the psychiatric comorbidities of HSCT, anxiety, depression, sleep and sexual disorders, delirium and post-traumatic stress disorder are the most studied conditions. Recently, more attention has been focused on the psychosocial burden of caregivers. Devising recommendations for the management of psychiatric symptoms and psychosocial interventions in HSCT sufferers and close relatives is a major concern to consultation-liaison psychiatrists and transplant teams. This review synthesizes and critically evaluates the current literature on the psychosocial aspects of HSCT and appraises the clinical significance of these outcomes. Issues of QOL assessment; psychosocial functioning and QOL in the course of HSCT; impact of graft-versus-host disease and other predictors of QOL and psychosocial functioning; comorbid psychiatric disorders; and interventions to maintain or improve QOL and reduce psychopathology and psychosocial burden on family members are presented.

Key Words: Hematopoietic stem cell transplantation; Psychosocial aspects; Quality of life; Psychopathology

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Core Tip: Over recent decades more attention has shifted to the psychosocial challenges associated with transplantation. The psychosocial difficulties accompanying transplantation are addressed in the context of both quality of life (QOL) and psychopathological research. Recently, more attention has been focused on the psychosocial burden of caregivers and psychosocial interventions in hematopoietic stem cell transplantation (HSCT) sufferers and close relatives. This review synthesizes the major issues on psychosocial aspects of HSCT including QOL research, psychosocial adaptation for HSCT, psychiatric comorbidities, and psychosocial interventions to improve QOL and reduce psychopathology in HSCT patients and close relatives.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has become a conventional and potentially curative treatment for various malignant and non-malignant hematological diseases. The number of survivors of malignant hematological conditions is rapidly increasing worldwide[1,2]. Despite recent advances in this field, transplant-related severe medical complications, including graft-versus-host disease (GVHD) and mortality, remain a major and well-documented concern[3-6]. As more sophisticated procedures have been developed and mortality rates have decreased over recent decades, attention has shifted to the psychosocial challenges associated with transplantation. The psychosocial difficulties accompanying transplantation are addressed in the context of both quality of life (QOL) and psychopathological research. The growing literature on the psychological symptoms and QOL associated with HSCT[7-11] has yielded inconsistent findings. Studies on the associations among predictors, physical and mental recovery from transplant, long-term psychosocial functioning, and QOL have also yielded conflicting results[12]. Recently, more attention has been focused on the psychosocial burden of caregivers. Based on the results of such studies, psychosocial interventions are being introduced to support HSCT recipients and their caregivers.

Among the psychiatric comorbidities of HSCT, anxiety, depression, sleep and sexual disorders, delirium and post-traumatic stress disorder (PTSD) are the most studied conditions[2,13]. Devising recommendations for the management of psychiatric symptoms and psychosocial interventions in HSCT sufferers and close relatives is also a major concern to consultation-liaison psychiatrists and transplant teams.

The aim of this review is to synthesize and critically evaluate the current literature on the psychosocial aspects of HSCT. The issues addressed include: (1) Assessment of QOL in HSCT; (2) Evaluation of the research on changes in psychosocial functioning and QOL in the course of HSCT; (3) Differences in QOL between patients treated with allogeneic (allo-HSCT) and autologous HSCT (auto-HSCT); and (4) Standard-dose chemotherapy, healthy matched controls, and population norms. In addition, the impact of GVHD, reduced-intensity conditioning (RIC) regimens and other predictors of QOL and psychosocial functioning are touched upon, highlighting the impact of comorbid psychiatric disorders. Interventions to maintain or improve QOL and reduce psychopathology and the psychosocial burden on family members are also described briefly.

DIAGNOSTIC TOOLS FOR SCREENING PSYCHOSOCIAL RISKS AND QUALITY OF LIFE IN HSCT PATIENTS

Historically, psychosocial evaluations were conducted to select suitable candidates for solid organ transplantation because of the limited supply of donor organs[14]. A further aim was to provide information for individualized treatment planning[15]. However, since positive associations between pretransplant psychosocial problems

and posttransplant medical and psychosocial complications have been reported[16-18], the emphasis on pretransplant psychosocial evaluation has shifted to identifying patients at increased risk (*i.e.*, patients with significant psychopathology, substance abuse or poor treatment adherence). With improving treatment outcomes and longer survival times, patients' QOL is becoming increasingly important reflected in the development of diagnostic instruments used to assess the QOL of different patient populations. The characteristics of commonly used diagnostic tools are summarized in Table 1[19-23].

PRE-TRANSPLANTATION PSYCHOSOCIAL CONSIDERATIONS

HSCT candidates commonly experience several treatment failures or relapses of cancer and suffer from physical and psychological distress even before HSCT, which is usually the final potentially curative treatment. Overestimation of the benefits and underestimation of the morbidity and mortality related to HSCT are regular psychological reactions[12]. An investigation of patients' prognostic understanding revealed that their perceptions were more optimistic than those of their doctors[24]. Patients whose prognostic perceptions were similar or identical to their doctors' opinions reported significantly elevated levels of depression[24]. Therefore, interventions for improving patients' prognostic understanding should be introduced rather during decision making than before hospitalization period. After that, psychological interventions are more appropriate to focus on enhancing coping strategies and maintaining an optimistic framework regarding outcomes.

A number of investigations have explored the impact of psychosocial risk factors on transplant-related mortality and morbidity, with conflicting results[18,25,26]. In a recent study, pre-transplant depression, particularly with comorbid anxiety, decreased the overall survival time after transplantation, while pre-transplant anxiety without depression had no impact on transplant-related mortality[27,28]. Psychological distress prior to HSCT is more likely to be manifested as severe anxiety than as depressive symptoms[13,29]. Anxiety symptoms prior to HSCT are related to uncertainty and anticipatory fear about the procedure, including the response to the transplant, management of isolation and potential complications[13,29]. The main predictors of pre-transplant psychosocial difficulties include younger age, cancer-related distress, low perceived control and poor physical functioning. Younger age and cancer-related distress predict anxiety symptoms, whereas poor physical functioning and low perceived control predict depression[29]. Overall, HSCT recipients who experience elevated psychosocial distress and low perceived control are at high risk for psychosocial morbidity and impaired QOL following transplantation[13].

Numerous investigations have concluded that anxiety, depression and QOL prior to HSCT predict QOL and psychosocial problems during and after HSCT[1,30-34]. Other risk factors include poor psychosocial functioning, while protective factors include good social support and coping skills. Consequently, pre-transplant screening for at-risk recipients should include an assessment of comorbidities, the functional status, psychosocial difficulties and social support[2].

PSYCHOSOCIAL PROBLEMS AND QOL DURING HOSPITALIZATION FOR HSCT

Hospitalization for HSCT includes a conditioning regimen, the transplantation procedure, engraftment and a post-transplantation period. Completing HSCT is physically and emotionally challenging for all patients. Recipients of auto-HSCT spend approximately 4 wk in hospital, while recipients of allo-HSCT spend even longer in strict isolation. During this treatment period, recipients' psychological well-being is mainly affected by acute physical side effects, isolation and dependence. Although post-transplantation physical and psychosocial complications, including their impact on QOL have been well described, only a few studies have focused on the inpatient period. Most of these studies detailed physical complaints and largely glossed over psychological difficulties[35]. Research on psychosocial issues has explored the adverse impact of psychological symptoms on treatment outcomes. Studies have primarily concentrated on anxiety and depression during the course of treatment and yielded contradictory results regarding the trajectory of these symptoms[2,36-39]. The

Table 1 Characteristics of diagnostic instruments used for screening psychosocial risks and quality of life in hematopoietic stem cell transplantation patients

Diagnostic instrument	Factors	Aim	No. of items	Score range	Ref.
Psychosocial Assessment of Candidates for Transplantation	4: Social support, psychological health, lifestyle factors, and understanding of transplant and follow-up	To stratify psychosocial risk in solid organ transplant recipients	8	8-40	Olbrisch <i>et al</i> [19], 1989
Transplant Evaluation Rating Scale	Not divided into factors	To assess the reliability and validity of the selection of transplant candidates	10	26.6-79.5	Twillman <i>et al</i> [20], 1993
Stanford Integrated Psychosocial Assessment for Transplantation	4: Patients' level of readiness and illness management; level of readiness of patients' social support system; psychological stability and psychopathology; and lifestyle and substance use	To assess the psychosocial variables and behaviors that frequently have negative effects on all types of transplant candidates	18	0-115	Maldonado <i>et al</i> [21], 2015
Functional Assessment of Cancer Therapy (FACT)-version 4	4: Physical well-being, social/family well-being, emotional well-being, and functional well-being	To measure dimensions of health-related quality of life in cancer patients	27	0-108	Cella <i>et al</i> [22], 1993
Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT)-version 4	5: Physical, functional, emotional and social well-being, and BMT-specific complaints	To evaluate multidimensional aspects of quality of life in BMT patients	27 (FACT) +23 (BMT specific)	0-200	McQuellon <i>et al</i> [23], 1997

FACT: Functional assessment of cancer therapy; BMT: Bone marrow transplant.

findings indicate a fluctuating, but generally decreasing, tendency in anxiety levels over the course of treatment compared with persistent pre-transplant anxiety, while depressive symptoms show a gradual posttransplant increase over time, regardless of their pretransplant level [8,35,36,40]. Mood and affective symptoms may remain unrecognized and interfere with medical treatment [12]. An estimated 20% of patients develop clinically significant psychiatric disorders during hospitalization for HSCT [40]. Anxiety, depressive, sleep and adjustment disorders are reported most frequently [2,35,40]. Depressive symptoms during hospitalization are inversely associated with the length of hospital stay, QOL during hospitalization, symptom burden, treatment adherence and mortality, and predict post-transplant QOL [18,40]. Furthermore, pre-transplant depressive and anxiety symptoms predict poor QOL and depressive symptoms during hospitalization [35]. Patients who develop depressive symptoms and experience a significant decline in QOL during hospitalization are more likely to experience treatment as a "traumatic event" and to develop PTSD symptoms later, while others might show positive post-traumatic personal growth in response to in-patient treatment [7,41].

PSYCHOSOCIAL PROBLEMS AND QUALITY OF LIFE FOLLOWING HSCT

Transplant-related mortality has significantly decreased over the past decades, yet long-term morbidity and late mortality remain persistent challenges. Despite the growing number of survivors, clinical experience has shown that patients often suffer from short- and long-term morbidity and deficits in QOL and psychosocial functioning [42]. Therefore, several studies have investigated QOL and psychopathological symptoms following HSCT, although these are heterogeneous in their study designs, patient populations, comparison groups, assessment tools and assessment time frames. Despite conflicting findings, there is preliminary evidence suggesting that patients continue to recover during the years following HSCT [9,10,43,44].

The trajectory of recovery after HSCT includes a particularly sensitive period marked by a high risk of lethal complications, with duration of approximately 100 d. Most patients suffer from medical complications during this acute post-transplant phase [45]; for example, in a recent study, only 13% of patients had no comorbidities while most of them had multiple comorbidities [46]. Another milestone in the course of recovery occurs at the end of the first post-transplantation year, when the strict management rules begin to ease. QOL has rather consistently been found to return to an acceptable level for most patients over the post-transplantation year, although some areas of functioning remain impaired [9,36,42,46,47]. Late post-transplant medical

complications, including chronic GVHD, secondary cancers, infections, persistent pain, fatigue, loss of appetite, physical weakness, sleep disturbances and drowsiness, can have major impacts on patients' psychosocial functioning and QOL[44,47-50]. Even if HSCT patients rate their QOL as satisfactory or good, it remains relatively poor compared with that of healthy controls and population norms[9,42,51-53]. Successful recovery after HSCT usually takes 3-5 years, starting with physical stabilization, then emotional stabilization and finally resumption of social functioning[38,54].

Comparisons of allo-HSCT and auto-HSCT recipients treated with standard-dose chemotherapy indicate similar or even greater impairments in QOL for allo-HSCT recipients and suggest different trajectories of recovery in the two groups[9,48,55-57]. The ability to draw conclusions from the literature is limited by confounding variables such as differences in age and pre-transplant comorbidities, higher rates of relapse in autologous transplant recipients and the presence of GVHD symptoms in allogeneic transplant recipients. Recovery is not a unidirectional process of improvement. Physical functioning generally improves before emotional and role functioning, although it can be affected by a variety of medical complications. Similarly, emotional recovery fluctuates over time[45]. There is great variability in patients' physical and mental recovery. While most patients experience stable physical and mental health following HSCT, a significant minority continue to show impaired physical and psychological functioning and are at risk for developing psychopathological symptoms[43]. The QOL literature mentions various factors that influence QOL after HSCT. Current research on QOL and HSCT focuses mainly on the relationship between GVHD and QOL. GVHD, particularly chronic GVHD, shows a consistent negative relationship with QOL[9,34,58,59]. There is a paucity of research examining the effects of non-myeloablative conditioning, such as RIC regimens, on QOL[34,60-62], although allo-HSCT is increasingly performed with RIC conditioning, particularly in elderly patients. Overall, the few studies on RIC regimens suggest that they have advantages in terms of QOL, compared with myeloablative conditioning[45,62].

Non-medical predictors, *e.g.*, socio-demographic factors, have also attracted scant research attention. Demographic factors such as younger age and female sex are associated with poorer QOL, and family relationships seem to be important determinants of physical and emotional recovery[34,58,63,64]. Recently, the impact of patients' socio-economic status (SES) on the outcomes of HSCT has received greater attention. Low SES tends to elevate transplant-related mortality. Economic influence is multifactorial, comprising not only the cost of treatment but also nutritional and hygienic conditions and treatment adherence[65]. Low income and unemployment have been associated with poor QOL in multiple domains following HSCT[66].

The association between pre-transplant psychological factors and QOL is a relatively well-studied area. Most authors agree on the predictive role of pre-transplant psychological distress—mainly anxiety and depression—in post-transplant QOL[34]. Identifying protective and risk factors is essential to devising and implementing psychosocial interventions.

Post-transplant psychological morbidity, and its association with QOL, is a major predictor of post-transplant QOL. A high prevalence of post-HSCT psychological distress, including symptoms of depression, anxiety, sleep disturbances and sexual problems, has been observed[13]. Most studies have found moderate to severe depressive and anxiety symptoms in a high proportion of HSCT patients[1,11,12,49]. Post-HSCT depression is common, even among patients with low pre-transplant levels of depressive symptoms and can persist for a long time post-bone marrow transplant (BMT)[8]. Depressive symptoms interfere with treatment adherence, adversely affect survival and decrease patients' perceptions of their QOL after transplantation[8,67]. Frequently identified predictors of depression in allogeneic transplant recipients are female sex, younger age, chronic pain and severity of chronic GVHD, while in autologous transplant recipients, only younger age and chronic pain are predictive[43]. There is moderate to strong evidence that pre-transplant psychological distress and GVHD predict post-transplant psychological distress, and that female sex and poor social support predict post-HSCT depression[8,34,38].

Studies exploring depressive and anxiety symptoms following HSCT have yielded heterogeneous findings. Overall, a significant minority (5%-40%) of patients experience high levels of anxiety and/or depressive symptoms before, during and after HSCT, with a gradual decrease during the years following the procedure[1].

Numerous investigations have compared QOL and affective symptoms in patients undergoing allogeneic and autologous transplantation, but the methodological diversity of these studies prevents firm conclusions from being drawn[45,55,57,68]. A recent review described the potential risk factors for poor QOL separately for allogeneic and autologous transplant recipients. Specifically, the review found

compelling evidence for GVHD and weak evidence for depression as risk factors for poor overall QOL in the allogeneic group, whereas no such relationships were observed in the autologous group[34]. Furthermore, there is convincing evidence that chronic GVHD predicts poor QOL, particularly in terms of physical well-being, while pre-transplant psychological distress predicts post-transplant psychological symptoms [34]. The difference in physical and psychological well-being between allogeneic and autologous transplant recipients is probably mediated by the effects of chronic GVHD [56].

There has been insufficient research on the adverse effects of clinically relevant anxiety and depressive symptoms on mortality and QOL following transplantation[18, 69]. Nevertheless, such research consistently shows the negative impacts of major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder and PTSD.

PSYCHIATRIC DISORDERS ASSOCIATED WITH HSCT

Life-threatening medical conditions and their treatments have been identified as stressors that precipitate the development of PTSD, especially in cancer populations; however, these can also promote post-traumatic psychological growth[7,70]. Several studies have reported a potentially positive impact of HSCT on psychosocial functioning and highlighted patients' interpersonal or spiritual post-traumatic growth. Patients are often able to reinterpret and transform the adversity of HSCT into a meaningful life narrative, despite their impaired QOL[7,9]. Overall, the literature reports a low to moderate prevalence of PTSD (3%-28%) in HSCT populations[1,2,41, 71,72]. Medical complications, pain, female sex, poor QOL and depression during hospitalization hinder social engagement and support, and avoidance-based coping predicts PTSD following HSCT[1,2,41,71].

Delirium is a frequent psychiatric syndrome in HSCT patients, with prevalence rates of approximately 35%-73% during hospitalization, primarily during the engraftment period[2,13]. In HSCT survivors, neurocognitive dysfunction affects attention, memory, mental processing, coordination and executive functioning[2,13]. Cognitive problems frequently accompany emotional disturbances and difficulties in physical functioning and management of HSCT-related symptoms, leading to poor QOL[73,74]. Sexual dysfunctions, including decreased libido, infertility, erectile and ejaculatory dysfunction, premature menopause and dyspareunia, are prevalent and persistent long-term consequences of HSCT[49,75-77]. Changes in body image, depressive and anxiety symptoms and chronic GVHD precipitate long-term sexual dysfunction and adversely affect QOL[1,77].

GVHD-RELATED PSYCHOSOCIAL COMPLAINTS

Despite prophylactic regimens, a significant number of recipients develop the acute (aGVHD) or chronic form of GVHD (cGVHD) following HSCT: aGVHD affects 30%-70% of recipients, while cGVHD occurs in 20%-70% of recipients[78,79]. cGVHD is a major complication in 40%-60% of patients after HSCT and is manifested in multiple organs, including the oral cavity, liver, lung, skin, and eyes[80]. Chronic GVHD is a frequent cause of long-term morbidity and non-relapse mortality, and affected patients have a significantly impaired QOL, compared with population norms and patients without GVHD symptoms[81,82].

The severity of cGVHD has an independent negative association with QOL[82-84]. Even mild cGVHD symptoms can decrease QOL to below population norms[83]. Similar to earlier findings[85,86], a recent large-scale study found that only currently active cGVHD impaired QOL, while resolved cGVHD had no impact on QOL after allo-HSCT[84]. Fluctuations in the severity of cGVHD symptoms reported by patients were significantly correlated with changes in their QOL ratings[87].

The results concerning the associations of age and sex with QOL in cGVHD patients are conflicting[82]. It is likely, however, that cGVHD has a major impact on the physical and functional domains of QOL. In a recent study of allogeneic transplant survivors, employment status was significantly associated with QOL, and this relationship was moderated by age and GVHD status[88]. Income and employment status were inversely associated with a higher symptom burden, but positively with physical and mental functioning, QOL and mortality in cGVHD patients[89]. Moreover, income independently predicted QOL[89], presumably because patients

with a higher SES have greater financial resources, resulting in better access to medication and supportive care.

Patients with cGVHD and high levels of depression and anxiety constitute a highly vulnerable population for poor functioning, impaired QOL and HCST-related mortality[90]. A recent prospective study that examined the associations between psychosocial factors and QOL in cGVHD patients found clinically significant depressive and anxiety symptoms in approximately one third of patients at different time points after HSCT[81]. The HSCT symptom burden predicted depression symptoms, a poorer functional status predicted anxiety symptoms, and both were associated with QOL. Coping was a mediating factor in this correlation: patients with dominantly negative emotion-oriented coping and less task-oriented and social diversion-oriented coping, who had higher symptom burden and worse physical functioning reported poorer QOL[81]. Therefore interventions to improve patients' coping skills may enhance QOL and reduce psychological distress.

PSYCHOSOCIAL INTERVENTIONS AND SUPPORT FOR HSCT PATIENTS

The extensive literature on psychosocial factors, especially depression and anxiety, at various stages of HSCT draws attention to the importance of psychological interventions. Surprisingly, however, only a few studies have tackled this topic even in recent years. The optimal approach consists of a thorough assessment of the patient's pre-HSCT psychosocial functioning, risk factors and current psychosocial situation, together with a brief screening of psychological symptoms and health-related QOL, to lay the foundation for targeted interventions and psychosocial support[12]. Screening and psychosocial support frequently involve family members and children. Psychological interventions before, during and after hospitalization comprise several treatment modalities such as relaxation and mindfulness training, communication techniques, psychoeducation and cognitive-behavioral therapy to enhance insight and strengthen coping skills[10,12,91] (see case vignette). For clinically significant anxiety and depressive symptoms, benzodiazepines and antidepressants are also recommended.

Education on HSCT is recommended for all recipients to improve their knowledge of medication side effects, risks and complications[92]. These educational interventions enhance patients and their families' knowledge about HSCT, reduce anxiety and depression and increase QOL[92]. In a recent qualitative study, patients expressed a desire for additional education about late complications and post-BMT QOL because they felt that complications were often unexpected, with profound negative effects on their QOL and recovery[93].

PSYCHOSOCIAL DIFFICULTIES AND SUPPORT FOR CAREGIVERS

Social support is a crucial factor in a transplant recipient's chance of survival[12]. Patients who receive effective instrumental and emotional support have better prospects of recovery from HSCT, while those beset with problematic social relationships, including critical, invalidating and pessimistic social environments, are less likely to survive[94].

The QOL of family members, also referred to as family caregivers in the literature, is clearly affected by the patient's condition and treatment. Both patients and family members experience very high levels of distress, anxiety, depression and poor QOL before hospitalization, and the patient's physical condition significantly affects their caregivers' well-being[95]. Hospitalization adversely affects caregivers' physical, emotional and role functioning, and increases the risk of depression[35]. Similar to patients, the long-term consequences of HSCT contribute to the development of caregivers' depression and poor QOL[96]. Further contributors to caregivers' poor post-HSCT QOL are female sex, a low education level, and patients' frequent relapses, immunosuppressive treatment and low QOL[97]. Depressive symptoms and sleep disorders appear to be more prevalent in caregivers than in the general population[12, 97]. SES factors such as family income may also influence caregivers' QOL and mood [96].

Despite growing interest in family caregivers' physical and psychological well-being, only a few recommendations for intervention and support for this vulnerable group have been made. The current trend is to manage caregivers' conditions independently of patient care[12]. Research exploring caregivers' pre-transplant

psychosocial functioning suggests that pre-transplant screening of distress creates an opportunity to identify at risk caregivers, decrease their distress and positively influence patients' outcomes[95]. A more detailed exploration of caregivers' experiences may be an appropriate way to conceive interventions targeted at the various stages of HSCT.

CASE VIGNETTE

John (not his real name), a 21-year-old man diagnosed with chronic granulomatous disease was treated with supportive psychotherapy for severe anxiety and depressive symptoms prior to allogeneic hematopoietic transplantation. Earlier John received steroid treatment that induced emotional turmoil and suicidal ideations leading to difficulties with social integration in high school. At that point, John also needed supportive psychotherapy. In this case, young age, history of psychiatric symptoms, IFN-gamma treatment, poor somatic status and low perceived control over physical condition were vulnerability factors for psychological symptoms. Before transplantation, John's psychopathological symptoms included insomnia, depressive mood, anhedonia, anergia, fear of death, and panic attacks. His psychiatric diagnosis was adjustment disorder. John's psychological difficulties before transplantation were described as ambivalent feelings concerning transplantation contrasting uncertainty and anticipatory anxiety and fear of death with hope to survive. Because of the severe somatic complaints and frequent hospital admissions, John had to interrupt his university studies and has become socially isolated. John also became dependent on his parents in most aspects of his daily life. Fortunately, his family provided him with appropriate practical and psychologically minded social support. Formal psychological treatment comprised relaxation and imaginative interventions to reduce anxiety and cognitive re-framing to maintain and enhance treatment adherence.

CONCLUSION

The current review synthesizes the main findings of the literature on QOL and psychosocial functioning in adult patients treated with HSCT and appraises the clinical significance of these psychosocial outcomes. Current research demonstrates that transplant recipients experience significant psychological distress, with elevated anxiety and depression and poor QOL, prior to HSCT. While anxiety tends to decrease gradually during the transplantation process, it can also become more intense and cross the diagnostic threshold for panic disorder, generalized anxiety disorder or PTSD. In a considerable proportion of patients, depression continuously increases during hospitalization and after HSCT, and may reach clinically significant levels in at-risk recipients. Anxiety and depressive symptoms interfere with treatment adherence and adversely affect patients' survival and perceptions of QOL after the transplant. Exploration of the trajectory of psychological symptoms over the course of HSCT has revealed important medical and socio-demographic risk factors that influence patients' psychological functioning at different time points associated with different stages of treatment.

The literature reviewed here indicates that patients with allo-HSCT experience greater impairment in QOL and differences in the trajectory of recovery, compared with patients undergoing either auto-HSCT or chemotherapy; however, some studies have reported opposite results[9]. This review also confirms the adverse impact of aGVHD and cGVHD on QOL, although the ongoing impact of resolved cGVHD remains uncertain. Although the literature on RIC conditioning is still limited, at present it does not appear to have a clear advantage over myeloablative conditioning or auto-HSCT.

There is compelling evidence that cGVHD predicts poor QOL, particularly in terms of physical well-being, while pre-transplant psychological distress predicts post-transplant psychological symptoms. Differences in physical and psychological well-being between allogeneic and autologous transplant recipients are probably mediated by the effects of chronic GVHD. Patients experiencing both cGVHD and elevated levels of depression and anxiety represent a highly vulnerable subpopulation for poor functioning and QOL and HSCT-related mortality.

Regarding interventions, most authors emphasize the need for a thorough evaluation of a patient's psychosocial history, psychological symptoms and health-related QOL to identify and implement targeted interventions and psychosocial

support. Although the efficacy of psychosocial interventions for improving QOL has been demonstrated, further exploration is warranted. Current research also underlines the importance of educational interventions to improve patients' knowledge about their condition, its treatment, and possible complications. Screening for psychological distress and the provision of education and support should involve family members, particularly caregivers, as they are also affected by their relatives' disease and its lengthy and complicated treatment.

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