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Psychological Considerations in Hematopoietic Stem Cell Transplantation

Hermioni L. Amonoo,

Brigham & Women's Hospital, Psychiatry; Dana-Farber Cancer Institute, Psychosocial Oncology and Palliative Care

Christina N. Massey,

Massachusetts General Hospital, Department of Psychiatry

Melanie E. Freedman,

Massachusetts General Hospital, Department of Psychiatry

Areej El-Jawahri,

Massachusetts General Hospital

Halyna L. Vitagliano,

Dana Farber Cancer Institute

William F. Pirl, and

Dana Farber Cancer Institute

Jeff C. Huffman

Massachusetts General Hospital, Department of Psychiatry; Harvard Medical School, Department of Psychiatry

Abstract

Background: In recent decades, advances in transplantation medicine and improved post-transplant care have enhanced morbidity and mortality outcomes from hematopoietic stem cell transplantations (HSCTs). However, patients undergoing HSCT report a high prevalence of psychological distress, which can negatively impact recovery, function, and health outcomes, including mortality and a higher risk of graft vs. host disease. Appropriate assessment and management of these psychological symptoms lead to better engagement with treatment and a variety of superior health outcomes. We therefore provide a narrative review of the prevalent psychological challenges that accompany HSCT and suggest management approaches to equip psychiatric consultants involved in the care of this patient population.

Methods: We have reviewed prior published work in PubMed, PsycInfo and Scopus electronic databases on the common psychological challenges in HSCT, their vulnerability factors, as well as practical interventions for managing these challenges.

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Results: We outline the phases of the HSCT hospitalization for clinicians who are not familiar with the process. We discuss common psychological challenges such as depression, delirium, and post-traumatic stress reactions, that accompany HSCT. We suggest an approach to a psychiatric consult during the HSCT hospitalization and discuss practical interventions for managing psychological challenges in this population.

Conclusions: Though pharmacological and behavioral interventions have been successfully used to treat psychosocial challenges in HSCT, further research is needed to understand the optimal psychiatric assessment tools, treatment strategies and the long-term psychiatric care needed to address psychiatric comorbidities in this growing patient population.

Keywords

Psychiatric Consult; Hematopoietic Stem Cell Transplant; Depression; Anxiety; Delirium; Posttraumatic Stress

Introduction

A growing number of patients have undergone hematopoietic stem cell transplants (HSCT) in recent decades with more than 50,000 HSCTs performed worldwide each year.¹ HSCT is usually reserved for patients with life threatening diseases to provide life prolonging or curative treatment.² Advances in transplantation medicine including improvement in supportive care and infection management, use of peripheral blood stem cells from unrelated or alternative donors, and improved post-transplant care have resulted in enhanced morbidity and mortality outcomes from HSCTs.^{3, 4}

Although most patients who undergo HSCT do not have psychiatric co-morbidity, a high prevalence of psychological distress [including depression symptoms (approx. 35%)⁵, delirium (approx. 35%)⁶ and PTSD symptoms (approx. 20%)⁷] is reported by these patients and observed by their clinicians.^{8–10} Psychological distress in HSCT patients is associated with worse health outcomes including increased mortality,¹¹ and higher risk of graft vs. host disease (GVHD).¹² Psychological stress-related factors potentially modulate cell engraftment and recovery following transplantation via the hypothalamic pituitary adrenal (HPA) and sympathetic nervous system (SNS) axes.¹² Hence, the implications of biobehavioral/psychological processes in the recovery following HSCT necessitates that psychological distress is assessed and addressed adequately during the HSCT process.

Historically, HSCT clinicians have perceived the physical and psychological burden associated with HSCT as expected and unmodifiable.¹³ However, a high level of emotional distress over sustained periods of time in HSCT patients may result in anxiety, depression or both.¹⁴ Adequate assessment and treatment of psychological symptoms during the HSCT recovery positively impact a patient's ability to engage and adhere fully with treatment, to better cope with the peaks and valleys of recovery and to have a better quality of life. The aim of this article is to provide a comprehensive narrative review of the common psychological challenges associated with the HSCT (from the preparation for the transplant to recovery) and to offer concrete recommendations and practical management strategies for consultation-liaison psychiatrists involved in the care of this growing patient population. The

HSCT process consists of different stages with somewhat distinct medical and psychological challenges. Hence, we first describe the stages of transplantation prior to the psychological challenges that are prevalent in this population.

Pre-Transplantation Psychological Considerations

Most patients are considered for HSCT after an extensive oncologic evaluation (which includes failed treatment modalities) by an HSCT oncologist. Transplanted stem cells can be from the patient themselves [autologous], or a donor [allogeneic] derived from bone marrow, peripheral blood or umbilical cord blood. The type of hematologic malignancies (including leukemias, lymphomas, myelodysplastic syndromes and myelomas) or benign hematologic conditions (e.g., aplastic anemia and bone marrow failure syndromes) determine the type of stem cells used in HSCT. In most HSCT centers, patients are required to undergo a psychiatric evaluation as part of the pre-transplant process. The pre-transplant psychiatric evaluation can serve as a good baseline for the patient's mental health and to prepare the patient for the HSCT admission.¹⁵ There is no standard mental health evaluation for this process and depending on an institution's resources, the pre-transplant mental health evaluation can be completed by psychiatrists, social workers or psychologists.

A detailed review of oncologic, medical, psychiatric and family psychiatric history provides insights into patients' risk for psychiatric disorders either in relation to or irrespective of HSCT status. Information from oncologists and primary care providers informs the medical and medication history. Some pertinent risk factors to assess include substance abuse history, neuropsychiatric limitations (e.g., memory problems) that could interfere with the required follow-up needed after HSCT and overall treatment compliance including medications. HSCT centers are not widespread and most patients travel a long distance from their supportive communities for an extended period of time to undergo treatment. Hence, a comprehensive evaluation of patients' expectations and social supports is imperative to understand potential psychosocial barriers to good coping.

Psychological risk factors rarely contribute to the decisions regarding HSCT eligibility and most HSCT centers will transplant the majority of eligible patients. However, all HSCT candidates should be screened (for common psychiatric symptoms in this population e.g., depressive symptoms, anxiety symptoms, PTSD symptoms and sleep problems) because of the negative impact of psychiatric disorders on recovery. In addition to identifying and communicating identified psychological risk factors to the primary HSCT team, it is especially important to proactively include recommendations for mitigating and managing these risk factors during the HSCT process and the recovery. For example, in a population at risk for worsening psychological distress during the HSCT process such as patients with pre-morbid depression, an antidepressant, supportive psychotherapy or social work evaluation prior to the transplant could help attenuate the potential negative impact of the depression during the HSCT hospitalization and recovery. Effective treatment of psychological challenges in the HSCT population results in improved outcomes.¹⁶

Phases of HSCT Hospitalization

The HSCT hospitalization consists of the conditioning regimen, the transplantation itself, the engraftment phase and the post-transplant phase. Below is a brief description of these transplantation phases.

Conditioning (Minus Days)

The HSCT process begins with a conditioning regimen which consists of chemotherapy and at times total body radiation. The conditioning regimen destroys patients' lymphocytes in preparation for the subsequent transplant which aims to restore immune function.¹⁷ Barring outpatient transplants,¹⁸ the conditioning regimen commences the inpatient admission for the HSCT, and the total duration is about six to eight days depending on the type of regimen (autologous vs. allogeneic). The conditioning days are sometimes referred to as the "minus days".

Transplantation (Day 0)

The second phase of the HSCT hospitalization is the stem cell infusion (commonly referred to as Day 0). Depending on response to the conditioning regimen, a small proportion of patients will go into the transplant with significant physical symptoms which impacts their level of psychological distress.

Engraftment (Plus Days)

The engraftment days, also referred to as the "plus days", follow the transplant. Transplanted stem cells start making new blood cells approximately 8–18 days or longer after the stem cell infusion depending on whether the transplanted cells are autologous vs. allogeneic. The combination of increased physical symptoms (e.g., nausea, anorexia, pain, diarrhea, fevers and hair loss) and other medical illnesses can result in significant psychological distress.

Post-transplant

The post-transplant period can be categorized into two separate phases [the acute post-transplant phase (the first 100 days) and the chronic post-transplant phase (>100 days and up to several years)] and the psychological distress associated with these phases could differ. The HSCT admission usually ends around day 14–20, and the routine follow-up care post HSCT until day 100 entails twice weekly outpatient visits for several weeks. The continued needed isolation (where patients are restricted from contact with large numbers of people or areas with crowds including restaurants) for the recovery continues into the first 100 days of the recovery.

Patients who usually maintain an active lifestyle at baseline report a significant amount of emotional distress during this phase of the recovery as they cannot engage in vigorous or outdoor activities that were previously considered meaningful or contributed positively to quality of life.¹⁹ Patients (especially allogeneic recipients) who also have a high burden of physical complications including severe GVHD or re-admissions to the hospital also report a higher level of emotional distress compared to patients (especially autologous recipients) who have uneventful recoveries.¹²

Common Psychiatric Manifestations in HSCT

A variety of psychological challenges are observed in HSCT patients at different stages of the transplantation process. In this section, we discuss the common psychological challenges that accompany the HSCT and delineate where normal psychological reactions transition to psychiatric disorders.

Anxiety

Although HSCT patients have multiple reasons to be anxious and different stages of the transplantation process are accompanied by unique themes of anxiety, anxiety is known to be heightened in the minus days as patients eagerly anticipate the transplantation itself.²⁰ Some patients worry about their response to the transplant, their quality of life in recovery while in isolation, and their ability to manage potential complications in recovery especially if they are far away from home and social support. Specific examples of anxiety themed thought distortions or schemas that are prevalent with HSCT patients are, a) “my donor was not a perfect (10/10) match so my leukemia would relapse” or b) “my toddler is going to forget who I am because I am going to be in the hospital for 30 or more days”. Potential responses to these thought distortions would be: a) validate the patient’s concern and then work with the HSCT clinician to educate the patient about outcomes with donors who are not perfect matches and b) explore with the patient how to stay engaged with children using technology like facetime during the potentially long HSCT hospitalization. The Lymphoma and Leukemia Society²¹ provides patients and caregivers general information about the HSCT process in preparation for the transplant. However, we are aware of no evidence-based patient materials about the HSCT admission that aims at reducing anticipatory anxiety for the transplant. There is increasing evidence to support the positive impact of communication skills training for oncologists. However, we are not aware of any oncology communication skills programs that specifically address the impact of HSCT clinician communication on patients’ anticipatory anxiety.^{22, 23} Anxiety may not necessarily meet criteria for an anxiety disorder. However, in a subset of patients, the nervousness, apprehension and worry is so excessive that it jeopardizes their ability to engage fully with treatment and the subsequent routine follow-up care.¹² For most patients, the potential etiologies of anxiety include a pre-morbid generalized anxiety disorder, specific phobia, panic disorder, adjustment disorder with anxiety, delirium and existential distress.

Post-Traumatic Stress Reactions

Historically, medical events and treatments have not been considered as traumatic events that precipitate post-traumatic stress disorder (PTSD). However, life threatening medical conditions and their treatment especially in the cancer population, have been identified as stressors that can precipitate PTSD.²⁴ The prevalence rate of PTSD in the HSCT population is 20%.²⁵ In addition to the fear of cancer recurrence as in most cancer patients, the HSCT hospitalization and acute recovery, which is unlike other cancer treatments, has been considered a traumatic event that can result in PTSD.⁸ HSCT patients can relive cancer and treatment experience with nightmares, flashbacks, or continuous thoughts about the HSCT process. These PTSD symptoms are not age dependent and can be similar to that of patients who do not have a cancer diagnosis.²⁶ In a prospective study that sought to understand the

predictors of worsening quality of life and PTSD symptoms, El-Jawahri and colleagues found that 28.4% of patients met criteria for PTSD and depression at 6 months post-HSCT.⁸ In addition, the study also found that a decline in quality of life and an increase in depressive symptoms during the HSCT hospitalization were important predictors of PTSD symptoms.

Sleep Disruption

Sleep disturbances are common among HSCT patients with more than 50% reporting sleep disruption before the transplant, up to 82% experiencing moderate to severe sleep disruption during the transplant hospitalization, and 43% post-transplant.²⁷ Different chemotherapy regimens as well as glucocorticoid treatment have also been associated with sleep disruption.²⁸ Specifically among HSCT patients, conditioning chemotherapeutic and alkylating antineoplastic agents such as busulfan and cyclophosphamide increase the risk of insomnia in patients.²⁹ Although obstructive sleep apnea (OSA) is a common sleep disorder among HSCT patients, most have not been officially diagnosed with the disease to receive adequate management.²⁷

Depression

Depression is relatively prevalent (35%) at all stages of the transplantation process and can interfere with recovery from the transplant.^{5, 30} In a prospective study of patients who received either autogeneic or allogeneic transplants at the Brigham and Women's Hospital or Dana-Farber Cancer Institute, 35% satisfied the criteria for depression, and depressed patients had a threefold greater risk of dying than non-depressed patients between 6 and 23 months after HSCT when other prognostic factors were adjusted for.⁵ As in most medical populations, depression in HSCT patients can be difficult to assess due to the potential increased burden of physical symptoms such as insomnia and poor appetite that may naturally accompany the HSCT recovery. Additionally, anhedonia can be difficult to assess in HSCT patients because the HSCT hospitalization and the acute recovery restrictions preclude patients from participating in activities they may typically enjoy. Depression observed in HSCT may also develop years after the transplant with the prevalence increasing until 5 years post-transplant.²⁰ Predictive factors for depression include a prior history of depression and medical comorbidities associated with the cancer and HSCT.^{31, 32} The differential diagnosis for depressive symptoms can be quite broad and includes major depressive disorder, adjustment disorder with depressed mood, persistent depressive disorder (dysthymia), demoralization, bipolar disorder and delirium. The evidence for depression screening or depression diagnostic tools specifically for the HSCT patient population are lacking although routine depression screening tools such as the Patient Health Questionnaire (PHQ-9) has been clinically useful.³³

Delirium

With an incidence range of 18–85%, delirium is the most common neuropsychiatric disorder in cancer patients.³⁴ The prevalence of delirium in HSCT is about 35% with the highest frequency two weeks following the HSCT in the engraftment and recovery days.^{7, 26, 35} As in most cancer patients, delirium is often unrecognized and undertreated in the HSCT population.²⁶ Pre-transplant risk factors for delirium in the HSCT population include lower cognitive function, evidence of renal dysfunction, decreased oxygen saturation level, lower

functioning, decreased white blood cell count (and its associated increased risk for rare infections), decreased hemoglobin, decreased platelet count and higher magnesium.^{36, 37} Interestingly, unlike other cancer patients, disease severity, functional status and age have not been reliable predictors of delirium in the HSCT population due to an overall healthy baseline for majority of patients who get transplanted.²⁶ For a given patient, the etiology of delirium is multifold. Common causes of delirium in HSCT patients include medications (e.g., steroids, analgesics, chemotherapy), infection, metabolic derangements, neutropenia, pancytopenia, and long hospitalizations. Delirium can often be accompanied by various psychiatric symptoms including depression, anxiety and psychosis. Additionally, patients with delirium during an allogeneic HSCT are significantly more likely to have persistent anxiety, fatigue and distress 80 days post transplantation with some psychological symptoms persisting for up to a year post HSCT.^{38, 39} Critical to managing the neuropsychiatric symptoms of delirium is treating the underlying medical condition that is usually driving the symptom presentation- for HSCT patients, the underlying medical condition could vary significantly depending on the type of transplant and its associated complications in the acute recovery period.

Neurocognitive Dysfunction other than Delirium

Neurocognitive dysfunction in HSCT survivors is a major cause of morbidity and mortality and its prevalence is up to 60% 22–82 months post-HSCT.⁴⁰ Cognitive deficits in the HSCT population span several cognitive domains including attention, memory, mental processing speed, coordination, and executive functioning.^{41, 42} HSCT patients who report cognitive problems are more likely to report difficulties with emotional and physical functioning as well as difficulty managing HSCT-related symptoms.⁴³ Risk factors for neurocognitive dysfunction include conditioning chemotherapeutic regimens that cross the blood brain barrier (e.g., busulfan, cytarabine arabinoside, fludarabine) and total body radiation, immunosuppressive therapy (e.g., steroids, tacrolimus) for GVHD, central nervous system infections and primary CNS disorders.⁴⁰ Neurocognitive dysfunction not only impacts function and quality of life but also psychological and social well-being of patients.⁴⁴ Although studies on preventative measures of neurocognitive dysfunction other than delirium in the HSCT population is limited, addressing sleep difficulties, depressive symptoms and fatigue may assist with improving cognitive functioning.⁴⁵

Adjustment reactions

The isolation and adjustment to a variety of restrictions (including a neutropenic transplant diet, social isolation or avoidance of large crowds) adds to the emotional challenge of the engraftment days. It is difficult to define what a “normal adjustment” to the HSCT is as this varies significantly among patients and can be dependent on many factors such as a person’s coping style and associated defense mechanisms. Coping mechanisms can be both helpful and/or maladaptive to patients and can impact how they manage their illness or the HSCT.⁴⁶ Planning, acceptance, humor and positive framing are active forms of coping, which can alter how one perceives stress. Avoidance, behavioral disengagement, or venting are less active ways of coping. Evidence suggests that an avoidant coping style, or methods of coping in which individuals do not actively try to gain mastery or control over potentially distressing or stressful events, is more likely to lead to increased emotional distress in HSCT

patients.^{47, 48} Difficulty coping can result in an adjustment disorder. A psychiatric assessment during the engraftment days may provide useful insights in delineating between a normal emotional response to the stressors associated with the transplant versus nascent psychiatric disorders that will benefit from aggressive treatment and management.

Demoralization

Although demoralization can be observed in HSCT patients at any stage of the treatment, the engraftment days are especially prone to demoralization due to length of isolation and hospitalization as well as increased prevalence of medical comorbidity.⁴⁹ Demoralized patients feel disempowered and helpless. However, demoralization differs from depression in that it lacks the persistent low mood seen in depression, normal fluctuations in mood are still preserved and the resolution of the adverse situation rapidly restores the capacity to feel enjoyment and hope.⁵⁰ For cancer patients with a long course of treatment and recovery such as in HSCT, demoralization can be persistent at any stage of the HSCT process and difficult to distinguish from other mood disorders.⁵¹

Psychiatric Consult during the HSCT Admission

The primary goal of new psychiatric consultations during the HSCT hospitalization is to determine whether observed or reported psychiatric symptoms represent normal reactions to a life-threatening illness, a new or recurrent psychiatric disorder, or a manifestation or side effect of the treatment.⁵² Assessing for psychiatric symptoms and disorders in HSCT patients, like most medical populations, can be challenging and complicated as the physical symptoms that manifest in various psychiatric disorders (e.g., fatigue and poor appetite in major depressive disorder) may result from the HSCT process or the complications that ensue from the HSCT itself. Hence, familiarity and expertise with both psychiatric disease management and the HSCT process is essential. Table 1 outlines our suggested considerations for an inpatient psychiatric consult for HSCT patients.

Vulnerability Factors for Psychological Challenges

Patient, disease and medication factors make an HSCT patient vulnerable for psychiatric comorbidities during the transplant process.

Patient Factors:

Older patients are more predisposed to certain psychiatric conditions such as delirium compared to younger patients.⁵⁴ Historically, women have a greater predisposition to certain mood disorders such as depression and anxiety.⁵⁵ A history of mental health problems results in a greater risk of developing psychiatric comorbidities.³⁵ Poorer pre-transplantation executive functioning is associated with higher delirium severity and neurocognitive dysfunction.⁵⁶ Social support plays a significant role in various health outcomes such as quality of life and functioning for HSCT patients.¹¹ Financial problems, lower educational levels and overall lower socio-economic status results in a greater predisposition to emotional problems.³⁵

Disease Factors:

A more aggressive cancer diagnosis (based on biological and genetic markers) and lack of responsivity to treatment yields a higher risk for psychological distress (especially anxiety) and psychiatric comorbidities.⁵⁷ A higher burden of medical comorbidities bears a higher level of emotional distress.^{31, 58} Rehospitalization after the transplant increases the risk of psychological issues as well.³²

Medication and Treatment Factors:

HSCT chemotherapeutic regimens cause a variety of side effects which contribute to the burden of physical symptoms. Hence both directly (as in the case of alkylating agents like cyclophosphamide) and indirectly, chemotherapeutic agents can impact the level of psychological distress and comorbidities in patients.⁵⁹ Whole brain radiation as part of their conditioning regimen also predisposes to a variety of neurocognitive and behavioral issues.⁴⁴ Medications such as steroids can also cause a wide variety of psychiatric syndromes including mood, anxiety, psychotic disorders as well as delirium.³⁵ Notably, the type of transplant (allogeneic vs. autologous) matters significantly and impacts the risk for psychological distress and psychiatric morbidity in HSCT patients. Specifically, the recovery and the risk of psychiatric comorbidity following an autologous and allogeneic transplant, especially during the survivorship phase, are very different as allogeneic recipients are at much higher risk for long-term psychological distress.

Practical Interventions for managing psychiatric disorders in HSCT

Both pharmacological and non-pharmacological interventions can be used to manage psychiatric disorders co-morbid with the HSCT process.

Psychopharmacological Interventions

Pharmacotherapy is commonly used to treat psychiatric symptoms in HSCT patients although the evidence and research has trailed behind clinical practice. Several classes of psychopharmacologic agents (including antidepressants, antipsychotics and anxiolytics) have been used with good efficacy.³⁴ A thoughtful consideration of drug-drug reactions, somatic symptom and adverse effect profiles (especially those pertaining to the bone marrow environment), and medical comorbidities is necessary for the selection of a pharmacological agent.³⁵ A comprehensive discussion of all the drug-drug interactions between psychopharmacological agents and the broad range of medications (e.g., antibiotics, immunosuppressants, chemotherapeutic regimens) used by HSCT patients is important but beyond the scope of this review.

Antidepressants from various classes such as selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) can effectively manage depression and anxiety symptoms. However, SSRIs and SNRIs can reduce platelet serotonin resulting in platelet dysfunction and increased risk of bruising and bleeding especially for HSCT patients.⁶⁰ Fluoxetine, paroxetine and sertraline should be used cautiously as they have the highest degree of serotonin reuptake inhibition and are more frequently associated with bleeding problems.⁶¹ Mirtazapine, an atypical antidepressant used primarily for the

treatment of depression can be especially useful in managing mood and anxiety symptoms in HSCT because of its additional anxiolytic, sedative, antiemetic and appetite stimulation properties. However, on rare occasions, mirtazapine can cause neutropenia and agranulocytosis.^{62, 63} Although antidepressants are the gold standard for managing anxiety symptoms, benzodiazepines can be used to manage acute or intermittent anxiety that may arise at different stages of the transplant process. Benzodiazepines rarely cause agranulocytosis but clonazepam and diazepam have been reported to cause thrombocytopenia, anemia and leukopenia.⁶⁴

Antipsychotic medications effectively manage the neuropsychiatric and behavioral issues that accompany delirium. Antipsychotics also have anxiolytic (e.g., quetiapine, olanzapine, haloperidol), antiemetic (e.g., olanzapine), appetite stimulation (e.g., olanzapine) and sedative properties in medical populations. However, several antipsychotic medications including olanzapine, clozapine, chlorpromazine, and haloperidol are associated with agranulocytosis and neutropenia.^{64–66}

Mood stabilizers and anti-epileptics (e.g., valproic acid and carbamazepine) used for patients with comorbid psychiatric disorders such as bipolar disorder can result in thrombocytopenia and neutropenia. Lithium, a standard mood stabilizer for bipolar depression, induces leukocytosis and thrombocytopenia. Valproic acid is also commonly used to manage agitation in patients with delirium whose medical problems prohibit the use of antipsychotic medications.⁶⁷

Non-Pharmacological Interventions

Behavioral interventions can successfully address psychological distress in HSCT patients although there are limited to no randomized controlled trials testing the efficacy of these interventions in this population.

Cognitive behavioral therapy (CBT) methods entail psychoeducation regarding how maladaptive thoughts, emotions, and behaviors can serve to maintain distress, approaches to identifying and changing distorted thinking, and learning more effective coping skills to manage the stressors associated with the treatment and recovery.⁶⁸ Forms of CBT are thought to be among the most efficacious psychotherapeutic treatments for a variety of different psychiatric syndromes.⁶⁹ Various subtypes (e.g., a telephone administered CBT therapy to reduce treatment related PTSD symptoms)⁷⁰ of CBT that have been used with HSCT patients include coping skills interventions targeted primarily at learning more effective ways to cope with emotional distress. Stress management with relaxation, a two-pronged program that is geared towards increasing awareness of triggers for stress while also teaching behavioral relaxation methods that help to slow heart rate, breathing rate, and decrease muscle tension have also been used. Relaxation and mindfulness-based⁷¹ interventions can also be used as a stand-alone treatment and is also sometimes combined with psychoeducation and other general lifestyle interventions (e.g., exercise programs).

Psychological interventions that provide the platform for patients to share their HSCT experience and stories can also reduce emotional and psychological distress.⁶⁸ For example, Rini and colleagues found that in 30 HSCT survivors who participated in a psychological

intervention where patients shared their experiences of the HSCT with their peers, patient stories made peers feel more prepared for the treatment and decision making, reduced fear and uncertainty, and fostered hope.⁷² Importantly, such interventions are not practical during the HSCT hospitalization as patients are in isolation from other patients.

Palliative care interventions benefit HSCT patients in myriad ways beyond management of physical symptoms. Palliative care interventions facilitate the discussion of end of life care preferences of patients with the overarching goal of maintaining the wellbeing of patients irrespective of goals of care or intended outcomes.⁷³ Recent studies of palliative care interventions on psychological challenges in HSCT have been very promising. For example, El-Jawahri and colleagues studied the impact of an inpatient palliative care intervention on patient's quality of life and outcomes and found that an integrated palliative care service with the HSCT admission resulted in improvements in depression and PTSD symptoms at 6-months post-transplant.⁸

Spirituality is a multidimensional construct that embodies both existential and religious faith practices via individuals' expression of meaning and connectedness to self, others or sacred things.⁷⁴ Spirituality has been historically associated with improved adjustment and functioning in a variety of cancer patients.⁷⁵ Specifically for HSCT, Wingard and colleagues found that in long-term survivors of HSCT, greater spiritual well-being was associated with better mental health.⁷⁶ Harris et al also found that in HSCT patients with chronic GVHD, patients who reported the lowest spiritual well-being reported worse physical, emotional, social and functional well-being.⁷⁷ Some HSCT centers such as the Dana-Farber Cancer Institute have the spiritual care resources for patients to have their stem cells "blessed" at the time of the stem cell infusion. At the Dana-Farber Cancer Institute, more than half of the allogeneic and autogeneic transplant patients agree to stem cell blessings-anecdotally, patients have reported this to reduce anxiety and promote hope and comfort during the transplantation.⁷⁸ Despite the mixed and limited evidence on the impact of religion and spirituality on psychological well-being of patients, spiritual care services, when available to some HSCT patients, may be beneficial in managing psychological distress.

Conclusion

Although in recent years HSCT has become a life-saving treatment for some patients with hematologic malignancies, there is a high prevalence of psychological distress and psychiatric comorbidities which impact quality of life, function and recovery. A diverse range of psychological challenges have been observed at different stages of the transplant process. Consultation liaison (C-L) psychiatrists are uniquely positioned to work with both oncological and HSCT clinicians in the management of psychiatric issues in the HSCT population. A comprehensive diagnostic approach that uncovers both physical and psychological symptoms with a nuanced understanding of how hematologic malignancies and the HSCT process naturally impact these symptoms is essential to inform psychiatric diagnosis and treatment strategies. Early identification of patient vulnerabilities to psychiatric comorbidities can also facilitate timely diagnostic assessment and treatment. Both pharmacological and behavioral interventions have been successfully used to treat psychosocial issues in HSCT although research and the evidence has trailed behind clinical

practice. Considering the complex nature of HSCT and the intensive prolonged recovery, further research is needed to understand the optimal psychiatric assessment tools, and treatment strategies needed to address psychiatric comorbidities in this growing and important population.

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References

1. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. *Bone Marrow Transplantation*. 2016;51:786. [PubMed: 26901709]
2. Wildes TM, Stirewalt DL, Medeiros B, Hurria A. Hematopoietic stem cell transplantation for hematologic malignancies in older adults: geriatric principles in the transplant clinic. *J Natl Compr Canc Netw*. 2014;12(1):128–36. [PubMed: 24453296]
3. Gratwohl A, Baldomero H, Passweg J, et al. Hematopoietic stem cell transplantation for hematological malignancies in Europe. *Leukemia*. 2003;17(5):941–59. [PubMed: 12750709]
4. Patel SA, Rameshwar P. Stem Cell Transplantation for Hematological Malignancies: Prospects for Personalized Medicine and Co-therapy with Mesenchymal Stem Cells. *Curr Pharmacogenomics Person Med*. 2011;9(3):229–39. [PubMed: 21892378]
5. Loberiza FR Jr., Rizzo JD, Bredeson CN, et al. Association of depressive syndrome and early deaths among patients after stem-cell transplantation for malignant diseases. *J Clin Oncol*. 2002;20(8):2118–26. [PubMed: 11956273]
6. Prieto JM, Atala J, Blanch J, et al. Patient-rated emotional and physical functioning among hematologic cancer patients during hospitalization for stem-cell transplantation. *Bone Marrow Transplant*. 2005;35(3):307–14. [PubMed: 15580279]
7. Bubalo J Managing the Mental Distress of the Hematopoietic Stem Cell Transplant (HSCT) Patient: a Focus on Delirium. *Curr Hematol Malig Rep*. 2018;13(2):109–13. [PubMed: 29404834]
8. El-Jawahri A, LeBlanc T, VanDusen H, et al. Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA*. 2016;316(20):2094–103. [PubMed: 27893130]
9. McQuellon RP, Russell GB, Rambo TD, et al. Quality of life and psychological distress of bone marrow transplant recipients: the ‘time trajectory’ to recovery over the first year. *Bone Marrow Transplant*. 1998;21(5):477–86. [PubMed: 9535040]
10. El-Jawahri AR, Traeger LN, Kuzmuk K, et al. Quality of life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. *Cancer*. 2015;121(6):951–9. [PubMed: 25469752]
11. Ehrlich KB, Miller GE, Scheide T, et al. Pre-transplant emotional support is associated with longer survival after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplantation*. 2016;51:1594. [PubMed: 27427918]
12. Costanzo ES, Juckett MB, Coe CL. Biobehavioral influences on recovery following hematopoietic stem cell transplantation. *Brain Behav Immun*. 2013;30 Suppl:S68–74. [PubMed: 22820408]
13. Lee SJ, Joffe S, Kim HT, et al. Physicians’ attitudes about quality-of-life issues in hematopoietic stem cell transplantation. *Blood*. 2004;104(7):2194–200. [PubMed: 15198954]
14. Smith HR. Depression in cancer patients: Pathogenesis, implications and treatment (Review). *Oncol Lett*. 2015;9(4):1509–14. [PubMed: 25788991]

15. Yalvac HD, Kotan Z, Tekgunduz E, Caykoylu A, Altuntas F. Could psychiatric assessment before hematopoietic stem cell transplantation predict the need for psychiatric consultation during transplantation period? *Transfus Apher Sci.* 2016;54(1):85–90. [PubMed: 26825282]
16. Amonoo HL, Barclay ME, El-Jawahri A, et al. Positive Psychological Constructs and Health Outcomes in Hematopoietic Stem Cell Transplantation Patients: A Systematic Review. *Biol Blood Marrow Transplant.* 2019;25(1):e5–e16. [PubMed: 30308327]
17. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. *Psychooncology.* 2009;18(2):113–27. [PubMed: 18677717]
18. Graff TM, Singavi AK, Schmidt W, et al. Safety of outpatient autologous hematopoietic cell transplantation for multiple myeloma and lymphoma. *Bone Marrow Transplant.* 2015;50(7):947–53. [PubMed: 25867651]
19. Hacker ED, Larson J, Kujath A, et al. Strength training following hematopoietic stem cell transplantation. *Cancer Nurs.* 2011;34(3):238–49. [PubMed: 21116175]
20. Kuba K, Esser P, Mehnert A, et al. Depression and anxiety following hematopoietic stem cell transplantation: a prospective population-based study in Germany. *Bone Marrow Transplant.* 2017;52(12):1651–7. [PubMed: 28892083]
21. Stem Cell Transplantation: Leukemia and Lymphoma Society; 2019 Available from: <https://www.lls.org/treatment/types-of-treatment/stem-cell-transplantation>.
22. Stovall MC. Oncology Communication Skills Training: Bringing Science to the Art of Delivering Bad News. *J Adv Pract Oncol.* 2015;6(2):162–6. [PubMed: 26649249]
23. Fallowfield L, Jenkins V. Current concepts of communication skills training in oncology. *Recent Results Cancer Res.* 2006;168:105–12. [PubMed: 17073196]
24. French-Rosas LN, Moye J, Naik AD. Improving the recognition and treatment of cancer-related posttraumatic stress disorder. *J Psychiatr Pract.* 2011;17(4):270–6. [PubMed: 21775828]
25. Hefner J, Kapp M, Drebing K, et al. High prevalence of distress in patients after allogeneic hematopoietic SCT: fear of progression is associated with a younger age. *Bone Marrow Transplant.* 2014;49(4):581–4. [PubMed: 24442247]
26. Weckmann MT, Gingrich R, Mills JA, Hook L, Beglinger LJ. Risk factors for delirium in patients undergoing hematopoietic stem cell transplantation. *Ann Clin Psychiatry.* 2012;24(3):204–14. [PubMed: 22860240]
27. Jim HSL, Evans B, Jeong JM, et al. Sleep Disruption in Hematopoietic Cell Transplantation Recipients: Prevalence, Severity, and Clinical Management. *Biology of Blood and Marrow Transplantation.* 2014;20(10):1465–84. [PubMed: 24747335]
28. Hjorth M, Hjertner O, Knudsen LM, et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. *Eur J Haematol.* 2012;88(6):485–96. [PubMed: 22404182]
29. Faulhaber GA, Furlanetto TW, Astigarraga CC, et al. Association of busulfan and cyclophosphamide conditioning with sleep disorders after hematopoietic stem cell transplantation. *Acta Haematol.* 2010;124(2):125–8. [PubMed: 20861613]
30. El-Jawahri A, Chen YB, Brazauskas R, et al. Impact of pre-transplant depression on outcomes of allogeneic and autologous hematopoietic stem cell transplantation. *Cancer.* 2017;123(10):1828–38. [PubMed: 28102896]
31. Kenzik K, Huang IC, Rizzo JD, Shenkman E, Wingard J. Relationships among symptoms, psychosocial factors, and health-related quality of life in hematopoietic stem cell transplant survivors. *Support Care Cancer.* 2015;23(3):797–807. [PubMed: 25193598]
32. Prieto JM, Blanch J, Atala J, et al. Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol.* 2002;20(7):1907–17. [PubMed: 11919251]
33. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–13. [PubMed: 11556941]
34. Fann JR. Neurological effects of psychopharmacological agents. *Seminars in clinical neuropsychiatry.* 2002;7(3):196–205. [PubMed: 12111674]

35. Rueda-Lara M, Lopez-Patton MR. Psychiatric and psychosocial challenges in patients undergoing haematopoietic stem cell transplants. *Int Rev Psychiatry*. 2014;26(1):74–86. [PubMed: 24716502]
36. Fann JR, Roth-Roemer S, Burington BE, Katon WJ, Syrjala KL. Delirium in patients undergoing hematopoietic stem cell transplantation. *Cancer*. 2002;95(9):1971–81. [PubMed: 12404292]
37. Beglinger LJ, Duff K, Van Der Heiden S, et al. Incidence of delirium and associated mortality in hematopoietic stem cell transplantation patients. *Biol Blood Marrow Transplant*. 2006;12(9):928–35. [PubMed: 16920558]
38. Fann JR, Alfano CM, Roth-Roemer S, Katon WJ, Syrjala KL. Impact of delirium on cognition, distress, and health-related quality of life after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2007;25(10):1223–31. [PubMed: 17401011]
39. Basinski JR, Alfano CM, Katon WJ, Syrjala KL, Fann JR. Impact of delirium on distress, health-related quality of life, and cognition 6 months and 1 year after hematopoietic cell transplant. *Biol Blood Marrow Transplant*. 2010;16(6):824–31. [PubMed: 20100587]
40. Buchbinder D, Kelly DL, Duarte RF, et al. Neurocognitive dysfunction in hematopoietic cell transplant recipients: expert review from the late effects and Quality of Life Working Committee of the CIBMTR and complications and Quality of Life Working Party of the EBMT. *Bone Marrow Transplant*. 2018;53(5):535–55. [PubMed: 29343837]
41. Syrjala KL, Dikmen S, Langer SL, Roth-Roemer S, Abrams JR. Neuropsychologic changes from before transplantation to 1 year in patients receiving myeloablative allogeneic hematopoietic cell transplant. *Blood*. 2004;104(10):3386–92. [PubMed: 15251983]
42. Booth-Jones M, Jacobsen PB, Ransom S, Soety E. Characteristics and correlates of cognitive functioning following bone marrow transplantation. *Bone Marrow Transplant*. 2005;36(8):695–702. [PubMed: 16086044]
43. Wu LM, Austin J, Hamilton JG, et al. Self-efficacy beliefs mediate the relationship between subjective cognitive functioning and physical and mental well-being after hematopoietic stem cell transplant. *Psychooncology*. 2012;21(11):1175–84. [PubMed: 21739524]
44. Harder H, Cornelissen JJ, Van Gool AR, et al. Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. *Cancer*. 2002;95(1):183–92. [PubMed: 12115332]
45. Ghazikhanian SE, Dorfman CS, Somers TJ, et al. Cognitive problems following hematopoietic stem cell transplant: relationships with sleep, depression and fatigue. *Bone Marrow Transplant*. 2017;52(2):279–84. [PubMed: 27941775]
46. Walshe C, Roberts D, Appleton L, et al. Coping Well with Advanced Cancer: A Serial Qualitative Interview Study with Patients and Family Carers. *PLoS One*. 2017;12(1):e0169071. [PubMed: 28107352]
47. Fife BL, Monahan PO, Abonour R, Wood LL, Stump TE. Adaptation of family caregivers during the acute phase of adult BMT. *Bone Marrow Transplant*. 2009;43(12):959–66. [PubMed: 19104493]
48. Weisman AD, Sobel HJ. Coping with cancer through self-instruction: a hypothesis. *J Human Stress*. 1979;5(1):3–8.
49. Lahijani S Mental Health Prior to Hematopoietic Cell Transplantation In: Sher Y, Maldonado JR, editors. *Psychosocial Care of End-Stage Organ Disease and Transplant Patients*. Cham, Switzerland: Springer International Publishing; 2019 p. 401–11.
50. Jacobsen JC, Maytal G, Stern TA. Demoralization in medical practice. *Prim Care Companion J Clin Psychiatry*. 2007;9(2):139–43. [PubMed: 17607336]
51. Vehling S, Kissane DW, Lo C, et al. The association of demoralization with mental disorders and suicidal ideation in patients with cancer. *Cancer*. 2017;123(17):3394–401. [PubMed: 28472548]
52. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics*. 2012;53(2):103–15. [PubMed: 22424158]
53. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*. 2005;53(4):695–9. [PubMed: 15817019]

54. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5(4):210–20. [PubMed: 19347026]
55. Seney ML, Sibille E. Sex differences in mood disorders: perspectives from humans and rodent models. *Biol Sex Differ*. 2014;5(1):17. [PubMed: 25520774]
56. Fann JR, Hubbard RA, Alfano CM, et al. Pre- and post-transplantation risk factors for delirium onset and severity in patients undergoing hematopoietic stem-cell transplantation. *J Clin Oncol*. 2011;29(7):895–901. [PubMed: 21263081]
57. Kohler N, Mehnert A, Gotze H. Psychological distress, chronic conditions and quality of life in elderly hematologic cancer patients: study protocol of a prospective study. *BMC Cancer*. 2017;17(1):700. [PubMed: 29070033]
58. Sherman AC, Simonton S, Latif U, Spohn R, Tricot G. Psychosocial adjustment and quality of life among multiple myeloma patients undergoing evaluation for autologous stem cell transplantation. *Bone Marrow Transplant*. 2004;33(9):955–62. [PubMed: 15034542]
59. Nerenz DR, Leventhal H, Love RR. Factors contributing to emotional distress during cancer chemotherapy. *Cancer*. 1982;50(5):1020–7. [PubMed: 7093922]
60. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging*. 2011;28(5):345–67. [PubMed: 21542658]
61. Halperin D, Reber G. Influence of antidepressants on hemostasis. *Dialogues Clin Neurosci*. 2007;9(1):47–59. [PubMed: 17506225]
62. Hartmann PM. Mirtazapine: a newer antidepressant. *Am Fam Physician*. 1999;59(1):159–61. [PubMed: 9917581]
63. Ahmed A. Neutropenia associated with mirtazapine use: is a drop in the neutrophil count in a symptomatic older adults a cause for concern? *Journal of the American Geriatrics Society*. 2002;50(8):1461–3.
64. Oyesanmi O, Kunkel EJ, Monti DA, Field HL. Hematologic side effects of psychotropics. *Psychosomatics*. 1999;40(5):414–21. [PubMed: 10479946]
65. Pick AM, Nystrom KK. Nonchemotherapy drug-induced neutropenia and agranulocytosis: could medications be the culprit? *J Pharm Pract*. 2014;27(5):447–52. [PubMed: 25124379]
66. Pirmohamed M, Park K. Mechanism of clozapine-induced agranulocytosis : current status of research and implications for drug development. *CNS Drugs*. 1997;7(2):139–58. [PubMed: 23338132]
67. Sher Y, Miller Cramer AC, Ament A, Lolak S, Maldonado JR. Valproic Acid for Treatment of Hyperactive or Mixed Delirium: Rationale and Literature Review. *Psychosomatics*. 2015;56(6):615–25. [PubMed: 26674479]
68. Baliouis M, Rennoldson M, Snowden JA. Psychological interventions for distress in adults undergoing haematopoietic stem cell transplantation: a systematic review with meta-analysis. *Psychooncology*. 2016;25(4):400–11. [PubMed: 26249330]
69. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res*. 2012;36(5):427–40.
70. DuHamel KN, Mosher CE, Winkel G, et al. Randomized clinical trial of telephone-administered cognitive-behavioral therapy to reduce post-traumatic stress disorder and distress symptoms after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2010;28(23):3754–61. [PubMed: 20625129]
71. Grossman P, Zvahlen D, Halter JP, et al. A mindfulness-based program for improving quality of life among hematopoietic stem cell transplantation survivors: feasibility and preliminary findings. *Support Care Cancer*. 2015;23(4):1105–12. [PubMed: 25297466]
72. Rini C, Lawsin C, Austin J, et al. Peer mentoring and survivors' stories for cancer patients: positive effects and some cautionary notes. *J Clin Oncol*. 2007;25(1):163–6. [PubMed: 17194913]
73. Levine DR, Baker JN, Wolfe J, Lehmann LE, Ullrich C. Strange Bedfellows No More: How Integrated Stem-Cell Transplantation and Palliative Care Programs Can Together Improve End-of-Life Care. *J Oncol Pract*. 2017;13(9):569–77. [PubMed: 28898603]
74. Leeson LA, Nelson AM, Rathouz PJ, et al. Spirituality and the recovery of quality of life following hematopoietic stem cell transplantation. *Health Psychol*. 2015;34(9):920–8. [PubMed: 25545043]

75. Cordova MJ, Cunningham LL, Carlson CR, Andrykowski MA. Posttraumatic growth following breast cancer: a controlled comparison study. *Health Psychol.* 2001;20(3):176–85. [PubMed: 11403215]
76. Wingard JR, Huang IC, Sobocinski KA, et al. Factors associated with self-reported physical and mental health after hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2010;16(12):1682–92. [PubMed: 20685400]
77. Harris BA, Berger AM, Mitchell SA, et al. Spiritual well-being in long-term survivors with chronic graft-versus-host disease after hematopoietic stem cell transplantation. *J Support Oncol.* 2010;8(3): 119–25. [PubMed: 20552925]
78. Cerundolo MM. Monthly Report of Stem Cell Blessings Brigham and Women's Hospital, Spiritual Care Department 2018.

Table 1-**Approach to an Inpatient Psychiatric Consult for a HSCT Patient**

Step	Explanation
Preparation	<ul style="list-style-type: none"> Obtain detailed medical history, stage in transplantation, hospital course and complications from the primary HSCT team Review the electronic medical records including both pertinent inpatient and outpatient medical records Review social work records Review any psychiatric records (including for prior psychiatric history and psychiatric medications) if available Review chemotherapeutic regimens used in the conditioning stage and/or radiation Review inpatient medications Inquire about behavioral issues and deficits in engagement with care from inpatient nursing team Review laboratory results Review brain imaging results
Patient Interview	<ul style="list-style-type: none"> Obtain a comprehensive history of both physical and psychiatric symptoms Inquire about pain symptoms Determine psychiatric history including prior psychiatric treatment and medications Conduct a safety assessment Gather social history including the nature of social supports, religion and spirituality factors Conduct mental status exam including a comprehensive cognitive screening instrument, e.g., MoCA⁵³
Differential Diagnoses	<ul style="list-style-type: none"> Consider common medical etiologies of neuropsychiatric symptoms e.g., rare infections [including from viruses (Herpes viruses like Human Herpes Virus 6, Epstein Barr viruses), parasites (toxoplasmosis), fungus (mucormycosis)], thyroid disease, and nutritional deficiencies in addition to psychiatric diagnoses Explore potential symptoms related to existential distress Elicit difficulty coping and adjustment issues that do not necessarily qualify for an adjustment disorder
Treatment/Interventions	<ul style="list-style-type: none"> Pharmacological interventions including psychiatric medications Non-pharmacological interventions e.g., cognitive behavioral therapy Spiritual care services Social work support
Considerations for liaison with care team	<ul style="list-style-type: none"> Awareness of the complex nature of the inpatient care team including medical house staff who may rotate quite often over the course of a transplant admission Familiarity with primary HSCT team who would likely follow patient over the course of the transplant for continuity Familiarity with inpatient social workers who follow patients closely