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Supportive Care of Hematopoietic Cell Transplant Patients

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Abstract

Hematopoietic cell transplant survivors face a number of challenges including low energy and stamina, “chemo-brain” and emotional distress, and late effects that can compromise functioning or lead to early mortality. This session will review the most recent interventions and recommendations to avoid or mitigate these complications.

INTERVENTIONS TO IMPROVE ENERGYAND STAMINA

Heather S.L. Jim

Patients undergoing hematopoietic cell transplant (HCT) experience significant fatigue and reduced physical functioning before transplantation. Both allogeneic and autologous transplants are associated with significant increases in fatigue in the acute posttransplantation period. On average, fatigue and physical functioning return to posttransplantation baseline in the years following transplantation [1]. Nevertheless, patients show significantly greater fatigue and reduced physical functioning compared with individuals without cancer [1]. Furthermore, fatigue and poor physical functioning can be distressing because they can interfere with return to work, school, and other daily activities [2]. As such, early identification and intervention in patients at risk for fatigue and poor physical functioning should be a high priority in supportive care.

Multiple mechanisms likely contribute to fatigue and reduced physical functioning in cancer patients. Data have implicated changes in energy metabolism, inflammation, and hypothalamic–pituitary–adrenal axis activity in cancer patients, particularly those treated with standard-dose chemotherapy. Depression and anxiety may also play a role in fatigue and reduced physical functioning secondary to cancer. The extent to which fatigue and reduced physical functioning result from these mechanisms in transplant patients is currently unclear but is under investigation. Recent data have implicated variation in genes responsible for inflammation (eg, tumor necrosis factor, interleukin-1B, and interleukin-6) as contributing to cancer-related fatigue [3]. Research is currently under way to replicate these findings in HCT patients.

A sizeable body of research suggests that behavioral and pharmacologic interventions can prevent or reduce physical deconditioning and improve quality of life in HCT patients. Randomized clinical trials (RCTs) of aerobic exercise and strength training have been

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conducted in inpatient, outpatient rehabilitation, and home-based settings. Supervised aerobic exercise in these trials typically consists of use of a stationary bicycle or treadmill 2 to 5 times per week, 20 to 30 minutes per session, at a pace that elevates the patient's heart rates. Strength training in these trials is typically conducted using weights or stretch bands. Data suggest that aerobic exercise and/or strength training can prevent loss of physical performance during hospitalization for transplantation, including loss of physical endurance, muscle strength, and performance status [4]. Aerobic exercise in the inpatient setting has also been shown to reduce the negative effects of transplantation on global quality of life and physical functioning [4]. Effects of inpatient aerobic exercise and strength training on other symptoms (eg, pain, diarrhea) and immunologic parameters (eg, leukocytes, platelets, time to engraftment) have been equivocal, however. Supervised outpatient aerobic exercise and strength training in the posttransplantation period have been shown to improve physical performance, including muscle strength, walking speed, and walking distance [5]. Similar benefits have been observed in an RCT of home-based aerobic exercise [6]. Additionally, non-randomized studies suggest that aerobic exercise and strength training may prevent or reduce fatigue and increase vitality. Taken as a whole, existing literature suggests that aerobic exercise and strength training interventions are efficacious in improving physical functioning in HCT patients. A large, multicenter RCT is currently under way to determine the effectiveness of home-based exercise in patients undergoing HCT.

Regarding pharmacologic interventions to reduce cancer-related fatigue and increase energy, research has been conducted on methylphenidate, dexmethylphenidate, dexamphetamine, and modafinil. Of note, no studies to date have yet examined these agents in HCT patients. Nevertheless, a mix of prospective, open-label studies and randomized, double-blind, placebo-controlled studies in cancer patients suggest that psychostimulants reduce fatigue. Some studies also suggest that psychostimulants reduce depression and pain [7,8], whereas effects on quality of life are equivocal [8]. Only 2 studies have been published on the effects of modafinil on cancer-related fatigue; both were open-label studies and both reported significant reductions in fatigue [9,10]. Although some studies have reported side effects of methylphenidate, dexmethylphenidate, and dexamphetamine, including insomnia, agitation, anorexia, nausea, vomiting, and dry mouth [7], studies of modafinil have generally reported that it was well tolerated. It should be noted, however, that most studies of psychostimulants to improve cancer-related fatigue have suffered from methodologic limitations such as small sample sizes and/or single-arm, open-label designs. As such, evidence supporting the use of pharmacologic interventions to reduce fatigue is preliminary but promising.

In summary, considerable progress has been made in identifying fatigue and reduced physical functioning as clinically relevant issues in HCT patients, understanding underlying mechanisms of cancer-related fatigue, and developing behavioral and pharmacologic interventions to increase energy and stamina. What is now needed are large, multicenter RCTs demonstrating the effectiveness of behavioral and pharmacologic interventions in the transplant setting. Additional research is needed to identify patients at risk for significant fatigue and compromised physical functioning so that they may benefit from early intervention.

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INTERVENTIONS TO IMPROVE CHEMO-BRAIN AND EMOTIONAL DISTRESS

Karen L. Syrjala

Introduction—Accumulated evidence suggests 3 summary statements about the cognitive and psychological health of patients receiving HCT: (1) they are highly resilient, and a majority will report competent cognitive function and emotional stability; (2) during treatment, a majority will manifest some decrements in both emotional distress and cognitive function; (3) from 10% to 40% will report neurocognitive deficits or psychologic needs that continue long term, depending on what is measured and the subgroup evaluated.

Neurocognitive deficits—The term “chemo-brain” is a colloquial term for a range of cognitive and psychomotor deficits that include difficulties in 4 areas: memory, sustained attention and information processing speed, executive function or what is often called multitasking such as shifting mental concepts, and hand–eye–brain coordination, also called psychomotor ability. Although some debates have questioned whether chemo-brain syndromes exist after cancer treatment, this issue is largely resolved with compelling longitudinal evidence that cognitive function does decline after HCT and recovers to some extent, but not entirely for all survivors by 5 years [1].

Studies indicate that most survivors function within the population-normative range after recovery from HCT. Many enter transplantation with some neurocognitive deficits particularly in memory, and have generalized decrements in function immediately following treatment. By 5 years, about 40% of HCT survivors continue with deficits that are largely mild [1]. Function recovers to within normal range in most areas by 5 years after treatment. Psychomotor function is particularly suppressed in about one-third even 5 years after treatment, and does not fully recover even after chronic graft-versus-host disease treatment is discontinued [1,2]. Memory difficulties also continue long term; however, those at most risk seem to have deficits that predate HCT [1,2]. Risk factors for neurocognitive deficits include lower socioeconomic status, total body irradiation, chronic graft-versus-host disease and its treatment, and delirium during acute treatment [1,3,4].

Studies testing cognitive rehabilitation interventions post-HCT have not yet found improvements in function. One barrier is that mechanisms for chemobrain are more speculative than definitive. Research with non-HCT cancer survivors has demonstrated variable efficacy in small studies to improve neurocognitive function using medications such as methylphenidate or modafinil. Studies that teach adults compensatory mechanisms for managing cognitive deficits have shown promise [5].

Emotional distress—Emotional distress is a broad term for a range of psychosocial issues that transplant recipients experience, including anxiety and depression, panic, and distress specific to their disease and transplant. Within the context of treatment and cancer-related distress, living with uncertainty and fear of recurrence dominate. However, additional stress is attributed to emotional issues such as posttraumatic stress, changes in relationships, grief and loss, adaptation to new limitations, demands such as work and financial limits, medical demands, and changes in self-image. Increasingly, researchers recognize that these negative emotional outcomes are often balanced with positive outcomes such as reappraisal of life priorities, benefit finding, spiritual connection, and posttraumatic growth.

Symptoms of emotional distress are most intense before transplantation and gradually resolve over the next 2 to 5 years [6]. Elevated levels of depression or anxiety have been detected in over one-half of those assessed pretransplantation and are associated with compromised quality of life and increased rates of mortality [6–8]. In the posttransplantation period, depression, anxiety, or posttraumatic stress have been identified in over 40% of survivors [6,7]. Research clearly indicates that spousal caregivers have even greater risk of emotional turmoil than patients, with depression, anxiety, and marital dissatisfaction elevated beyond levels seen in patients for the first 2 years after treatment. Spouses report a higher rate of negative changes (24%) than patients (15%), and patients report a higher proportion of positive changes (85%) than spouses (76%) [9]. Risk factors for psychological difficulties include more severe transplantation experience, less social constraint, greater spiritual well-being, and less general anxiety [10]. This combination has predicted 56% of the variance in mental health in long-term survivors. Autologous HCT recipients have lower rates of emotional distress only during the first 6 months after treatment [6]. Age has not been found to be a risk factor for emotional distress. Although females are generally expected to report more emotional distress than males, in transplantation this effect has not been consistent. The strongest predictor of long-term emotional health seems to be emotional health before and immediately following transplantation. At the most, one-half of HCT recipients with psychological needs receive treatment.

Although clinical trials have demonstrated efficacy in reducing distress in cancer patients, few of these have yet been tested in HCT recipients. In addressing emotional needs of HCT patients, 1 consideration is that assessment is, in itself, a form of intervention [7]. The distress thermometer, a tool first presented through the National Comprehensive Cancer Network guidelines, has demonstrated sensitivity and specificity in screening for emotional distress in patients. Assessment provides an opportunity for the patient to begin talking about and labeling his or her experiences and emotions. Indeed, this is the foundation for most psychologic interventions. To better address the emotional needs of HCT patients and caregivers, the greatest research need is to develop and test resource-conserving, sustainable interventions targeted to those at greatest risk, which can be provided through brief sessions, can be self-directed, or that use technologies such as the phone or Internet to reach long-term survivors.

Conclusions—Now that chemo-brain and emotional distress complications have been well defined during and following HCT, further research needs to more clearly define risk

factors and move toward understanding the biologic and behavioral mechanisms, as well as determining treatments for these complications that have significant impact on long-term quality of survival.

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RECOMMENDED SCREENING AND PREVENTIVE PRACTICES FOR LONG-TERM SURVIVORS OF HCT

Doug Rizzo

Approximately 50,000 patients undergo HCT worldwide each year. Advances in transplantation techniques and supportive care practices have led to progressive improvements in survival for HCT recipients in the last 2 decades. As patients survive long term after transplantation, they are at risk for developing late complications related to pre-, peri-, and posttransplantation exposures. Recognizing the need for systematic long-term follow-up of HCT survivors, the Center for International Blood and Marrow Transplant Research, the European Group for Blood and Marrow Transplantation, and the American Society of Blood and Marrow Transplantation developed consensus recommendations for screening and preventive practices for autologous and allogeneic HCT survivors in 2006 [1,2]. The working group reconvened in 2011 to update the guidelines, and invited participants from other international HCT societies to add a global perspective to the recommendations. Updated recommendations will be presented.

The proposed guidelines focus on risks faced by patients who have survived 6 months or more following transplantation and address autologous and allogeneic, and pediatric and adult HCT recipients. Because long-term HCT recipients may no longer be followed by transplant centers and may have returned to the care of community healthcare providers, the

guidelines are geared toward providers who do not routinely care for HCT recipients as well as those who do. To improve accessibility of the guidelines for clinicians, mobile applications are available for common cellular phone platforms at (http://www.marrow.org/PHYSICIAN/Medical_Education/Clinical_Guidelines_App/index.html). The National Marrow Donor Program (NMDP) also publishes a patient-friendly version of follow-up guidelines at (www.marrow.org).

Malignancy is the primary indication for HCT. There has been increasing recognition of the role of patients in their cancer survivorship experience. The 2006 Institute of Medicine Report “From Cancer Patient to Cancer Survivor: Lost in Transition” highlights the importance of engaging cancer patients in surveillance, recognition, and management of late effects of treatment [3]. One of the primary recommendations of this report is the provision of a comprehensive care summary and follow-up plan for every patient. Further, it is recommended that the care plans used by providers be based upon “systematically developed, evidence-based clinical practice guidelines, assessment tools and screening instuments.” One of the principal goals of the post-HCT recommendations developed through this global collaboration is to provide a template from which providers can engage patients with treatment summaries and care plans. We anticipate that patients may be able to use these guidelines to establish a long-term follow-up care plan in consultation with their healthcare providers based on their individual exposures and risk factors.

Most of the recommendations were derived from retrospective studies that have identified specific complications in long-term survivors and the risk factors associated with them, although in some cases they are based on evidence from non-HCT settings or expert consensus. There remains a paucity of clinical trials focused on screening and preventive practices among HCT survivors, and the need for more research in this area, including randomized or controlled trials, is clear. The recommendations represent sensible practices to optimize outcomes, and although they are strongly encouraged for all recipients, they should not be judged as mandatory. In fact, it should be recognized that in some areas of the world, resource constraints and access to medical care after HCT may limit full implementation of the recommendations.

A broad constellation of medical issues faced by late survivors of transplantation are addressed. Aside from health screening applicable to the general population, recommendations are provided for complications involving the following systems: immunity and infections, ocular, oral, respiratory, cardiovascular, liver, genitourinary, muscle, and connective tissue, skeletal, nervous system, endocrine, mucocutaneous, psychosocial/sexual, and second malignancy screening. Although most of the late complications addressed pertain particularly to allogeneic recipients, autologous recipients are at risk for many of the late complications and may experience unusual toxicity or immune impairment following transplantation that places them at risk similar to allogeneic recipients (eg, exposure to prolonged steroids). Therefore, although some of the recommendations do not typically apply to autologous recipients, providers should remain alert to these complications in all patients.

The practice of HCT is continuously changing. Some examples of such changes include emerging indications of transplantation (eg, autoimmune diseases, sickle cell disease), increased utilization of newer donor sources (eg, umbilical cord blood and haploidentical donors), decreased use of total body irradiation for conditioning and evaluation of novel therapies as part of HCT (eg, posttransplantation maintenance therapy in myeloma). Nonmyeloablative and reduced-intensity conditioning regimens offer the ability to perform transplantation for a larger number of older patients. The risks and constellation of late complications may change as newer practices in transplantation become more prevalent.

Providers should be cognizant of any unique exposures and risks associated with these practices (eg, delayed immune reconstitution in umbilical cord blood recipients) when considering a long-term follow-up care plan for their patients. These screening guidelines will require additional revisions over time to accommodate evolution in exposures associated with HCT.

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