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Review article

Frailty and stem cell transplantation in the older patient with cancer

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ABSTRACT

Age, performance status, and single organ comorbidities have been typically used to assess the suitability of patients for stem cell transplantation (SCT). Until recently, these criteria, combined with poor outcomes, have excluded many older patients from SCT. Improvements in supportive care, reduced-intensity conditioning regimens, and more tolerable graft-versus-host disease (GVHD) prophylaxis have increased the number of older individuals now considered to be viable candidates for SCT. However, this raises concerns about the tolerability of SCT for older persons. Many SCT recipients present with fatigue, weakness, dyspnea, sleep disturbance, and anorexia in the post transplant period, symptoms consistent with a frailty syndrome. These observations, plus the fact that SCT is increasingly offered to older patients, suggest the need to use assessment tools that are appropriate for this population and able to assess frailty. Comprehensive geriatric assessment (CGA) needs to be tailored specifically to the SCT patient. CGA may prove useful in identifying and risk stratifying those older SCT recipients most likely to become frail following transplantation. Such insight would allow the early use of pharmacologic and rehabilitative interventions that could be targeted to help minimize the toxicity associated with SCT. Frailty caused by SCT may also provide a model of accelerated frailty due to aging, as many similarities may exist in the two syndromes.

Contents

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1. Introduction

Stem cell transplantation (SCT) is an important therapeutic intervention for the treatment of a variety of hematologic cancers including leukemia, lymphoma, myeloma, myleodysplastic syndromes, and bone marrow failure states.[1–5] In this procedure hematopoietic cells are collected either from a donor (allogeneic) or from the patient himself/herself (autologous). Patients then undergo a conditioning regimen to prepare the patient to receive the collected cells. Previously these regimens have involved high dose chemotherapy and total body radiation and caused significant toxic effects. More recently the use of total body radiation has declined, although nonablative radiation is still used, and the doses of preparative chemotherapy have been lowered resulting in reduced treatment toxicities.[6] Following completion of this conditioning regimen, the collected stem cells are then infused into the now immunocompromised host. Over the next few weeks, these stem cells establish a new hematopoietic and immune system in a process called engraftment. During this period recipients remain at high risk for developing infections and acute graft vs. host disease. The stem cells, also referred to as the graft, may mount an attack against the recipient's normal cells, called graft-versus-host disease (GVHD). Common regimens to prevent GVHD include immunosuppressive agents like cyclosporine or tacrolimus and methotrexate. Acute and chronic GVHD are treated with corticosteroids.[7] Despite these potential treatment toxicities SCT offers the only hope of cure for many malignancies.[6]

Historically, chronological age, performance status, and single organ comorbidities have been used to identify appropriate patients for SCT. Narrow criteria often denied those who most frequently develop hematologic tumors – i.e. the elderly patient – access to this potentially curative treatment. However, reduced intensity conditioning regimens, enhanced supportive care, and more tolerable immunosuppression have facilitated the use of SCT in older oncology patients who were previously considered ineligible.[8] Despite these advances, toxicities associated with this procedure, such as acute graft vs. host disease, remain a significant problem. The estimation of transplantation tolerance in older patients is of growing concern.

For younger SCT candidates, chronological age provides a reasonably good measure of health status. For older SCT candidates, age provides a poor index of health status, because aging involves a more complex construct consisting of a number of domains including comorbid illness, functional status, nutrition, and psychosocial health. As such, instruments that assess these domains in older patients that comprise a comprehensive geriatric assessment may provide useful predictive information regarding transplantation tolerance. Additionally, questions regarding frailty in this patient population must be addressed. Frailty is a syndrome characterized by a progressive loss of function due primarily to sarcopenia and osteopenia, poor nutrition, increasing disability, and possibly impaired cognition.[9,10] Frailty can be clinically identified by the presence of 3 or more of the following criteria: self-reported physical exhaustion or poor endurance, weakness as measured by grip strength, unintentional weight loss of 10 lb or more in a year, slow gait or walking speed and low levels of physical activity.[10] It is reasonable to suggest that frailty status at the time of SCT may influence transplantation tolerance. Furthermore, toxicities associated with transplantation may bring about the onset of frailty or amplify an already existing frailty syndrome. In either case, the use of a geriatric assessment tool that assesses frailty may provide useful clinical information in both the pre- and post-transplant setting. The purpose of this review is to discuss the potential concerns regarding toxicity in older SCT recipients and specifically address the possibility that SCT may be associated with a frailty syndrome similar to the frailty of aging.

2. SCT in Older Persons

With a few notable exceptions, many hematologic malignancies increase in incidence with advancing age. For example, the median age of diagnosis of acute myelogenous leukemia is 65 years, with the incidence increasing from 1.7 per 100,000 for persons <65 years and 16.4 for those >65 years. While the incidence of acute lymphocytic leukemia peaks at 10 years, a second smaller rise in incidence is seen in persons older than 70. The average age of diagnosis of myelodysplastic syndrome is approximately 70 years. Until recently, these ages have been considered to be prohibitively old for such interventions as SCT.[11]

A number of host factors, including chronological age, immunologic senescence, presence of frailty, and a higher incidence of clinical comorbidities are generally thought to render older potential SCT recipients too physiologically incompetent to successfully overcome the toxicities of this procedure.[12] In addition, age-associated decline in drug metabolism and excretion may expose already weakened organ systems to greater effective drug doses of chemotherapy for a longer period of time. Elderly patients are also more likely to receive stem cells from a matched unrelated donor (MUD) as the matched sibling pool declines as people age.[13] The use of cells from MUD donors increases the risk of transplant-related morbidity and mortality in part due to lower rates of engraftment.[14] Chromosome abnormalities appear more frequently in older patient populations with malignancies such as acute myelogeneous leukemia, myleodysplastic syndrome (MDS) and acute lymphocytic leukemia (ALL), and the increasing incidence of such errors have been associated with an inferior treatment outcome.[15,16]

Despite these challenges, the use of SCT in the treatment of hematologic malignancies in the elderly has increased in recent years.[11] Long-term survival after allogeneic SCT has

improved due to a number of factors, including the use of non-myeloablative regimens and/or reduced intensity conditioning regimens, the use of peripheral blood stem cells rather than harvested bone marrow cells, and the use of more targeted therapies. Improved post-transplant patient care, advances in immunosuppression therapy, and better graft vs. host prophylaxis have also reduced the toxicity of SCT or improved the ability of patients to tolerate adverse effects.[17] Older individuals appear to derive benefit from undergoing SCT,[12] and recent improvements in long-term survival have been seen despite the increasing treatment of older, sicker patients.[18] Among 372 persons 60 to 75 years of age treated with allogeneic SCT using non-myeloablative regimens, 5-year survival was 23% to 69%, depending on the level of comorbidity and disease risk, but age was not a predictor of survival.[19]

3. Frailty Syndrome and SCT Toxicity

Many patients who have undergone SCT experience physical symptoms such as fatigue, weakness, reduced activity levels and psychological stressors including depression and anxiety and are at increased risk for osteoporosis, sarcopenia, and weight loss.[20] These symptoms are generally attributed to the toxic effects of SCT and post-transplant medical management, and resemble the characteristics of frailty mentioned above.[17] The net effect of frailty is generally recognized to be a loss of physiologic reserve that diminishes one's ability to tolerate stress, leading to increased risks of hospitalization, further loss of function, and mortality.[10]

The prevalence of the frailty syndrome and whether there is a relationship with age and frailty after SCT has not been explored. It is possible that SCT patients of all ages are susceptible to frailty after treatment. However, the frailty syndrome is more prevalent with increasing age, because older persons are at higher risk of developing the conditions that contribute to frailty, independent of cancer or cancer treatment.[21] Cancer may place additional frailty risk on an older person, as older persons with cancer have a higher prevalence of frailty compared to those without cancer.[22] This raises the possibility that the older SCT recipient may face the additional health burden of frailty as a consequence of treatment. Early identification of frailty coupled with a comprehensive treatment plan can successfully result in improved physiological function thus reducing frailty and, hopefully, its consequences.[9] As such, identifying SCT candidates who are at increased risk for developing frailty or determining which patient characteristics increase vulnerability to the frailty syndrome becomes an important component of the pre-transplant evaluation.

4. Usefulness of Frailty Biomarkers in SCT Patients

An important aspect of the pathophysiology of frailty is a dysregulation of inflammatory pathways and of the coagulation system.[23] Frail older persons have evidence of dysregulation of multiple systems, including immune, endocrine, hematologic, cardiovascular, and musculoskeletal.[24] Thus, measuring circulating biomarkers might contribute to the clinical diagnosis of frailty and/or its progression. Candidate biomarkers associated with an abnormal inflammatory status include soluble inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These are produced in excess in states of chronic inflammation and promote further inflammation. Interleukin-6 promotes the synthesis of acute phase proteins such as C-reactive protein (CRP) and serum amyloid A.[25,26] Interleukin-6 also creates a state of insulin resistance, increased catabolism and negative nitrogen balance resulting in sarcopenia, or loss of lean muscle mass. Other effects of soluble inflammatory cytokines include anorexia, osteopenia, low-grade anemia, decreased serum albumin and cholesterol.[26,27] Functional decline, a hallmark of frailty, has been associated with increased IL-6 levels in community dwelling elders.[28,29] Increasing IL-6 levels have been shown to independently predict increasing incidence of the development of frailty.[24]

Other potential biomarkers include neuroendocrine compounds such as insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone sulfate (DHEAS), C-reactive protein (CRP), D-dimer, and markers of depressed nutritional status including serum albumin and cholesterol.[26,27] Several studies conducted with community dwelling adults have associated increased levels of inflammatory cytokines, CRP and D-dimer with increased mortality and disability.[30–33] Collectively, assessment biomarkers which define the inflammatory state may prove valuable in identifying those SCT recipients who are at increased risk for developing frailty post transplant. However, many factors related to hematologic malignancies and SCT itself may affect multi-system function and immune dysregulation in the SCT patient, suggesting that the use of these biomarkers alone may not be adequate to identify frailty in the SCT setting.

5. Potential Use of Comprehensive Geriatric Assessment in SCT

Comprehensive geriatric assessment (CGA) consists of multidimensional, multidisciplinary diagnostic instruments designed to assess the medical, psychosocial and functional capabilities and limitations of elderly patients. CGA has been used to predict life expectancy and tolerance to cancer treatment as well as to identify risk factors for adverse treatment outcomes, including malnutrition, depression, loss of physical function, and lack of social support in oncology patients.[34–37] The ultimate goal of CGA is to improve outcomes of cancer treatment in older persons found to have deficits by discovering which areas need further optimization prior to or during treatment.[36,38]

The use of CGA has not been specifically evaluated to risk stratify SCT patients for toxicity and other outcomes. Comorbidity and performance status have been shown to predict SCT outcomes,[39] but the development of frailty per se as well as associated functional consequences has not been explored.[40] Whether frailty may be present prior to SCT is also unknown, and could impact the risk of frailty after SCT. Evaluation for fitness for SCT includes a multi-organ assessment of comorbidity[41] as well as performance status. However, the correlation between performance status and frailty is not established, and most patients who present for SCT have a good performance status;

8.7% of patients ages 18 to 83 years had a Karnofsky performance status <80% at the time of SCT.[18] CGA has been shown to provide additional information that is distinct from performance status and is independently predictive of post-treatment toxicity in older persons with a variety of cancers.[42] The use of CGA has been advocated to identify those older SCT candidates who may be at higher risk for SCT-related toxicity, including frailty.[17]

The use of CGA in the SCT population needs to be evaluated for several reasons. Some tools, such as a comorbidity index, may perform better (i.e. improved specificity), if developed specifically for SCT recipients.[41] Patients who currently undergo SCT undergo an extensive pre-SCT screening to ensure adequate performance status, social support, adherence to therapy, tolerance to prior chemotherapeutic regimens, and cardiopulmonary fitness. They represent a highly select group of patients, and thus, a standard CGA may not detect vulnerability to toxicity. Although physical performance testing is not consistently included in CGA for oncology patients, tests of gait speed and grip strength are parts of a frailty evaluation that might identify SCT patients with subtle baseline deficits.[43]

6. Treatment of Frailty in SCT Patients

If SCT is associated with a post-transplant frailty syndrome, understanding whether this syndrome is distinct from frailty of aging and whether it is mediated by similar inflammatory pathways would also help elucidate the biology of frailty and suggest possible treatment strategies. The ability to improve frailty related to SCT might represent a model by which frailty associated with aging could be treated. Although a number of pharmacologic and non-pharmacologic options have been evaluated to treat frailty, there is no specific treatment for frailty associated with aging.[44] Interventions are aimed at delaying further deterioration of performance and treatment of precipitating or underlying conditions.[45] Possible interventions include exercise, hormonal therapy, and nutritional supplementation.

The loss of muscle mass and strength in frailty can be reversed by exercise. Exercise can also improve gait, mobility, performance of activities of daily living and quality of life.[45] In a study involving frail elderly adults, those who underwent a program of physical therapy had a slower rate of decline in their functional performance over time than the control group.[46] However, the benefits of exercise were observed in those with moderate frailty but not in those with severe frailty. In another study, Sullivan et al., found that progressive resistant muscle strength (PRMS) training was well-tolerated among frail elderly patients and it improved muscle strength.[47] Exercise has been studied in allogeneic SCT patients, showing improvements in muscle strength, endurance, fatigue, and emotional state in patients in a physical therapy intervention.[48]

There are a number of hormonal pathways that have been evaluated as treatments for frailty, with mostly disappointing results. Frailty is associated with declines in anabolic hormones such as testosterone, growth hormones (GH) and IGF-1.[49,50] In addition there is general state of insulin resistance leading to a state of catabolism and negative nitrogen balance. GH supplementation increases lean tissue mass and decreases fat mass, but this has not translated into increased muscle strength and function,[51,52] and GH have numerous side effects.[27] The use of testosterone in the elderly is associated with changes in body composition, particularly an increase in muscle mass and a decrease in body fat. These changes are small and in many cases, are not associated with much increase in strength.[53,54] DHEA has been reported to increase body mass and lower body fat especially in the short term, probably by increasing IGF-1. In the long term, its use has shown no particular benefits.[55] Finally, vitamin D supplementation may improve muscle strength as vitamin D deficiency has been associated with muscle weakness in the elderly.[50]

7. Conclusion

SCT is increasingly used in older persons, a population at higher risk for developing hematological cancers. This patient population is at risk for being frail at the time of transplantation or developing frailty secondary to post-transplant treatment toxicities. Because frailty is associated with increased mortality and morbidity, identifying the presence of frailty prior to transplant would assist in identifying the most suitable candidates for this procedure and allow for the use of interventions to counter the adverse effects of frailty. By the same token identifying the risk that individual SCT recipients face for becoming frail would allow for the timely or preventative use of countermeasures to frailty.

Author Contributions

All authors contributed to the conception and design, analysis and interpretation of studies, and to drafting and/or revising the manuscript critically for intellectual content.

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