Biol Blood Marrow Transplant xxx (2016) 1–8

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Characterization and Risk Factor Analysis of Osteoporosis in a Large Cohort of Patients with Chronic Graft-versus-Host Disease

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Article history:
Received 4 March 2016
Accepted 16 April 2016

Key Words:
Chronic graft-versus-host disease
Allogeneic hematopoietic stem cell transplantation
Osteoporosis
Late effects
Supportive care
Platelets

A B S T R A C T

The National Institutes of Health's Chronic Graft-versus-Host Disease (cGVHD) Consensus Project Ancillary and Supportive Care Guidelines recommend annual assessment of bone mineral density (BMD) to monitor bone health. The study of osteoporosis in patients with cGVHD has been limited to small numbers of patients, and the guidelines are based on experience with other chronic diseases and expert opinion. We hypothesized that the prevalence of osteoporosis is high in a cohort of 258 patients with moderate to severe cGVHD because of prolonged exposure to risk factors for osteoporosis after allogeneic hematopoietic stem cell transplantation. We defined osteoporosis using BMD criteria (T-score ≤ -2.5) at 3 anatomic sites—the femoral neck (FN), lumbar spine (LS), and total hip (TH)—and characterized risk factors through univariate and multivariate analyses. We found that low body weight (FN, $P < .0001$; LS, $P = .0002$; TH, $P < .0001$), malnutrition (FN, $P < .0001$; LS, $P = .03$; TH, $P = .0076$), higher platelet count (FN, $P = .0065$; TH, $P = .0025$), higher average National Institutes of Health organ score (FN, $P = .038$), higher prednisone dose (LS, $P = .032$), lower complement component 3 (LS, $P = .0073$), and physical inactivity (FN, $P = .01$) were associated with osteoporosis in at least 1 site. T-scores were significantly lower in the FN compared with the LS or TH ($P < .0001$ for both). The prevalence of osteoporosis and osteopenia was high (17% and 60%, respectively), supporting current recommendations for frequent monitoring of BMD. The association of higher platelet count in patients with cGVHD and osteoporosis has not been reported previously and represents a new area of interest in the study of osteoporosis after allogeneic hematopoietic stem cell transplantation.

INTRODUCTION

Improvements in the safety and efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) have resulted in an increased number of long-term survivors, along with the need to identify and treat late complications that arise in this unique group of patients. Chronic graft-versus-host disease (cGVHD) is a common cause of morbidity and nonrelapse mortality in long-term survivors of allo-HSCT, with an estimated incidence of 30% to 70% [1,2].

Presented in part as an oral presentation at the 2015 ASBMT/CIBMTR Bone Marrow Transplantation Tandem Meetings.

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Financial disclosure: See Acknowledgments on page 7.

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http://dx.doi.org/10.1016/j.bbmt.2016.04.012
1083-8791/

It is characterized by donor-derived lymphocyte infiltration and immune reaction against host tissues, causing significant symptom burden and functional impairment among patients recovering from allo-HSCT [1-4].

Osteoporosis is another significant source of morbidity in patients after allo-HSCT [5]. In this disease process, rapid resorption and subsequent loss of bone density occur in the first 1 to 2 years after transplantation, with recovery occurring in some, but not all, affected anatomic sites [6-10]. Contributing factors include myeloablative conditioning, secondary hypogonadism, abnormal calcium and vitamin D metabolism, reduced mobility, and use of immunosuppressive medications, such as glucocorticoids and calcineurin inhibitors [6,11-14]. These 2 drug classes are associated with altered metabolism and absorption of calcium, phosphate, and vitamin D, as well as with trabecular bone loss at the spine and femoral neck (FN) [6,13-17]. In addition, hyponatremia, an emerging contributor to osteoporosis, has been reported after allo-HSCT [18-20].

Bone loss is an immune-mediated process in which several cytokines create an imbalance between bone resorption and bone formation via a pathway of the receptor activator of nuclear factor-κB, its ligand, and osteoprotegerin [21]. After allo-HSCT, patients experience various immunologic processes, including cytokine storm and GVHD, which may contribute to the development of osteoporosis [22]. This is of particular concern to patients and clinicians owing to the painful and debilitating fractures that can lead to reduced mobility and impaired quality of life [5]. A recent retrospective analysis of more than 3500 allo-HSCT recipients found that 5% experienced a fracture during a median post-transplantation follow-up of 85 months [23].

The National Institutes of Health (NIH) Chronic GVHD Consensus Project ancillary and supportive care guidelines recommend annual monitoring of BMD and calcium and vitamin D levels [24]. Antiresorptive therapy is suggested for patients with a BMD-derived T-score <-1.5, and referral to an endocrinologist is recommended for evaluation and treatment of secondary endocrine causes. These guidelines for osteoporosis are based on experience with other diseases and expert opinion. Previous studies addressing osteoporosis in allo-HSCT recipients have found the following associations of GVHD-related variables with osteoporosis: cumulative dose of glucocorticoids and calcineurin inhibitors, duration of therapy with glucocorticoids and calcineurin inhibitors, severe acute GVHD, any cGVHD, and cGVHD severity [7,8,11,13,14,22,25-27].

The aim of the present study was to determine the prevalence of osteoporosis in a large, well-annotated cohort of patients with moderate to severe cGVHD as defined by NIH criteria, and to identify possible risk factors and correlates. We hypothesized that patients who are more severely affected by cGVHD are also predisposed to osteoporosis owing to increased exposure to risk factors such as immune dysregulation, secondary hypogonadism, reduced mobility, and prolonged use of immunosuppressive therapy. Given this hypothesis, we expected to find a high prevalence of osteoporosis in this population.

METHODS

Patients

Patients were enrolled on the NIH protocol "Factors Determining Outcomes in Patients with Graft-versus-Host Disease" (NCT00092235), a National Cancer Institute Institutional Review Board–approved cross-sectional study in which patients provided written consent to undergo a 1-week comprehensive multidisciplinary evaluation. Patients were seen by subspecialists in dentistry, dermatology, gynecology, ophthalmology, pain and palliative care, rehabilitation medicine, and transplant clinicians and assessed using the NIH cGVHD diagnostic and staging system [28-30]. In addition to collecting demographic, laboratory, and histopathology data, patients underwent dual-energy X-ray absorptiometry (DEXA) to determine BMD at the FN, LS, and TH.

A total of 337 patients were enrolled in this protocol between October 2004 and June 2014. For the purpose of this study, 79 patients were excluded, including 30 adult patients without DEXA data, 27 pediatric patients, 14 patients who were not diagnosed with cGVHD at evaluation or failed to complete the study, and 8 patients whose DEXA yielded insufficient data (no T-score, likely due to artifacts in scans), resulting in a study population of 258 patients.

Outcomes and Variables

DEXA was performed using Hologic scanners (Delphi, n = 174; Discovery C, n = 74; and QDR4500, n = 10; Hologic, Marlborough, MA). BMD values at each anatomic site were converted to T-scores via comparison to a race- and sex-matched reference population of healthy young adults using manufacturer databases. Osteoporosis was defined using World Health Organization criteria, in which T-score of ≤ -2.5 indicates osteoporosis, a T-score between -2.5 and -1.0 indicates osteopenia, and a T-score of ≥ -1.0 is normal [31]. Patients, regardless of age or sex, were divided into 2 groups, osteoporosis and nonosteoporosis, at each location based on their T-scores, and potential risk factors for osteoporosis were compared between the 2 groups. Patients with osteopenia were placed in the nonosteoporosis group.

Potential risk factors for osteoporosis in this study were classical risk factors for osteoporosis, including age, sex, body weight, malnutrition (assessed using the Patient-Generated Subjective Global Assessment [PG-SGA] malnutrition screening tool recommended by the American Society of Parenteral and Enteral Nutrition), physical inactivity (assessed using the PG-SGA activities and function evaluation), serum 25-hydroxyvitamin D deficiency, hypocalcemia, hyponatremia, hypogonadism (assessed based on serum levels of estradiol, follicle-stimulating hormone, luteinizing hormone, and testosterone), hyperparathyroidism, thyroid dysfunction, history of alcohol consumption (yes versus no; self-reported current or previous alcohol consumption of any frequency or duration), history of cigarette smoking (yes versus no; self-reported current or previous smoking of any frequency or duration), current use of selective serotonin reuptake inhibitors (SSRIs; yes versus no), and current use of proton-pump inhibitors (PPIs; yes versus no) [32-34].

In the risk factor analysis, we also considered transplantation characteristics, including total body irradiation (yes versus no), intensity of conditioning (myeloablative versus nonmyeloablative/reduced-intensity conditioning), HLA match (match versus mismatch), donor relationship (related versus unrelated), indication for allo-HSCT, and time since transplantation.

Finally, we considered a number of variables reflecting cGVHD activity and severity, including NIH global score; individual NIH organ scores; average NIH organ score (sum of all NIH organ scores divided by the number of organs assessed; 7 for males, 8 for females) [29]; time since diagnosis of cGVHD; body surface area of deep and superficial sclerotic skin involvement; serum markers of inflammation (platelet count, complement component 3 [C3], complement component 4 [C4], C-reactive protein [CRP], and albumin); number of previous systemic immunosuppressive therapies for cGVHD; intensity of current immunosuppression, defined according to Mitchell et al. [4] as none, mild (single-agent prednisone <0.5 mg/kg/day), moderate (prednisone ≥ 0.5 mg/kg/day and/or any single agent/modality), or high (≥ 2 or more agents/modalities with or without prednisone ≥ 0.5 mg/kg/day); and current systemic glucocorticoid dose converted to equivalent prednisone dose.

Statistical Analysis

Separate statistical analyses were conducted for each of the 3 anatomic sites at which BMD was assessed: FN, LS, and TH. For evaluation of factors associated with osteoporosis, continuous parameters were compared between the osteoporosis and nonosteoporosis groups using the exact Wilcoxon rank-sum test. The Fisher exact test was used to compare dichotomous parameters, the Mehta modification to the Fisher exact test was used to compare categorical parameters, and a Cochran-Armitage test for trend was used to compare ordered categorical parameters [35,36]. Once factors were identified as being potentially associated with osteoporosis in a given site, multiple logistic regression analysis using backward selection was used to identify factors that potentially could be jointly predictive of osteoporosis.

To determine factors associated with continuous raw T-scores in the 3 sites, Spearman correlation analysis was used to find the correlation between raw T-scores and continuous parameters. The magnitude of the correlation coefficient was used to gauge the strength of the correlation as follows: $|r| > 0.70$, strong correlation; $0.50 < |r| < 0.70$, moderately strong