ASBMT
American Society for Blood and Marrow Transplantation

Accelerated Bone Mineral Density Loss Occurs with Similar Incidence and Severity, But with Different Risk Factors, after Autologous versus Allogeneic Hematopoietic Cell Transplantation

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Bone mineral density (BMD) loss occurs commonly in patients after allogeneic hematopoietic cell transplantation (HCT), primarily because of steroid use, but little is known about BMD change post-autologous HCT. In a prospective study of 206 consecutive first HCT patients, we measured acute BMD change at the lumbar spine and dual femur between baseline and day +100, and evaluated risk factors for bone loss. Accelerated BMD loss in this 4-month period occurred after both autologous and allogeneic HCT with similar severity (median, 0.03 g/cm^2 versus 0.03 g/cm^2 at the spine; 0.03 g/cm^2 versus 0.05 g/cm^2 at the femur, respectively). This is equivalent to 7 to 17 years' worth of bone loss by aging. Risk factors for BMD loss were different between autologous and allogeneic HCT patients: lymphoma was associated with greater bone loss after autologous HCT than myeloma, whereas higher steroid dose was the most significant risk factor after allogeneic HCT. Multivariable risk models explained 11% to 30% of the variation in HCT-related BMD change. Surprisingly, BMD loss post-autologous HCT occurred with similar incidence and severity to allogeneic HCT, even in the absence of steroid use. Evaluation of clinical strategies to prevent and reverse HCT-related BMD loss is necessary in both autologous and allogeneic HCT patients.

Biol Blood Marrow Transplant 16: 1130-1137 (2010)

KEY WORDS: Bone mineral density, Autologous HCT, Allogeneic HCT, Risk factors

INTRODUCTION

Hematopoietic cell transplantation (HCT) cures patients with otherwise fatal hematologic diseases [1], making quality of life among survivors an increasingly important issue to be addressed. Accelerated bone mineral density (BMD) loss is a common complication after both solid organ and stem cell transplantation, characterized by rapid bone loss, which persists for many years [2-8]. This accelerated premature bone aging exponentially increases the risk of fractures, where a 10% to 15% BMD loss approximately doubles the fracture risk [9,10].

Our previous retrospective study demonstrated that BMD loss occurs frequently after allogeneic HCT, even in the absence of steroid exposure, and that antiresorptive bisphosphonate treatment was effective in reversing the bone loss in osteoporotic patients [11]. Several other studies have also demonstrated efficacy at reversing BMD loss post-HCT with bisphosphonates [12-17]; however, vitamin D with or without calcium supplementation, and hormone replacement therapy have failed to prevent or reverse bone loss [12,14,18,19].

Although risk factors for BMD loss after allogeneic HCT with myeloablative (MA) conditioning have been described [6,7], there are no data on the incidence and severity of BMD loss after allogeneic HCT with NMA or reduced-intensity conditioning (RIC) regimens. Moreover, for patients undergoing autologous HCT, BMD change has only been reported in small series with inconsistent findings. In a retrospective cross-sectional study of 68 autologous HCT patients, 28% had osteopenia or osteoporosis at the spine and 54% at the femur a median of 4.2 years after transplant [20]. Another study of 10 autologous

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Financial disclosure: See Acknowledgments on page 1136.

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Received January 13, 2010; accepted February 19, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.02.017

HCT patients followed for 12 months after transplant showed a nonsignificant reduction of BMD at the spine (−1.1%) but an increase at the femur (1.5%) [21]. These results conflict with a prospective study including both autologous and allogeneic HCT patients, which reported a nonsignificant loss at the spine (−2.4%) and a significant BMD loss at the femur (−3.8%) at 3 months after transplant [22].

In the present study, we sought to compare the incidence, severity, and risk factors for BMD loss between autologous and allogeneic HCT patients. Steroid exposure is infrequent after autologous HCT, but shows a strong correlation with BMD loss after allogeneic HCT; therefore, we hypothesized that incidence and risk factors for accelerated BMD may differ between these 2 HCT patient groups.

MATERIALS AND METHODS

Patient Population

Beginning in January 2006 as part of routine clinical care, dual-energy X-ray absorptiometry (DXA) scans and serum levels of 25-hydroxyvitamin D (25-OHD), parathyroid hormone (PTH), and calcium were prospectively measured at baseline and day +100 after transplantation in patients undergoing autologous and allogeneic HCT in the Blood and Marrow Transplantation Program at Roswell Park Cancer Institute (RPCI). No vitamin D or routine calcium supplementation was given during this time period. Calcium replacement was only administered for critical values of ionized calcium <1.19 mmol/L. By January 2009, a total of 206 adult (≥18 years) patients underwent their first HCT, 197 (96%) of whom had a baseline DXA scan a median 20 days pre-HCT. The most common reason for not obtaining a baseline DXA was because of the patient's weight exceeding the maximum limit of the DXA scanner (300 pounds). Of those with a baseline DXA scan, 146 (74%) had a second DXA scan a median 98 days post-HCT. The reasons for not obtaining a follow-up DXA scan were because of early death or relapsed disease (N = 37) or unstable medical status (N = 14). This study was reviewed and approved as a nontherapeutic protocol by the institutional review board (IRB) at RPCI. All data presentations have been deidentified.

Autologous High-Dose Therapy and Allogeneic Conditioning Regimens

High-dose therapy regimens before autologous HCT varied by underlying disease, age and performance status. In the 102 autologous HCT patients with a baseline DXA scan, these regimens included: cyclophosphamide (C) + carmustine (B) + etoposide (V) (N = 37), 120-200 mg/m^2 melphalan (M) (n = 32), busulfan (Bu) + C (n = 26), or total body irradiation (TBI) based (N = 7). Conditioning regimens before allogeneic HCT also varied by underlying disease, age, and performance status. MA regimens in the 95 allogeneic HCT patients with a baseline DXA scan included: C + 1200-1350 cGy TBI (n = 16), Bu + C (n = 12) or V + TBI (n = 1). RIC regimens included: fludarabine (Flu) + M (n = 57) or Flu + C ± other (n = 9).

Graft-versus-Host Disease (GVHD) Prophylaxis and Treatment

Prophylaxis for GVHD varied by age, underlying disease risk, donor relation, stem cell source, and protocol. In the 95 allogeneic HCT patients who had a baseline DXA scan, these regimens included: tacrolimus (FK) + methotrexate (MTX) + mycophenolate mofetil (MMF) (N = 38), FK + MMF (N = 29), FK + MTX (n = 22), or other (N = 6). Tacrolimus levels were checked twice weekly to maintain levels between 5 and 15 ng/mL. It was initially given intravenously and converted to oral once patients tolerated oral medication, and was tapered in the absence of GVHD beginning at day +30 for high-risk disease or day +100 for low-risk disease. MTX was dosed at 2.5, 5, or 10 mg/m^2 and given on days +1, +3, +6 ± day +11, depending on age, donor relation, stem cell source, and underlying disease risk.

First-line treatment for acute GVHD (aGVHD) was escalation of calcineurin inhibitor to the maximum dose tolerated by renal function and initiation of methylprednisolone 2 mg/kg for 3 days. If there is no response after 72 hours of corticosteroids, additional treatment was initiated either through enrollment on a steroid-refractory GVHD protocol or per the program's standard operating procedure for GVHD treatment.

BMD Measurement

BMD at the lumbar spine (average of L2, L3, and L4) and at the dual femur (average of 2 entire femora) was quantified by DXA scans using a single GE® Lunar Prodigy™ scanner (GE Medical Systems, Piscataway, NJ). The coefficient of variance was 0.94% at the spine and 0.76% at the femur. To adjust for random errors with repeated measurements, we defined a "significant" change of BMD according to the criteria recommended by the International Society of Clinical Densitometry that the least significant change between 2 consecutive DXA scans must exceed 2.77 times the coefficient of variance [23]. This translates to a minimum change of 2.6% at the spine and 2.1% at the femur in our study. In addition, we also annualized BMD loss rates in our patients and compared those to the expected normal rates in the general population between 20 and 89 years of age: 0.1% at the spine and 0.3% at the femur in males and 0.4% at the spine and 0.6% at the femur in females [24].