



Osteoporosis After Blood and Marrow Transplantation: Clinical Aspects

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Osteoporosis • Bone marrow transplantation • Osteopenia • Late effects

INTRODUCTION

As the number of long-term survivors of bone marrow transplantation (BMT) increases, attention must turn to the late complications of this procedure. One such late complication is osteoporosis, a decrease in skeletal bone mass. In the short term, osteoporosis seems trivial compared with a diagnosis of cancer, but for those cured of their disease, this condition contributes to chronic morbidity and mortality. For example, hip fractures resulting from osteoporosis are associated with long periods of immobility and restrict the patient's lifestyle. Fifty percent of patients who sustain an osteoporosis-related hip fracture require assistance with activities of daily living, and 25% require placement in long-term care facilities [1]. Osteoporotic hip fractures also affect patient mortality. Elderly patients who suffer an osteoporosis-related hip fracture have an increased 1-year mortality rate of 12% to 37% [2]. Early recognition and treatment of osteoporosis should therefore be integral components of the follow-up of long-term BMT survivors.

DEFINITIONS

Osteopenia is a systemic condition characterized by a reduced bone mass and increased susceptibility to bone fracture. Osteoporosis is a more severe reduction in bone mass and a greater susceptibility to bone fracture. These conditions are differentiated by the degree of reduction in bone mass and can be quantified by T and Z scores. The T score relates a patient's bone mass to the peak bone mass of a healthy young adult. A T score of 0 represents mean peak adult bone mass, and a T score of -1 represents bone mass of 1 standard deviation below this mean. Using this scoring system, osteopenia is defined as a T score between -1 and -2.5. Osteoporosis is defined as a T score below -2.5. The Z score is similar to the T score but uses mean bone mass

from an age- and sex-matched control as the reference value. T and Z scores can be translated into risk of fracture. The relative risk of fracture doubles for every standard deviation below adult peak bone mass [3]. Thus, a T score of -1 indicates a 2-fold increase in fracture risk, and a T score of -2.5 indicates a 5-fold increase in fracture risk.

The actual incidence of fracture depends on the age and sex of the patient as well as on the bone density. De Laet et al. [4] related the Z score, age, and sex of the patient to the incidence of fracture in an elderly Dutch population. Based on their calculations, a 65-year-old woman with a Z score of -2.5 had a 1-year risk of hip fracture of 1%. If this patient maintained the same bone density over time, her 1-year fracture risk increased to 5% by 80 years of age. Because most BMT recipients are under the age of 60, their absolute risk of fracture is low at the time of initial evaluation. However, as they age, their fracture risk increases to significant levels, especially if there is further bone loss.

RISK FACTORS FOR OSTEOPOROSIS

The risk factors for osteoporosis among BMT survivors can be divided into general risk factors, risks related to the underlying disease, and risks attributable to the BMT and its complications (Table 1).

General risk factors for osteoporosis include older age [5], a thin body habitus [6,7], and a family history of osteoporosis [8] or low-trauma fractures [7]. Smoking [9,10], physical inactivity [7], and a diet low in calcium or vitamin D [7] also reduce bone density.

The patient's underlying disease can also contribute to a reduced bone density. For example, multiple myeloma is associated with systemic osteoporosis as a result of increased osteoclast activity [11]. In a study of 25 patients with myeloma [12], 48% had osteoporosis in the lumbar

Table 1 . Risk Factors for Osteoporosis in BMT Patients

General Risk Factors	
	Older age
	Thin body habitus
	Family history
	Smoking
	Physical inactivity
	Diet
Underlying Disease	
	Myeloma
	Hodgkin's disease
	Non-Hodgkin's lymphoma
	Acute lymphoblastic leukemia
	Chronic lymphocytic leukemia
	Acute promyelocytic leukemia
BMT	
Early	
	High-dose chemotherapy
	Marrow reinfusion
	Medications (glucocorticoids, cyclosporine, granulocyte colony-stimulation factor)
Late	
	Hypogonadism

spine or femur. Patients with stage III or IV disease had a lower bone density than those with stage I or II disease. By multiple regression analysis, cumulative prednisone dosage correlated with decreased bone density. Patients treated for Hodgkin's disease are also at risk for decreased bone density. In a study of 29 men with a mean age of 35 years treated for Hodgkin's disease with chemotherapy + radiation, the mean Z scores of the lumbar spine and femoral neck were -0.7 and -0.4, respectively [13]. The exact incidence of osteoporosis is unknown for this group, because the T scores were not reported. However, 14 of 29 patients had Z scores less than -1.0 in the femoral neck or lumbar spine. Decreased bone density also has been reported after chemotherapy for acute lymphoblastic leukemia [14], and chronic lymphocytic leukemia [15] probably secondary to the induction chemotherapy and the prednisone. High doses of retinoids can induce osteoporosis [16], so patients treated with all-trans retinoic acid for acute promyelocytic leukemia are also probably at risk for decreased bone density.

Autologous and allogeneic BMT predisposes to the loss of bone mineral density through both early and late mechanisms. Evidence exists for an immediate effect of the high-intensity chemotherapy and marrow reinfusion on bone turnover [17,18]. Serum osteocalcin, a marker of bone formation, is reduced from the day of marrow infusion and remains low for 12 weeks after BMT [17]. Furthermore, cross-linked type 1 collagen, a marker of bone resorption, is increased during the first 3 weeks after BMT and remains elevated for 12 weeks [17]. The mechanism by which BMT alters bone metabolism is not entirely clear. Potentially, the high-intensity chemotherapy associated with transplantation damages the osteoblasts and their precursors. Alternatively, the bone loss may be mediated by cytokines released at the time of transplantation. For example, BMT is known to

stimulate the release of tumor necrosis factor, which inhibits osteoblasts and stimulates osteoclasts [19,20].

Medications used around the time of BMT also contribute to the early reductions in bone density. Glucocorticoids are used in the treatment of acute and chronic graft-versus-host disease after allotransplantation. In addition, patients with myeloma, lymphoma, and Hodgkin's disease who undergo autotransplantation are likely to have heavy steroid exposure as part of their induction and salvage regimens. By univariate and multivariate analysis, Ebeling et al. [21] reported that steroid use before BMT and cumulative steroid doses after BMT are associated with decreased bone density. Steroids reduce bone density through multiple mechanisms. These agents inhibit bone formation by inhibiting osteoblast function and differentiation of osteoblast precursors into mature osteoblasts [22,23]. Steroids also increase bone resorption by increasing parathyroid hormone production, which stimulates osteoclast activity [24]. Steroids, by inhibiting luteinizing hormone, follicle-stimulating hormone, and androstendione production, inhibit sex hormone production [25].

Cyclosporine, used to treat graft-versus-host disease, is associated with a reduction in bone mineral density by decreasing body stores of magnesium [26]. Magnesium is a major component of bone and is required for the hydroxylation of vitamin D in the liver.

Administration of granulocyte colony-stimulating factor (G-CSF) also decreases bone density. Long-term G-CSF administration can induce osteoporosis in patients with congenital neutropenia [27]. Similar results can be seen in transgenic mice overexpressing G-CSF [28]. Short-term exposure to G-CSF alters biochemical markers of bone turnover. Six days of G-CSF administration decreases serum osteocalcin in BMT patients and marrow donors. Osteocalcin levels decline within the first 3 days of G-CSF administration and return to normal within 2 days of cessation [29]. In addition to impairing bone formation, short term G-CSF exposure also increases bone resorption. Urinary deoxypyridinoline, a marker of bone resorption, is increased from the first day of G-CSF administration and remains elevated for 7 days after stopping G-CSF [29]. In mice, 7 days of G-CSF treatment increases the number of mature osteoclasts in bone. Although the short-term exposure to G-CSF increases bone metabolism, as demonstrated by serum and urine markers, it is unknown whether these temporary changes translate into decreased bone density.

The late effects of BMT on bone density are due primarily to gonadal damage caused by the transplant. Alkylating agents and total-body irradiation used in the high-intensity regimen before BMT damage the ovaries [30,31] and the testes [32,33]. As a result of damage to the ovaries, all women become menopausal immediately after BMT [30,31,34]. Women who are younger than 25 years at transplantation and who do not receive total-body irradiation are likely to regain cyclic estrogen secretion after autotransplantation, but all others usually remain menopausal [34]. Thus, many women are rendered permanently menopausal at a young age and are at risk for significant bone loss.

In the general population, women who become menopausal experience an accelerated rate of bone loss. Bone mineral density decreases by approximately 5% within the

first 2 years of menopause, but this bone loss can be prevented by hormone replacement therapy [35].

As a result of testicular damage induced by the high-intensity regimen before BMT, men may become deficient in testosterone. We have reported that 38% of men have decreased testosterone after autotransplantation [36]. The lack of testosterone produces a decline in bone mass similar to the loss of estrogen [37]. Unlike our observations in women, the testicular damage does not appear to be reversible [36].

INCIDENCE OF OSTEOPOROSIS IN BMT SURVIVORS

Several studies have documented the incidence of osteopenia or osteoporosis after BMT. Many patients have lost bone density before BMT, but further losses occur after the transplantation. Valimaki et al. [38] studied 44 adults (22 women and 22 men) before and after allotransplantation. The median age of the patients was 40 years. At the time of initial evaluation before BMT, 39% of patients had evidence of osteopenia or osteoporosis in the lumbar spine, and 25% of patients had evidence of osteopenia or osteoporosis in the femoral neck. One year after BMT, the percentage of patients with osteopenia or osteoporosis in the lumbar spine or femoral neck increased to 50% and 45%, respectively. One year after BMT, there was a mean loss of bone density in lumbar spine and femoral neck of 3.5% and 8%, respectively. Comparable results were obtained by Sullivan et al. [39], who studied a similar population.

Castaneda et al. [40] studied bone density in 27 menopausal women a mean of 33.6 months after BMT. The mean age of the patients was 31.3 years. Fourteen patients had undergone allotransplantation, and 13 received an autotransplant. At the time of evaluation, 9 of 27 (33%) had osteopenia at the lumbar spine, and another 5 of 27 (18%) had osteoporosis. Only 1 woman received hormone replacement therapy (HRT) at the time of evaluation, and none received calcium or vitamin D supplements. Because bone density tests were not performed before transplantation, it is not known how much of the bone loss is attributable to the BMT. In a smaller study, Castelo-Braco et al. [41] reported on 13 women 13 months (mean) after BMT. Eight women underwent autotransplantation, and 5 received an allotransplant. All 13 women were menopausal after BMT, and none received HRT at the time of initial evaluation. Nine of the 13 (70%) had evidence of osteopenia or osteoporosis in the lumbar vertebrae.

Recently, we studied the incidence of decreased bone mineral density among autotransplantation patients at our institution [42]. We evaluated bone density at the lumbar spine and femoral neck in 33 of 35 consecutive patients (17 women and 16 men) attending our Autotransplant Long-term Follow-up Clinic. Patients, median age 50 years, were evaluated a median of 4.4 years after autologous BMT. At the lumbar spine, 11 of 33 patients (33%; 4 men and 7 women) had osteopenia, and 1 man (3%) had osteoporosis. At the femoral neck, 15 patients (45%; 7 men and 8 women) had osteopenia, and 5 (15%; 2 men and 3 women) had osteoporosis. No patient sustained a bone fracture after autotransplantation. By univariate and multivariate analysis, only older age at evaluation was predictive of decreased bone density. Thus, most of our patients have decreased

bone mineral density after autotransplantation, and men and women are equally affected.

Ebeling et al. [21] followed bone density changes in 39 patients (19 women and 20 men) prospectively for 1 year after auto- or allotransplantation. They compared bone density before and after transplantation. Among the autotransplant recipients, bone density in the lumbar spine and femur was essentially normal before transplantation and did not decrease after BMT. In contrast, bone density was lower among the allotransplant recipients before transplantation and was decreased by 2% and 10% in the vertebrae and femoral neck bone, respectively, 1 year after BMT. Bone loss correlated with cyclosporine use and the cumulative prednisone dose. The lack of osteopenia and osteoporosis among autotransplantation patients stands in contrast to the other reports [40-43]. This difference may be due in part to the early use of estrogen replacement by Ebeling et al. [21]. All women received HRT starting 2 months after autotransplantation. The authors also did not comment on calcium and vitamin D supplemental intake by their patients.

The risk of bone fracture after BMT is not well characterized. Rib and vertebral fractures have been reported as ranging from 1% to 9% [21,39,43]. As the number of older long-term BMT survivors increases, a greater appreciation of the incidence of osteoporosis-related bone fractures after transplantation is likely.

EVALUATION OF BONE DENSITY

Currently, bone density is typically evaluated by dual-energy x-ray absorptiometry. In this procedure, a low-intensity x-ray beam rapidly scans the desired sites. Based on the amount of x-ray transmission through the bone, the bone density is calculated. The bone density is compared with normal values from healthy young adults and age- and sex-matched controls to derive the T and Z scores, respectively. In practice, the most common sites for evaluation are the femur and the lumbar spine. These sites are chosen because they represent common sites of osteoporotic fractures. When interpreting the results of bone density for the lumbar spine, it is important to remember that the bone density can be falsely elevated by degenerative disease of the spine [44].

Bone turnover can be measured by serum and urine markers such as urinary hydroxyproline and serum osteocalcin. In postmenopausal women, biochemical markers of bone metabolism have been shown to correlate with results of bone densitometry [45,46]. These markers can also predict who will respond to bisphosphonate treatment for osteoporosis [47]. Nonetheless, biochemical markers are not widely used outside the research setting. In part, the lack of acceptance stems from a lack of consensus on when to order these tests and how to incorporate the results into treatment algorithms. Furthermore, these tests are expensive and can be performed only in specialized laboratories. Currently, these markers are not required and are not sufficient to diagnose osteoporosis or osteopenia. Since biochemical markers of bone turnover identify patients at risk for bone loss before changes in bone density occur, perhaps future patients will be selected for treatment based on biochemical evidence of bone turnover before there is any loss of bone density.

Table 2 . Secondary Causes of Osteoporosis

Medications
Glucocorticoids
Antiepileptic drugs
L-Thyroxine
Heparin
Endocrine disorders
Hyperparathyroidism
Hyperthyroidism
Cushing's disease
Premature gonadal failure
Hematologic disorders
Multiple myeloma
Hodgkin's disease
Non-Hodgkin's lymphoma
Gastrointestinal disorders
Malabsorption syndromes
Chronic liver disease
Rheumatologic disorders
Rheumatoid arthritis
Ankylosing spondylitis

In the general population, the initial evaluation of osteoporosis or osteopenia includes a screen for secondary causes of osteoporosis (Table 2). Investigations include measurement of serum calcium, alkaline phosphatase, and thyroid-stimulating hormone. A complete blood count and serum immunoglobulins are also recommended. The yield of these investigations among BMT survivors is unknown, but it seems reasonable to order these tests to define their usefulness.

TREATMENT AND PREVENTION

The treatment and prevention of osteoporosis include lifestyle modifications and medical therapy. Patients should be advised to stop smoking, reduce alcohol consumption, and engage in regular low-impact exercise.

Most of the recommendations on the treatment and prevention of osteoporosis are based on the general medical literature. Few studies have examined the impact of medical therapy on the prevention and treatment of osteoporosis after BMT. Castelo-Braco et al. [41] evaluated the impact of HRT on bone density after transplantation. They examined the effects of HRT in 13 menopausal women after auto-transplantation or allotransplantation. The median age of the 13 women was 29.9 years. All patients had an increase in their bone density at the lumbar spine after 1 year of HRT. The median increase in bone density was 8.9%, with a range of 0.65% to 11%. This study contained too few patients to examine the impact of HRT on fracture rate after BMT. However, a study in postmenopausal women demonstrated that HRT increases mean bone density in the spine by 5.1%, which translated into a 39% risk reduction in fracture rate [48]. The ideal time to commence HRT is within the first 3 years of the onset of menopause, because this is the period of most rapid bone loss [35,49]. The optimal dura-

tion of HRT is unknown, but whenever HRT is stopped, the accelerated rate of bone loss returns [48]. Therefore, lifelong replacement therapy might be required. Because all women undergoing BMT become menopausal immediately after transplantation, consideration should be given to starting all women on HRT after transplantation.

A concern regarding HRT in this population is the potentially increased risk of breast cancer. The studies on the risk of breast cancer from HRT are contradictory, but any increase in the risk of breast cancer is small [50-52]. Fortunately, BMT itself does not increase the risk of breast cancer [53]. However, patients with a history of Hodgkin's disease and mantle radiation therapy already have a particularly high risk, with a 35% lifetime risk of breast cancer [54]. For patients with a high risk for breast cancer, the selective estrogen agonist raloxifene is an attractive alternative to estrogen. Raloxifene increases bone density and does not stimulate the proliferation of breast or endometrial tissue [55,56]. Before raloxifene becomes more widely used, studies must show that it decreases fracture rate in addition to increasing bone mineral density.

The effects of fluoride exemplify the importance of demonstrating that a therapy decreases the fracture rate as well as increases the bone mineral density. Fluoride stimulates bone formation through an unknown mechanism. Fluoride supplementation results in large increases in bone density, but it has little, if any, effect on the fracture rate [57-59]. The reason for this discrepancy is unknown. Because of its lack of benefit on fracture rate, fluoride is no longer widely used in the treatment of osteoporosis.

Calcitonin is a peptide normally synthesized by the thyroid C cells. It inhibits osteoclasts and thereby decreases bone resorption [60]. In early postmenopausal women, the intranasal form of calcitonin has not been shown to prevent bone loss [61]. In 1 study in older postmenopausal women, calcitonin decreased the number of fractures, but the absolute number of fractures in the study was small [62]. Therefore, because of the expense and questionable benefit of calcitonin, it is not generally used for the prevention or treatment of osteoporosis. It does, however, have a role in the treatment of pain from an acute vertebral fracture [63].

Deficiencies of calcium and vitamin D lead to increased parathyroid hormone production and subsequent bone loss. In a randomized trial of 389 healthy subjects older than 65 years, calcium and vitamin D supplementation increased bone density and decreased the incidence of nonvertebral fractures [64]. Other studies have confirmed these findings [65].

Valimaki et al. [38] conducted a randomized trial of calcium, calcium and intranasal calcitonin, or placebo in 61 adults after allotransplantation. Treatment was started at the time of BMT and continued for 1 year. Compared with placebo, calcium with or without intranasal calcitonin did not prevent bone loss after BMT. The lack of effect of therapy in this trial may be multifactorial. First, most trials that examine the effects of calcium on bone density also include a supplement with vitamin D. Second, the women in this trial did not receive HRT. Finally, the patients who experienced GVHD required treatment with steroids. In the face of steroid use and estrogen deficiency, calcium and calcitonin may not be sufficient to prevent bone loss. To

Table 3 . Treatment Approach for Osteopenia and Osteoporosis

T score -1 to -2.5
Lifestyle modification
Calcium and vitamin D supplements
Hormone replacement therapy if hypogonadal (estrogen, testosterone, raloxifene)
T score <-2.5
As above and
Bisphosphonates

date, only bisphosphonates have been shown to prevent steroid-induced bone loss [66].

Bisphosphonates are pyrophosphate analogs that inhibit osteoclast function by increasing osteoclast apoptosis. Bisphosphonates decrease bone fractures and increase bone density in patients with osteoporosis. In a randomized trial, the bisphosphonate alendronate prevented bone loss and decreased bone turnover in patients receiving long-term, low-dose glucocorticoids [66]. Alendronate is poorly absorbed and has a potentially serious side effect of severe esophagitis [67]. Therefore, it must be taken with a full glass of water 30 minutes before a meal. After taking alendronate, the patients must then remain upright for 30 minutes. Etidronate, a less potent bisphosphonate than alendronate, also is widely used in the treatment of osteoporosis in the general population. Like alendronate, etidronate increases bone density in patients with osteoporosis [68,69]. Etidronate is given in a cyclical schedule: 14 days of etidronate followed by 76 days of calcium supplementation. The absorption of etidronate is reduced by calcium. Therefore, foods with a high calcium content should not be consumed within 2 hours of taking etidronate.

CONCLUSION

Based on the available evidence, we make the following recommendations to our patients regarding the treatment and prevention of osteoporosis (Table 3). We advocate early detection and aggressive treatment to prevent osteoporosis. We recommend that bone densitometry be performed as part of the pretransplantation evaluation to assess the degree of bone loss before transplantation. After transplantation, we repeat the bone densitometry yearly for at least the first 2 years. In patients with decreased bone mineral density, we continue yearly bone densitometry. In patients with well-preserved bone density, the densitometry can be repeated every 3 to 5 years. However, the scans are obtained earlier if the patient acquires new risks for bone loss.

Patients with a T score of -1 to -2.5 in either the femur or the lumbar spine are offered lifestyle counseling. They are encouraged to quit smoking, adopt a high-calcium diet, and commence regular low-impact exercise. In our program, lifestyle counseling is provided by the clinic nurses. In other centers, special multidisciplinary osteoporosis clinics have been created, which include dietitians, physical therapists, and pharmacists. For patients with

osteopenia, we recommend supplementation with calcium (1500 mg/day) and vitamin D (400 IU/day). We also suggest that menopausal women commence HRT. Women who have a history of Hodgkin's disease or mantle radiation or who have an increased risk for breast cancer are offered raloxifene instead. Men with decreased testosterone are given testosterone replacement therapy either intramuscularly or transdermally. For patients with a T score less than -2.5, we offer the latter therapy in addition to alendronate (10 mg/day). Patients with myeloma may substitute monthly intravenous pamidronate or daily oral clodronate for alendronate. Both pamidronate and clodronate decrease skeletal events in patients with myeloma. The choice between pamidronate and clodronate is mainly determined by availability and cost as well as by patient and physician preferences.

In conclusion, osteopenia and osteoporosis are common complications of BMT. Many patients have significant bone loss before transplantation and experience further decreases in bone density after transplantation. Since early recognition and aggressive treatment of bone loss can prevent bone fracture, we suggest that bone densitometry and aggressive preventive therapy should be integral components to follow-up of long-term BMT survivors.

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