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REVIEW

Bone management in hematologic stem cell transplant recipients

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Abstract

Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with some malignant and non-malignant hematological diseases. Advances in transplantation techniques and supportive care measures have substantially increased the number of long-term HSCT survivors. This has led to an increasing patient population suffering from the late effects of HSCT, of which, bone loss and its consequent fragility fractures lead to substantial morbidity. Altered bone health, with consequent fragility fractures, and chronic graft-versus-host disease (GVHD) are factors affecting long-term quality of life after HSCT. Hypogonadism, HSCT preparative regimens, nutritional factors, and glucocorticoids all contribute to accelerated bone loss and increased fracture risk. Management strategies should include bone mineral density examination, evaluation of clinical risk factors, and general dietary and physical activity measures. Evidence has accumulated permitting recommendations for more attentiveness to evaluation and monitoring of bone health, with appropriate application of osteoporosis pharmacotherapies to patients at increased risk of bone loss and fracture.

Keywords Bone loss · Bone marrow · Bone mineral density · Fracture · Hematopoietic stem cell · Transplantation

Introduction

Autologous or allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients with some malignant and non-malignant hematological diseases. HSCT has substantially increased the number of long-term survivors of hematologic malignancies, secondary to advances in transplantation techniques and supportive care measures. As a consequence, early and late complications of HSCT have achieved greater importance. Bone loss and its clinical

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manifestation of fragility fractures is an important long-term complication leading to substantial morbidity [1].

HSCT-related bone loss is multifactorial and incompletely understood, occurring through a complex interaction of pre-, peri-, and post-HSCT factors [2]. The complex interplay of cytokines belonging to the tumor necrosis factor (TNF) superfamily, the receptor activator of nuclear factor-kappa B ligand (RANKL), and osteoprotegerin (OPG) [3] leads to an imbalance between bone formation and resorption with resulting bone loss [4] before and after the HSCT procedure. Risk factors may be physiologic (aging, menopause in women, decline in androgen levels in men) or be related to HSCT preparative regimens or graft-versus-host disease (GVHD) prevention and treatment (Table 1) [14]. For example, glucocorticoids are the best example of drug-induced perturbation of the RANKL/OPG pathway promoting bone loss [9]. Glucocorticoids can both increase bone resorption and decrease bone formation in a dose- and duration-dependent manner. Factors other than glucocorticoid use can promote bone loss post-HSCT, including hypogonadism (secondary to chemotherapy and total body irradiation), secondary hyperparathyroidism due to poor calcium and vitamin D nutrition, and the effects of chemotherapy-induced toxicity to bone cells and, importantly, bone marrow stromal cells.

Epidemiology of osteoporosis and fracture in adult patients undergoing HSCT

Adult HSCT recipients generally are younger than patients with postmenopausal osteoporosis, usually with a relatively short pre-existing illness [15]. Overall, the prevalence of osteoporosis and osteopenia is relatively low at 4% and 24%, respectively, when measured after chemotherapy, but prior to HSCT [16]. The prevalence of osteopenia in adults with HSCT is close to 50% after 4–6 years; that of osteoporosis approaches 20% by 2 years after HSCT [17]. In studies of long-term allogeneic HSCT, a large portion (52%) of HSCT survivors has osteopenia at the femoral neck [18–20]. More than 50% of patients undergoing allogeneic or autologous HSCT suffer bone loss over the long term [11]. Variable bone loss, often rapid, may occur at the proximal femur, less at the spine, in the first 12 months, particularly after allogeneic HSCT [15, 21, 22]. At 1 year after allogeneic HSCT, lumbar spine bone mineral density (BMD) decreased by 4.8%, and total proximal femoral BMD decreased by 12.3%. The lumbar spine bone decrease was correlated to increased serum IL-6 and TNFα by 3 weeks after HSCT [23]. The decline in spine BMD is associated with the cumulative glucocorticoid and cyclosporine dose. Patients with acute GVHD ≥ grade II had greater spine bone loss than patients with GVHD ≦ grade I [23]. In contrast, after autologous HSCT, although femoral neck bone loss is less (4%), it is not recovered after 2 years, while spine BMD returns to baseline [24]. In a prospective series of 180 autologous HSCT patients followed for a median of 5.4 years and compared with 20 patients who received only chemotherapy, the BMD decrease was greater in older patients but was also seen in younger patients: 35% of patients aged 25–35 years and 77% of those aged over 55 years had T-scores of < -1. Bone loss was greatest in the first year after autologous HSCT, with the incidence of osteopenia/osteoporosis reaching 65% in the HSCT population vs. 5% in the control population. Some recovery was noted for spine and radius BMD beginning 2 years after autologous HSCT with maintenance of BMD thereafter [5]. Autologous HSCT differs from allogeneic HSCT in that GVHD does not occur and long-term glucocorticoid use is much less frequent [25].

Fracture risk is increased after HSCT. A large retrospective study of 7620 patients undergoing HSCT over 15 years showed 8% (602 patients) sustained fractures. Risk factors for fracture included age older than 50 years, multiple myeloma, a solid tumor, or an allogeneic HSCT. The relative risk was increased eightfold and seven- to ninefold, in women and men, respectively, compared with 45- to 64-year-old individuals from two population-based cohorts [26, 27]. A substantial number of patients with multiple myeloma, who are known to be a risk of fracture independently of transplant, were included in this study [28]. The risk was higher in allogeneic than in autologous HSCT [27]. In another retrospective cohort study of 4160 control cancer patients and 1040 cancer patients who underwent HSCT, the risk of fracture was 1.4 times higher in the HSCT group compared to the non-HSCT group. Vertebral fracture was the most common fracture site in the HSCT group (68.4% of fractures) [29]. Other studies suggest that fracture risk may not be increased after an allogeneic HSCT; however, the cohorts were small and under-powered and the non-capture of asymptomatic fractures could not be ruled out [30].

Multiple myeloma presents its own unique concerns, both from the lytic bone lesions and from generalized bone loss related to the disease and its treatment. Generalized bone loss can result from cytokine activation of osteoclasts with decreased osteoblastic activity. Chemotherapy and autologous stem cell transplantation are common treatment modalities; less often allogeneic HSCT is utilized. Intravenous bisphosphonates are of clinical benefit in the treatment of bone disease in patients with multiple myeloma, first reported with pamidronate infusions where there were benefits to hypercalcemia, pain, quality of life, fractures, and overall survival [31]. Zoledronic acid was demonstrated more effective than pamidronate and recently, monthly denosumab injections have been shown to give similar benefits to zoledronic acid infusions [32].

Immunological factors

The interaction between hematopoietic bone marrow cells and bone cells has become a subject of intense interest in recent

Table 1 Risk factors for bone loss pre- and post-stem cell transplantation

Pre-HSCT risk factors	Post-HSCT risk factors
Advanced age [5]	Graft-versus-host disease [6]
Female sex [5]	Calcium and vitamin D insufficiency leading to secondary hyperparathyroidism [7]
Chemotherapy [8]	Glucocorticoids [9]
Hypogonadism [10]	Renal dysfunction [11]
	G-CSF treatment [12]
	Renal wasting of calcium or magnesium [13]

years, referred to as osteoimmunology [33, 34]. A cross-talk between the immune system and bone is well recognized with systemic and local bone loss as a consistent consequence of infection, inflammation, and autoimmune disorders [35].

Osteoclast differentiation is facilitated by bone marrow stromal cells, which provide physical support for nascent osteoclasts and produce soluble and membrane-associated growth factors [36]. Two necessary cytokines required for osteoclast formation are RANKL and macrophage colony-stimulating factor (M-CSF), which are primarily produced by bone marrow stromal cells, osteoblasts, and activated T cells [37]. RANKL is a TNF superfamily member, which exists in membrane-bound and soluble forms. It is produced by osteoblasts and binds to the transmembrane RANK receptor on osteoclasts and osteoclast precursors. Osteoprotegerin (OPG), secreted by osteoblasts and numerous hematopoietic cells, acts as a decoy receptor for RANKL and thereby inhibits osteoclast activation. The balance between RANKL and OPG controls bone remodeling [37].

Other cytokines are responsible for the upregulation of osteoclast formation in several pathologic conditions such as inflammation, cancer, and estrogen deficiency. The most important one is TNFα, which upregulates the stromal cells production of RANKL and M-CSF [38] and increases the responsiveness of osteoclast precursors to RANKL [39]. TNFα not only increases osteoclast formation and stimulates osteoclast activity [40] through a direct action independent of RANKL [41], but also inhibits the osteoblastogenesis, by blocking the differentiation of new osteoblasts from their progenitors and suppressing mature osteoblast function [42].

Among other cytokines, IL-1 promotes RANKL expression by bone marrow stromal cells and osteoblasts and stimulates osteoclast lifespan and activity [43]. IL-7 is a powerful lymphopoietic cytokine that may induce bone loss by T cell- and B cell-mediated mechanisms [44]. Initially described as an anti-osteoclastogenic cytokine (because of its power to inhibit osteoclastogenesis in vitro) [45], IFNγ promotes bone resorption and causes bone loss in disease experimental models and in several conditions in humans [46]. IL-23 has recently been linked to inhibition of osteoclast formation, by presumably inhibiting the activity of osteoclastogenic Th17 lymphocytes [47]. In patients with autologous or allogeneic HSCT, bone turnover markers and inflammatory cytokines are increased [23]. The closer the proximity of chemotherapy to HSCT is, the greater the magnitude of bone loss at the hip [48].

Recently, genetic variants (SNP) have been associated with accelerated declines in bone density after HSCT [49]. Sixteen SNPs were associated with spine or femoral BMD loss, three of which have been previously implicated in genome-wide association studies of bone phenotypes (COL1A1, RANKL, and ESR1).

Osteoimmunology also encompasses the relationship between mesenchymal stem cell systemic infusion and its effect on bone cells and GVHD. Early reports suggest a beneficial effect of mesenchymal stem cell infusion on GVHD, possibly leading to less need for glucocorticoid therapy and potentially less bone loss [50]. Some preclinical studies have shown that allogeneic mesenchymal cell therapy promotes osteoblastogenesis and prevents glucocorticoid-induced osteoporosis [51]. Clinical trials of MSC therapies that involve different diseases and conditions such as osteoporosis and GVHD are ongoing. Due to the immunomodulation and immunosuppressive properties of MSCs, MSC infusion may play a role in bone health in the future [52].

Features promoting bone loss in HSCT patients

Over the last 10 years, survivorship of patients undergoing HSCT has improved due to advances in supportive care and HSCT techniques. This has led to an enlarging and older patient population more likely to experience the late effects of HSCT, of which, bone loss and fractures lead to substantial morbidity.

Bone metabolic changes

The pattern and type of bone disease following HSCT differs from other forms of osteoporosis occurring after transplantation of solid organs, due to the younger age of recipients and the possible effect of the underlying hematologic disease and its treatment [15, 17]. Reports on HSCT and bone loss incorporate various hematologic disorders and to date, there are no reports that distinguish the risk of bone loss according to the underlying hematologic disease.

Bone loss occurs at all skeletal sites, but is greatest at the proximal femur [53]. It takes place during the first 3 to 12 months after HSCT, with marked declines in bone density especially at femoral site detected within the first 100 days post-allogeneic HSCT [22, 54]. Thereafter, a slow and incomplete recovery of bone density may take place at the femur

over months to years, depending on patients' other risk factors and therapies [55].

A two- to threefold reduction in progenitor cells in the bone marrow of auto- and allo-HSCT recipients compared to normal donors is observed after HSCT and may contribute to the mechanism of bone loss [56]. A marked and permanent quantitative and qualitative defect in marrow osteogenic cells has been reported, suggesting that inability to store a normal number of osteoblast precursors in the bone microenvironment may account at least in part for severe bone loss after both auto- and allo-HSCT [14]. The reduced repopulating capacity of osteoblast precursors is a multifactorial process likely related to effects of chemotherapy/radiotherapy, endocrine disorders, immunosuppressive therapies, and altered balance of cytokines and growth factors.

In some solid tumors, multiple myeloma, and certain types of lymphoma, there is a propensity for spread and growth in the bone through the formation of osteolytic bone lesions [57, 58]. These tumors produce cytokines, which enlist normal host osteoclasts to resorb bone. Granulocyte colony-stimulating factor (G-CSF) is secreted by osteoblasts and stimulates osteoclastogenesis in vivo and in vitro, but at a much lower rate than other colony-stimulating factors (M-CSF and GM-CSF). G-CSF support after high-dose chemotherapy and G-CSF hematopoietic cell mobilization are often part of standard HSCT therapeutic regimens, and its administration not only mobilizes granulocytes, but also increases the numbers of osteoclast precursors and osteoclasts. Short-term G-CSF thus induces osteoclastic bone resorption and may be a factor in the pathogenesis of osteoporosis following HSCT [12].

Kidney-liver dysfunction, vitamin D, and hypogonadism

Recipients of allo-HSCT may experience renal dysfunction and altered vitamin D metabolism, in various degrees resulting from HSCT and its related therapies (cyclosporine, amphotericin). Non-malignant late effects of HSCT on liver function can be seen including chronic GVHD or consequences of iron overload. Altered kidney and liver function as well as gastrointestinal symptoms lead to a reduced intake and altered metabolism of calcium and vitamin D, sometimes resulting in secondary hyperparathyroidism and increased osteoclastic bone resorption [11].

There can be reduced serum levels of 25-hydroxyvitamin D_3 in the course of allo-HSCT by reduced sun exposure and vitamin D-deficient diets [11, 14]. A decline in estrogen in women and testosterone in men is associated with bone loss [59]. This is relevant as premature ovarian failure and hypogonadism are the most common long-term endocrine effects affecting young patients after HSCT. Ovarian failure occurs in 70–95% of young women after HSCT [60–62]. Secondary ovarian insufficiency in premenopausal women who receive chemotherapy or whole body irradiation is well established, with less than 30% recovering post-transplant [10, 55].

Role of glucocorticoids and calcineurin inhibitors

In most series, bone loss is more severe and occurs over a longer time frame after allo-HSCT than after auto-HSCT [24, 55]. Both transplant types are preceded by a similar intensity of conditioning. The main differences between these two approaches are related to the involvement of the immune system, as allo-HSCT is associated with a greater cytokine release, the possibility of GVHD, and the use of immunosuppressive treatments, all of which will predispose to greater bone loss [6, 63].

The use of chronic high-dose glucocorticoids is known to increase the risk of osteoporosis-related fractures [9]. The principal mechanisms responsible for induced bone loss are as follows: an increased apoptosis of osteoblasts and osteocytes; inhibition of osteoblast bone formation (reduced expression of TGF-β and inhibition of BMP2 and IGF-1 effects); decreased proliferation and differentiation of periosteal precursor cells.

Chemotherapy regimens used in most lymphoid malignancies include short courses of glucocorticoids. By contrast, the onset of GVHD in the post-transplant setting is the main reason for high-dose and prolonged glucocorticoid therapy. Many studies in long-term HSCT survivors have confirmed the correlation between bone loss and the use of glucocorticoids; patients on high-dose long-term glucocorticoids are candidates for early introduction of preventive measures, to maintain bone health [64].

Calcineurin inhibitors such as cyclosporine (CSP) and tacrolimus (FK506) contribute to bone loss associated with transplantation. Since glucocorticoids are usually co-prescribed with CSP, it has been difficult to define its contribution to clinical bone loss [14, 55]. CSP-induced bone loss occurs mainly at sites rich in cortical bone and is related to dose and duration of exposure. The exact mechanism of CSP's effects on osteoblasts and osteoclasts is still unclear. CSP induces higher bone turnover independent of renal function, decreases osteoblast proliferation, and decreases magnesium stores, important for vitamin D hydroxylation [65]. Recently, systemic lupus patients treated with CSP alone were found to have increases of FGF 23, which correlated with CSP cumulative dose, possibly etiologic in bone loss [66]. It remains debatable whether GVHD itself or its treatment in the form of glucocorticoid or cyclosporine has the greatest impact on bone health.

Radiotherapy and chemotherapy

Radiotherapy to bone has been associated with osteoporosis and increased bone fragility [67]. There is some evidence that

pelvic radiation reduces BMD by 11% at the femoral neck at 6 months in a prospective longitudinal study [68]. A full understanding of the pathophysiology underlying the radiation-induced bone loss is still missing, but cell cultures and preclinical studies have shown that irradiation increases osteoblast apoptosis and reduces osteoblast number, indicating that a decrease in bone formation may be an important contributor to bone loss [69]. Direct bone damage is mediated by increased osteoclast activity leading to increased bone resorption and porosity. There are also some data indicating that radiation can cause damage to bone matrix and the vascular supply to bone.

Patients receiving standard dose chemotherapy for hematological malignancies may be at risk of bone loss due to direct effects on osteoblasts. Some chemotherapy regimens (methotrexate, cyclophosphamide, and cisplatin) have a direct toxic effect on bone cell function [11, 14]. Methotrexate (MTX)-induced osteopenia has been widely studied in patients with rheumatoid arthritis; MTX has been shown to inhibit osteoblast proliferation and activity and stimulates osteoclast recruitment [70]. High-dose cyclophosphamide may induce nephrotoxicity and hypophosphatemia, also associated with decreased osteoblast activity [8, 71]. Cisplatin induces hypomagnesemia (causing decreases in 25-hydroxyvitamin D) and hypocalcemia (leading to increased parathyroid hormone (PTH) levels).

Role of conditioning

In most studies on long-term bone complications in HSCT, conventional myeloablative conditioning regimens were applied [72, 73]. Over the last 10 years, non-myeloablative or reduced intensity regimens (RIC) for HSCT have become more common, reducing treatment-related mortality and morbidity [74]. RIC-HSCT regimens are frequently used in older patients. There are no studies addressing whether less intensive chemotherapy will be less harmful to bone. However, this might be counterbalanced by the older age of recipients and the higher incidence of GVHD with consequent immunosuppressive treatments in RIC-HSCT [74].

Lifestyle habits and comorbidities associated with bone loss

There are numerous comorbidities and adverse lifestyle habits associated with bone loss and fracture in postmenopausal osteoporosis, many of which are FRAX risk factors. There are no published reports of the interaction of FRAX risk factors with the added risks of HSCT, though it might be assumed that risks such as smoking, alcohol, prevalent fracture, and rheumatoid arthritis might be additive in these patients.

Bone marrow imaging: current method and recent advances

Most malignant hematological disorders are associated with bone marrow (BM) infiltration. Magnetic resonance imaging (MRI) is a non-invasive method to assess the nature and content of BM, although the gold standard for evaluating BM infiltration is bone marrow biopsy [75]. T1-weighted sequences provide optimal differentiation between normal and pathological tissues (which have a high signal), allowing evaluation of the cellular content of BM, where the intensity of signal is directly proportional to the amount of fat in BM. T2-weighted sequences with fat suppression or STIR (short T1 inversion recovery) show a high signal in regions of high cellularity [76].

Immediately after HSCT, BM displays a low signal on T1-weighted sequences and a high signal on T2-weighted images, suggesting peri-treatment edema. After around 3 months, BM appears as a characteristic "target image" with a hyper-intense zone (at the region rich in fat) surrounded by a hypo-intense halo in T1-weighed sequences, representing the hematopoietic repopulation of the bone. Later, this signal difference disappears, and a year after allo-HSCT, the image becomes more homogeneous with conversion into fatty marrow. Such BM changes are likely reflective of a good recovery of BM function.

There are a number of MRI artifacts after HSCT. Allogeneic transplants may display a high signal on T1-weighted sequences. However, the type of HSCT, autologous or allogeneic, does not affect the MRI image [77].

Positron emission tomography with 18-fluorodeoxyglucose (18-FDG) integrated with computed tomography (PET-CT) evaluates metabolic functioning of tissues. PET-CT can estimate the extramedullary extent of hematological disease. Resolution of areas of tracer accumulation after HSCT is an indicator of survival [78].

Published guidelines for HSCT management

Guidelines for screening and prevention of bone loss for long-term HSCT survivors were published in 2006 by the European Group for Blood and Marrow Transplantation (EBMT), Center for International Blood and Marrow Transplant Research (CIBMTR), and the American Society for Blood and Marrow Transplantation (ASBMT) [79]. The recommendations were reviewed and updated in 2012 by an international group of experts including members from EBMT, CIBMTR, ASBMT and Asia-Pacific Blood and Marrow Transplantation Group, Bone Marrow Transplant Society of Australia and New-Zealand, East Mediterranean Blood and Marrow Transplantation Group, and Sociedade Brasileira de Transplantante de Medula Ossea [80]. As rapid bone loss

usually takes place 3–12 months post-transplantation, guidelines recommend dual X-ray absorptiometry (DXA) at 1 year after transplantation and at an earlier time point for patients with GVHD and prolonged glucocorticoids and/or calcineurin inhibitor exposure. All HSCT patients should also receive dietary and lifestyle advice, including calcium and vitamin D supplementation, physical activity, and fall prevention. Sex hormone therapy should be considered in menopausal women and in hypogonadal men. Bisphosphonate therapy should be considered in patients with osteoporosis or who are at high risk of bone loss and/or fracture.

Evaluation of patients pre-/post-HSCT

Despite a lower fracture risk in autologous than in allogeneic HSCT, the following guidances concern both types of HSCT, taking into account however that most of the therapeutic trials have been conducted in the latter.

Bone mineral density assessment

Dual-energy X-ray absorptiometry (DXA) is a measurement of areal BMD, used to diagnose osteoporosis on the basis of the T-score (T-score − 2.5 and below), comparing a patient's BMD with normative data from young women at peak bone mass. For children and adults aged < 50 years, Z-score (which is the comparison of the measured BMD with the mean BMD of an age-/gender-matched population) is the preferred method of reporting BMD [81]. Accepted sites for the diagnosis of osteoporosis include the femoral neck, total hip and spine (one-third radius, if hip or spine sites are not valid); the lowest score is used for diagnosis. The risk of fracture in older adults increases roughly twofold for each SD decrease in BMD [82].

FRAX®

Integrating clinical risk factors with BMD in assessing fracture risk [83], FRAX is an evidence-based calculation of a patient's 10-year probability of major osteoporotic fracture (spine, hip, forearm, and proximal humerus) and hip fracture. FRAX utilizes age, sex, body mass index, personal and family history of fracture, smoking, alcohol intake, chronic glucocorticoid use, rheumatoid arthritis, other causes of secondary osteoporosis, and femoral neck BMD. FRAX is widely used in the non-transplant setting to evaluate the need for therapy for osteoporosis. A recent retrospective review of FRAX for the prediction of fracture after HSCT showed that FRAX had a modest ability to predict osteoporotic fracture [84].

Bone turnover markers

Bone turnover is the principal factor influencing both the quality and the quantity of bone in the adult skeleton. High bone turnover in postmenopausal women leads to bone loss and altered bone microarchitecture. Bone turnover can be assessed indirectly by measuring biochemical bone turnover markers, categorized as bone formation markers (osteocalcin (OC), bone alkaline phosphatase (BAP), type 1 procollagen-N propeptide (P1NP)) and bone resorption markers (deoxypyridinoline (DPD), type 1 collagen cross-linked N-telopeptide (NTX), type 1 collagen cross-linked C-telopeptide (CTX), tartrate-resistant acid phosphatase 5b (TRAP 5b)), either in blood or urine. Bone turnover markers are an independent predictor of fracture risk, synergistic with BMD, but cannot be used to diagnose osteoporosis [85]. Bone turnover markers may be a useful tool to assess drug efficacy; serum CTX is markedly suppressed by antiresorptive therapy and serum P1NP shows an early and substantial increase to bone anabolic therapy with teriparatide [86]. CTX and P1NP are the preferred resorption and formation markers recommended to be used in all clinical trials [87]. However, the value of bone turnover markers in clinical practice is limited by intra- and inter-assay variability.

Vitamin D

Vitamin D deficiency is common in allo-HSCT patients [88]. This may be the result of decreased sunlight exposure from prolonged hospital stays, isolation, and low outdoor physical activity during chemotherapy. Gastrointestinal GVHD after HSCT may further limit absorption of vitamin D. Some medications such as calcineurin inhibitors, amphotericin, and glucocorticoids used in HSCT patients, as well as accompanying renal insufficiency, can interfere with vitamin D metabolism, leading to vitamin D insufficiency or impaired conversion of vitamin D to active metabolite vitamin D. In a retrospective study at MD Anderson Hospital (Houston, USA), Joseph et al. found that the median vitamin D level in patients undergoing transplantation was 16 ng/mL (40 nmol/L), with 70% of patients being vitamin D-insufficient [7]. Similarly, Urbain et al. [89] recently reported that in a cohort of allo-HSCT patients, 25-hydroxyvitamin D concentrations were 16.4 ± 8.9 ng/mL (41 nmol/L), with 89% of patients having insufficient levels. Moreover, vitamin D deficiency before HSCT was associated with an increased risk of GVHD [90]; vitamin D is known to play a role in the differentiation process of hematopoietic precursor cells [11].

Strategy

All candidates should be evaluated with DXA hip and spine as soon as HSCT has been planned. In older individuals or patients at risk, spine X-rays or vertebral fracture assessment by

DXA (VFA) should be performed to identify vertebral fractures. FRAX most likely underestimates fracture risk in this population. An evaluation of the common modifiable risk factors of osteoporosis and fractures should be undertaken. These include hyperparathyroidism, hypogonadism, smoking, use of loop diuretics and low intake of dietary calcium and protein, and vitamin D insufficiency [22]. Individuals with osteoporosis who are awaiting HSCT should be evaluated and treated similarly to others with osteoporosis. Follow-up DXA is recommended as early as 3 months post-HSCT in patients at high risk; lower risk patients may be followed with DXA at annual intervals. Screening intervals may be reduced or extended based on BMD measurement and the presence or absence of other risk factors (e.g., age, gender, low body weight, hypogonadism, time since transplantation, ongoing use of glucocorticoids).

Treatments considerations

Vitamin D and calcium

Calcium supplementation alone is not effective in preventing bone loss after HSCT [91]; however, an adequate intake of calcium (800–1200 mg/day) via dietary sources and/or supplements should be recommended. Vitamin D supplementation (at least 800 IU/day) is also recommended as vitamin D deficiency has a high prevalence and may contribute to low bone mass in patients after HSCT [92, 93]. In addition, the efficacy of osteoporosis medications has predominantly been demonstrated in the presence of vitamin D and calcium supplementation [94]. Therapy should achieve serum 25-hydroxyvitamin D levels of > 30 ng/mL (75 nmol per liter) [93]. An increase in cardiovascular risk in patients taking calcium supplements has not been validated in a recent meta-analysis of older individuals; cardiovascular risk related to calcium supplements has not been shown in HSCT patients [95]. Other non-pharmacological measures include regular weight-bearing physical activity, smoking cessation, and measures to prevent falls; efficacy of these measures has also not been assessed in HSCT patients.

Bisphosphonates

Bisphosphonates are the drugs that have been most often studied to prevent HSCT-induced bone loss. Therapeutic regimens varied widely and most of these studies include small and often heterogeneous populations and did not consider the T-score before therapy or other risk factors for fracture. Only seven randomized trials of antiresorptive therapy have been published (Table 2). The control group most often received calcium and vitamin D supplements alone. One study evaluated two different bisphosphonates [97]. Oral risedronate was used in two studies [54, 97], pamidronate in two [96, 98], and zoledronic acid in four [97, 99, 101, 102]. With the exception of the risedronate study, more intensive schedules than the ones shown to be effective for the treatment of postmenopausal osteoporosis have been used [103].

The majority of patients were enrolled in trials evaluating pamidronate. Kananen et al. randomized 99 patients prior to HSCT with or without 60 mg pamidronate infusions before and 1, 2, 3, 6, and 9 months after HSCT [96]. Lumbar spine BMD remained stable in the pamidronate group, but despite the relatively high doses of pamidronate, BMD still decreased at the femoral neck and total hip. Using even higher doses of pamidronate, comparable to the ones used for the treatment of bone metastases [104], Grigg et al. reported similar findings [98]. They randomized 116 patients to receive calcitriol and calcium with or without monthly 90 mg pamidronate infusions for 1 year. Pamidronate prevented BMD loss at the lumbar spine but BMD still declined at femoral neck and total hip, although the decrease was significantly less in the pamidronate group than in the control group. One year after therapy, only the BMD benefit at the total hip remained significant between the two groups. The infusion of three monthly doses of zoledronic acid (4 mg) after allogeneic HSCT increased both lumbar spine and femoral neck BMD at 12 months compared to pre-treatment BMD [97, 102].

In summary, bisphosphonates generally prevented bone loss [98, 101] or increased bone mass [97, 102]. A meta-analysis confirmed that bisphosphonates, and in particular, zoledronic acid, are promising in the prevention of HSCT-induced bone loss [28].

Although these studies have shown that bisphosphonates are well tolerated and can prevent or mitigate bone loss after HSCT, available data are insufficient to demonstrate the superiority of a specific agent or dosing schedule over another. The majority of studies have treated patients for 12 months but the optimal duration of therapy is unknown. Grigg et al. have shown persistence of bone loss after discontinuation of pamidronate [98]. Fracture data are not available in any of the studies.

Prophylactic treatment with bisphosphonates regardless of baseline T-score should be strongly considered, especially in patients receiving glucocorticoids for GVHD after HSCT, since these patients are at even higher risk for bone loss. Stern et al. showed that spine BMD did not predict fracture risk and, like glucocorticoid-induced osteoporosis, fractures may occur in patients with only slightly reduced T-scores [53]. Furthermore, the onset of bone loss may be rapid, occurring within the first months after HSCT.

Long-term bisphosphonate treatment may be associated with serious bone adverse effects with a very low incidence. Osteonecrosis of the jaw (ONJ) is defined as a bone exposure within the buccal cavity lasting for more than 8 weeks, which may occur more frequently after a tooth extraction or oral

Table 2 Randomized trials of therapies to prevent bone loss in HSCT patients: BMD results at 12 months post-transplant

Study author	Intervention	*n*	BMD lumbar spine (percent change)	BMD total hip (percent change)	BMD femoral neck (percent change)
Valimaki et al. 1999 [91]	Calcium/vitamin D versus intranasal calcitonin	12	− 4.1		− 8.2
		12	− 4.1		− 8.2
Tauchmanovà et al. 2003 [54]	Calcium/vitamin D versus risedronate 35 mg per week	17	− 3.1	− 4.1	− 4.2
		17	5.9	1.3	1.3
Kananen et al. 2005 [96]	Pamidronate 60 mg IV 0, 1, 2, 3, 6, 9 months plus estrogen versus estrogen alone	50	–	− 5.5	− 4.2
		49	− 2.9	− 7.8	− 6.2
Tauchmanova et al. 2006 [97]	Calcium/vitamin D versus estrogen versus risedronate versus zoledronic acid 4 mg monthly × 3	15	− 4.3		− 4.2
		15	–		–
		15	5.8		–
		10	8.6		5.4
Grigg et al. 2006 [98]	Pamidronate 90 mg IV monthly plus HRT plus calcitriol versus HRT plus calcitriol	63	2.1	− 3.1	− 2.3
		53	− 2.6	− 8.2	− 11
Hari P et al. 2013 [99]	Calcium/vitamin D versus zoledronic acid 4 mg 0, 3, and 6 months	29	− 5.0		− 6.0
		32	4.2		2.0
Grigg A et al. 2017 [100]	Pre-transplant zoledronic acid 4 mg IV followed by post-transplant zoledronic acid 4 mg IV determined by a risk-adapted algorithm	70			− 2.9

HRT hormone replacement therapy

surgery. The frequency associated with high-dose bisphosphonates for bony metastatic disease is estimated between 1 and 5% [105], but there are no data specific to HSCT patients. A recent review and international consensus of ONJ in patients on osteoporosis doses of bisphosphonate reported the frequency to be between 1 and 90 per 100,000 patient years [106]. There are no data concerning bisphosphonate-associated atypical femoral fractures in this population.

Menopausal hormone therapy

Estrogen-/progesterone-based menopausal hormone therapy (MHT) is generally recommended in patients with premature ovarian failure to prevent diseases associated with estrogen loss [107]. Possible complications associated with MHT in postmenopausal women, such as an increased risk of thromboembolism, stroke, and breast cancer, are not applicable in women before age 45 years.

A lesser decline in BMD in young female patients receiving MHT in comparison with patients without MHT has been reported [97]. However, MHT has not been consistently shown to prevent BMD loss after HSCT [64, 96]. Therefore, MHT alone may constitute insufficient treatment for the multifactorial bone loss in patients after HSCT.

Selective estrogen receptor modulators

The selective estrogen receptor modulator raloxifene is an antiresorptive therapy reducing postmenopausal bone loss, preventing vertebral fractures, and with reductions in breast cancer incidence; there are no data in HSCT patients [108].

Denosumab

Denosumab, a fully human monoclonal antibody to RANKL, is an effective antiresorptive therapy for osteoporosis, leading to significant reductions in the risk for hip, vertebral, and non-vertebral fractures in postmenopausal osteoporosis [109]. Denosumab could be quite promising in preventing bone loss after HSCT because of its potent anti-osteoclastic activity, its larger effect on cortical bone than bisphosphonates, and its lack of renal toxicity [110]. Denosumab's antiresorptive effects are more rapidly reversible on discontinuation of therapy as compared with bisphosphonates; a long-term strategy is therefore required [111]. A case report of a young woman on dialysis after allo-HSCT for acute myeloid leukemia reported improvements in BMD after treatment with denosumab [112]. Controlled clinical trials are required to evaluate the role of denosumab in HSCT patients.

Parathyroid hormone-derived peptides

Teriparatide has been shown to have superior BMD effects compared with bisphosphonate in glucocorticoid-induced osteoporosis [113]. PTH or PTHrP analogs (such as abaloparatide) might be interesting alternatives to antiresorptive therapy because of their stimulating effect on bone formation. PTH or PTHrP analogs are, however,

contraindicated in patients with radiotherapy to the skeleton or any malignant diseases of the skeleton, excluding HSCT patients from currently available bone anabolic therapy. There is no experience with PTH or analogs in patients after HSCT and it is unlikely that a therapeutic trial will ever be conducted.

Romosozumab, a sclerostin monoclonal antibody, releases osteoblasts from inhibition by sclerostin with resultant increases in BMD and fracture reduction in postmenopausal women with osteoporosis. Regulatory approval of romosozumab awaits confirmation of cardiovascular safety and specific trials in the HSCT population will be required.

Algorithm for management of bone health in allogeneic HSCT patients

Risk factors predicting bone loss

Risk factors for bone loss following HSCT are multifactorial and include the HSCT preparative regimen, induction of premature menopause, weight loss, and medications used in the prevention and treatment of acute and chronic GVHD. Reduced intensity conditioning regimens are increasingly used and are associated with less organ toxicity but it is unknown if they are associated with a reduction in bone loss.

The integration of clinical risk factors with femoral neck BMD has been operationalized into the FRAX 10-year fracture risk probability. FRAX is not applicable in patients under the age of 40 and has not been validated in the HSCT population. Patients with GVHD typically are given high doses of glucocorticoid and the dose of glucocorticoid is not included in FRAX calculations.

Secondary causes of bone loss may coexist in this HSCT population. For this reason, secondary causes of bone loss should be evaluated with measurement of calcium, phosphate, ALP, TSH, creatinine (estimated glomerular filtration rate (eGFR)), and 25-hydroxyvitamin D (25-OHD). In some clinical circumstances, PTH, morning testosterone, estradiol, FSH, and LH could be measured (Fig. 1).

When to test BMD

Evaluation of BMD at hip and spine prior to HSCT is recommended due to prior morbidity and exposure to chemotherapy agents potentially harmful to bone. Most guidelines recommend DXA within 1 year of transplant [73, 79, 117]. Post-transplant declines in BMD are not predictable. For this reason, BMD measurement should be repeated in patients not given pre-transplant bone resorption inhibitors, 3 months after HSCT (Fig. 1). If patients have been given zoledronic acid pre-transplant, a repeat BMD 1 year after the treatment is recommended. Individual patients with specific clinical concerns may require follow-up evaluations at an earlier time point. It should be noted that many studies of antiresorptive therapy in this population use higher doses of bisphosphonate than are indicated for postmenopausal osteoporosis. There are data indicating that BMD may be low in patients many years after HSCT. For this reason, BMD should be monitored periodically in patients who have had HSCT in the past [55].

Diet and lifestyle recommendations

General good nutrition is required for optimal bone health. Food intake and gastrointestinal (GI) absorption are reduced after HSCT and may be more problematic with GI GVHD. Because of frequent post-HSCT nutritional deficiency, attention to adequate caloric intake with the addition of total parenteral nutrition (TPN) if required early post-HSCT is desirable.

Adequate intake of calcium, protein, and vitamin D is recommended [55]. Although dairy intake should be encouraged, calcium supplements could be used to supplement patients' need for 1000–1200 mg elemental calcium from diet and supplement combined.

Baseline assessment of serum 25-hydroxyvitamin D may help to determine patients in need of a loading dose of vitamin D prior to transplant. A loading dose of vitamin D_3 (for example, 50,000 to 100,000 IU) prior to HSCT would aid in ensuring vitamin D sufficiency throughout the critical first 3 months [118].

All patients should be educated about general exercise and lifestyle interventions to reduce bone loss such as regular weight-bearing and muscle-strengthening exercises and avoidance of tobacco and excessive alcohol intake.

Intervention thresholds, factors influencing intervention thresholds

Intervention with pharmacotherapy in HSCT patients should be recommended earlier than in patients with postmenopausal or idiopathic osteoporosis. We have previously recommended earlier intervention at a higher BMD threshold for patients on aromatase inhibitor or androgen deprivation therapy [119]. Intervention with intravenous zoledronic acid should be considered if pre-HSCT BMD T-score $\leqq$ -1.5 at any one of the relevant sites (total hip, femoral neck, lumbar spine) and if renal status permits. Denosumab could be considered in patients with renal impairment, who are not candidates for bisphosphonate. Denosumab 60 mg twice yearly compared with placebo effectively prevented clinical fractures in postmenopausal women with breast cancer who received an aromatase inhibitor, irrespective of baseline age or BMD [120]. Parenteral antiresorptive therapy is preferred due to the potential for poor absorption and adherence associated with oral therapy [121], as well as GI side effects in this population who are at particular risk (Fig. 1).

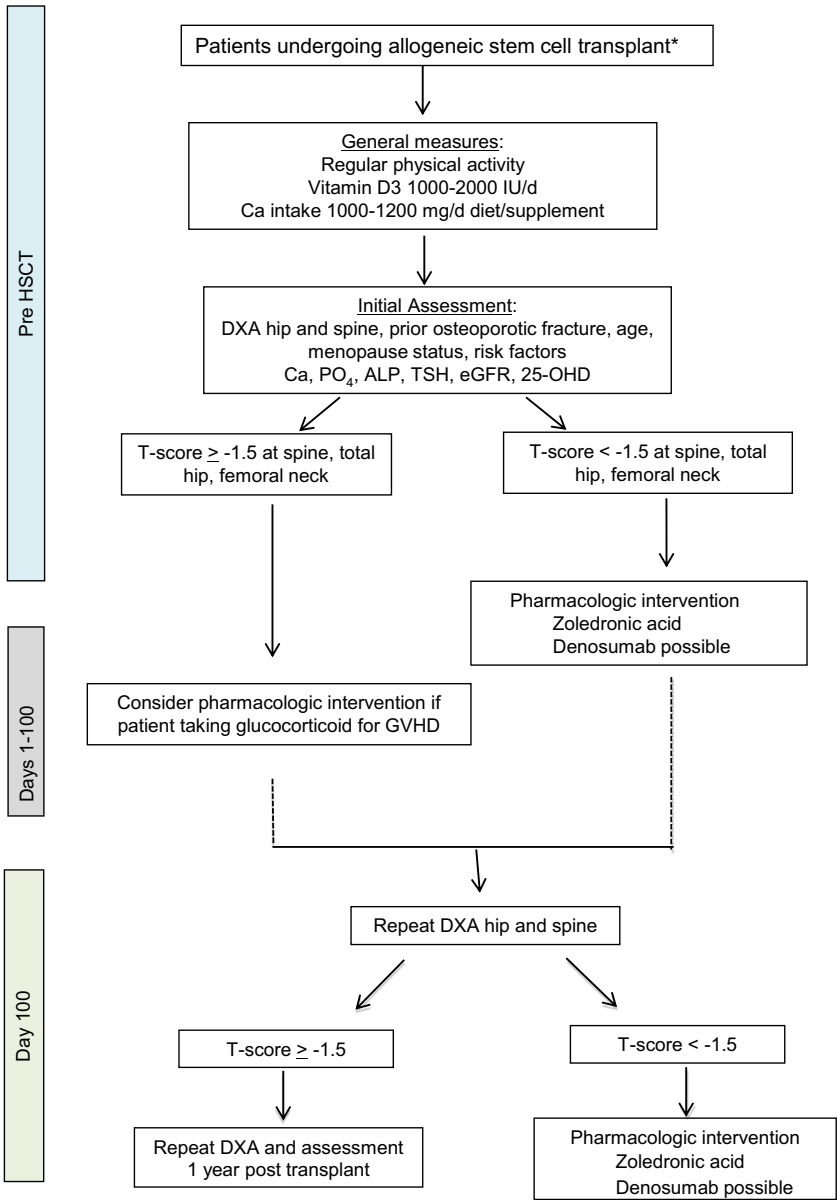

Fig. 1 Management algorithm for patients undergoing allogeneic stem cell transplant. The proposed algorithm represents expert opinion, analogous to similar algorithms created to aid clinicians in the management of glucocorticoid-induced osteoporosis [114]. The asterisk symbol represents patients receiving an autologous HSCT with an underlying multiple myeloma [115, 116]

All patients receiving prolonged courses of glucocorticoids for GVHD are at high risk for bone loss and fracture. In addition, the duration of glucocorticoid therapy is often unpredictable. Therefore, prophylaxis with bisphosphonates, ideally zoledronic acid 5 mg intravenously, may be given regardless of the T-score. Additional risk factors such as prevalent fragility fracture should be considered. Recent data demonstrate greater effectiveness of denosumab in preventing glucocorticoid-induced bone loss as compared with risedronate [122].

In younger women with treatment-induced amenorrhea post-HSCT, estrogen-based MHT may prove to be an effective antiresorptive therapy and perhaps show additive benefits with regard to cardiovascular disease [123], although it does not prevent glucocorticoid-induced bone loss in this population [96, 124].

Obstacles to implementation of bone health guidelines for HSCT recipients

Despite convincing data that bone loss is common post-HSCT, many HSCT patients are not monitored for bone health and the majority does not receive prophylactic intervention.

Pre-HSCT bone densitometry screening, using DXA, can identify patients with pre-existing osteopenia/osteoporosis, who may benefit from early interventions to prevent or reverse transplant-related bone loss. Given the high rates of early transplant-related mortality and relapse, concerns have been raised that such an approach may not be cost-effective [73].

The risk of renal dysfunction in patients receiving intravenous zoledronic acid for osteoporosis is small. Transient increases in serum creatinine are observed 9–11 days after

zoledronic acid infusion [125]. It is recommended that patients should be well-hydrated and not receiving agents that are known to possibly adversely affect renal function [126]. Zoledronic acid dosing pre-transplant is best administered in advance of HSCT conditioning and GVHD prophylaxis. Challenges exist in administration in the early post-transplant period due to the frequent use of calcineurin inhibitors.

Denosumab is a promising agent for prevention of bone loss in HSCT patients. Inhibiting the immunomodulatory effect of RANKL on both the innate and adaptive immune systems, denosumab theoretically could increase the risk of infection and/or disease relapse in HSCT patients. If denosumab had favorable immunomodulatory effects in these patients, there might also be a reduction in GVHD; controlled clinical trials are required.

Conclusions

HSCT procedures are increasing in frequency and HSCT patients are living longer leading to a focus on long-term outcomes. Bone health comes to the fore as one of the most significant morbidities post-HSCT.

Sufficient evidence has accumulated in HSCT patients to make recommendations for more aggressive monitoring of bone health and more appropriate application of osteoporosis pharmacotherapies to patients at high risk of bone loss and fracture.

Compliance with ethical standards

Conflicts of interest P Hadji received honoraria, travel grants, and scientific research grants from Amgen, Eli Lilly, MSD, Novartis, Pfizer, Procter & Gamble, and Roche. D Kendler received honoraria, speakers bureau, and/or research grants from Amgen, Eli Lilly, MSD, Pfizer, Astrazenica, and Astellas. T de Villiers has acted as a consultant or speaker for the following companies: Abbott, Amgen, Aspen, MSD, Pfizer. R Rizzoli received fees for consultancy or lectures from Danone, EffRx, Nestlé, ObsEva, and Radius Health. PR Ebeling received research grants, honoraria, and/or speakers' fees from Amgen, Eli Lilly, Novartis, and Gilead. J Cannata-Andia received honoraria and scientific research grants from Amgen, Shire, and VIFOR/Fresenius. JJ Body, ML Brandi, MJ Cannata-Ortiz, A El Magrahoui, G Guglielmi, and DD Pierroz have no conflict of interest to declare.

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