Curr Osteoporos Rep (2013) 11:305–310
DOI 10.1007/s11914-013-0180-1

OSTEOPOROSIS AND CANCER (P TAXEL, SECTION EDITOR)

Osteoporosis after Stem Cell Transplantation

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Published online: 8 November 2013

Abstract With long-term survival for recipients of autologous and allogeneic hematopoietic cell transplantation (HCT) increasing, the recognition of late complications such as decreased bone mineral density leading to osteoporosis (OP) has also increased. With an incidence that is reported to affect as many 50 % of allo HCT recipients, studies continue to mount supporting the need and success in treatment of this HCT complication. In this review, we highlight the major pathological mechanisms behind the development of OP, its diagnosis, and the literature supporting consensus treatment recommendations while noting areas of uncertainty that need further research.

Keywords Osteoporosis · Allogeneic stem cell transplant · Autologous stem cell transplant · Review · Osteopenia · Skeletal complications

Introduction

Over the last 10 years, survivorship of patients undergoing autologous and allogeneic hematopoietic cell transplantation (HCT) has improved due to advancements in supportive care practices and a better understanding of HCT techniques [1]. This has led to an enlarging patient population suffering from the late effects of HCT, of which, bone loss and its clinical manifestation in the form of fragility fractures, osteoporosis (OP), and osteopenia leads to substantial morbidity. This review will focus on the prevailing mechanisms felt to be behind the development of OP after HCT, its diagnosis. and the considerations for treatment recommendations in these patients.

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Biology and Pathophysiology of Bone Remodeling

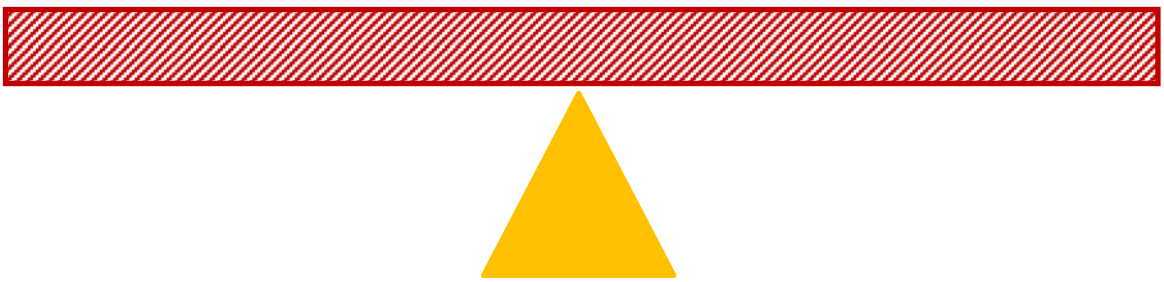
The dynamics of bone remodeling have recently been reviewed with specific reference to the oncology patient by Lustberg et al [2••]. Worth highlighting is the complex interplay of cytokines belonging to the tumor necrosis family (TNF), the receptor activator of nuclear factor-kappa B ligand (RANKL), and osteoprotegerin (OPG). RANKL is produced by osteoblasts and binds to RANK, which is expressed on the cell surface of osteoclasts leading to differentiation and activity, ie, bone resorption. OPG, a decoy receptor also made by osteoblasts, inhibits this interaction thereby decreasing osteoclastic activity and allowing bone formation. It is the imbalance between these 2 processes that leads to the pathophysiology experienced by patients before and after the HCT procedure. Many factors can influence this equation (Table 1); notably these range from the physiologic, such as the premature induction of menopause in women, to the loss of normal androgen levels in men. They may also be related to HCT preparative regimens or graft-vs-host disease (GVHD) preventative and treatment measures [3]. Steroids are one of the best examples of the perturbation that occurs within the RANKL/OPG pathway promoting bone loss. Depending on dose and duration of use, steroids lead to a resorptive environment as they decrease sex hormones and stimulate RANKL while also decreasing OPG production [4].

Scope of Bone Loss in Transplant Patients

The incidence of OP and osteopenia is reported to range anywhere from 3 % to as high as 70 % after allogeneic or

Table 1 Risk factors for osteoporosis development post-transplant

Factors affecting bone metabolism
Renal dysfunction: decreased vitamin D production, wasting of calcium or magnesium
Corticosteroids: inhibition/apoptosis of osteoblastic activity
Oncologic therapy (Chemo, TBI): hypogonadism and direct effects on osteoblasts
Calcineurin Inhibitors: direct renal effects
Graft versus host disease: malabsorption, wasting of vitamin D, calcium



autologous HCT [5–15]. The temporal sequence of bone loss after HCT has been well reviewed [4, 16] and an early phase of BMD loss that occurs within the first 6 to 12 months at all skeletal sites is well recognized. Shortly thereafter recovery begins, initially, in the lumbar spine and then a much slower improvement at the femur takes place that may take months to years. Whether baseline levels of BMD are ever reached again depend upon continued risk exposure, particularly, the ongoing treatment of graft vs host disease (GVHD). This loss, followed by slow recovery, has been estimated to increase the risk of hip fractures as much as 2–3 times above baseline though the true incidence of fracture post HCT is unknown. Clinically, though BMD loss occurs in HCT patients, this does not always correlate with fracture risk as noted by Savani et al [17].

Diagnosis of Bone Loss and Osteoporosis

Bone mineral density (BMD) is determined through the use of dual-energy X-ray absorptiometry (DEXA) in the detection of patients with possible OP. A T-score is calculated by comparing an individual's BMD with that of a reference population 20–40 years of age and of the same gender. This is the preferred method of reporting in post-menopausal women and men ≥50 years. A Z-score is calculated by comparison of a patient's BMD with the mean of an age and sex-matched population. Scores are expressed as standard deviations from population norms with the World Health Organization (WHO) classifying normal as a T score≥-1 or a Z-score>-2.0, osteopenia or low bone mass as a T-score of<-1 and>-2.5, and OP as a T-score≤-2.5±fragility fractures or a Z score≤-2 with history of fractures [18]. However, many recognize the inherent limitations in the use DEXA as fractures often occur at scores that do not meet true OP criteria [19, 20]. Because of this, the WHO developed the Fracture Risk Assessment Tool (FRAX; http://www.shef.ac.uk/FRAX/) to assist in the estimation of an individual's 10-year risk of osteoporotic fracture; however, data on its applicability to the HCT population is still lacking. Because of its allowance for a more personal risk assessment, many consensus groups are now beginning to consider it in treatment recommendations [21–24] with most using a 10-year probability for hip fracture ≥3 % or major osteoporotic fracture of ≥20 % as indications for therapy initiation.

Treatment of HCT-Associated Bone Loss

A variety of treatments to abort the BMD loss early after HCT and into the first few years have been reported [5, 7, 9–15, 25–27]. Much of the data, while providing a basis on which to

build, have been in uncontrolled studies with small patient populations. Consistent definitions of osteopenia and OP have also not been used across these studies. Because of this, clinicians are left with the difficult determination of appropriate dosing and selection of agents with which to treat patients. Treatments generally include optimization of vitamin D (VD) and calcium intake according to recommended guidelines, hormone replacement therapy (HRT), and use of bisphosphonates (BP) in addition to lifestyle changes, eg, cessation of smoking/drinking, improvement in nutrition, exercise, and prevention of falls.

Calcium and Vitamin D Supplementation

Though generally recommended, the exact dose and formulation of calcium and VD is not well known. In a recent meta-analysis of a non-HCT, non-osteoporotic, post-menopausal population, the U.S. Preventive Services Task Force (USPSTF) could not recommend VD doses >400 international units (IU) or calcium doses >1000 mg for primary prevention of fractures; however, doses lower than these were recommended against [28]. It stands to reason that HCT patients are more at risk for lower levels of calcium and VD given the use of medications that interfere with VD metabolism, presence of renal dysfunction, and due to GVHD of the gastrointestinal (GI) tract, which may impair VD absorption. Indeed, 2 recent reports by Sproat et al [29] and Joseph et al [30] documented surprisingly high incidences of VD deficiency in 90 % and 70 %, respectively, of patients undergoing allogeneic HCT. In the latter report, incidences of /OP/osteopenia ranged from 22 %–83 % of patients whether patients were identified as VD replete or not highlighting the importance of other factors in the development of BMD loss. Perhaps confirming that more than just supplementation is needed, at least 2 randomized studies have shown that repletion of calcium or VD/calcium only was not enough to prevent BMD loss post-HCT [9, 12].

Hormone Replacement Therapy

The routine use of HRT in non-HCT female populations are recommended in cases of premature ovarian failure until the median age of natural menopause (51 years) and for osteoporosis prevention in those at high risk for fracture based upon data demonstrating fracture reduction [31]. HRT use must be tailored to thrombotic and solid tumor (breast, ovarian) risk. In HCT-populations, however, the use of HRT has not consistently been shown to prevent BMD loss when compared with other active agents [5, 9, 10, 15]; hence, while HRT in HCT patients is likely warranted in cases of younger HCT patients or high fracture risk populations, no exact dose, duration, or formulation can currently be recommended.

Bisphosphonates

In the modern era, BPs have become the most frequently prescribed therapies for HCT-associated BMD loss and OP in general. In nearly all prospective HCT trials, these anti-resorptive drugs demonstrate an increase in BMD in the early post-HCT period and during their continued use [9–11, 13, 25–27], (Table 2). Several key points, however, deserve

Table 2 Bisphosphonate therapy trials (controlled and uncontrolled) for adult transplant-associated osteoporosis

Study authors (reference)	No. patients	Trial design	Findings
Hari et al [32••]	11	ZA pre-HCT and at 3, 6 mo. post in patients with OA or OP only	ZA increased BMD at FN and LS
Ganguly et al [33]	17	ZA pre-HCT and at 6 mo. post	ZA prevented BMD loss at all sites at 12 mo.
Hausmann et al [34]	36	ZA every 3 mo. × 24 mo.	ZA increased BMD at LS and FN.
Grigg et al [13]	49	HRT/Ca/calcitriol +/- Pam monthly × 12 mo.	Pam reduced bone loss at FN,LS, hip but did not prevent bone loss from baseline at these sites. Gains lost at 1 y after therapy.
Tauchmanova et al [9]	60*	Ca/VitD vs	Ca/VitD, Ca/VitD/HRT did not prevent bone loss at LS or FN;
		Ca/VitD/HRT vs Ca/VitD/Ris wk vs Ca/VitD/ZA monthly × 3mo × 12 mo.	Ris improved LS BMD from baseline and prevented FN loss; ZA improved both LS and FN BMD, more so than Risedronate
Kananen et al [10]	66	Ca/VitD/HRT +/- Pam at HCT and 1, 2, 3, 6, 9 mo post-HCT	Pam decreased bone loss at LS and decreased loss at other sites but did not prevent BMD loss
Tauchmanova et al [11]	34	Ca/VitD +/- Ris wk × 12 mo.	LS BMD improved while overall FN BMD was stabilized
Chae et al [26]	18	ZA 2 mo post-HCT then q3mo × 24 mo.	ZA prevented bone loss at 1 y post-HCT
D'Souza et al [27]	12	ZA x 1 dose in high-risk patients only	ZA decreased BMD loss in most patients but LS loss still occurred in some patients
Tauchmanova et al [25]	30	Ca/VitD +/- ZA 4 mg IV monthly	ZA significantly improved BMD loss at FN and LS

BMD bone mineral density, *Ca* calcium, *FN* femoral neck, *HRT* hormone replacement therapy, *LS* lumbar spine, *Pam* pamidronate, *Ris* Risedronate, *VitD* Vitamin D, *ZA* zoledronic acid.

attention. When dealing with these therapeutics, there is no clear-cut preferred agent that has yet emerged, and patient preference and tolerance often dictates the choice of agent. Oral agents may not be preferred in cases of lingering GI GVHD or in the profound debilitation that sometimes occurs after HCT making intravenous (IV) formulations more appealing. Amongst the IV formulations, pamidronate (PAM) and zolendronic acid (ZA) are the most studied; however, they can be associated with the rare complications of osteonecrosis of the jaw (ONJ) and subtrochanteric femoral fractures.

Interesting findings from a few studies deserve mention when considering treatment in HCT patients. In a prospective study by Grigg et al [13], PAM was reported to reduce bone loss at the femoral neck (FN), lumbar spine (LS) and hip, but overall BMD did not return to baseline levels. In addition, once therapy was stopped, BMD began to decrease again within 12 months calling into question whether agent potency matters and the ideal length of therapy for HCT patients.

A recently published, randomized study from Hari et al has added further support for the use of BPs, with ZA, before and after HCT, particularly in high risk populations [32••]. Patients were screened with DEXA prior to HCT and if determined to have BMD consistent with osteopenia, they were then randomized to receive best supportive care with or without ZA given pre-HCT, and at 3 and 6 months post-HCT. Of the 30 patients eligible for analysis (11 on treatment, 13 controls), the ZA arm demonstrated a mean BMD improvement at the femoral neck of 0.018 g/cm^2 compared with a worsening in the non-ZA group of -0.054 g/cm^2. The study was confounded by a lower rate of overall survival in the treatment cohort; however, pre-HCT comorbidity may have also played a role in this. There were no reported cases of ONJ in this series.

Two other recent publications also report on the use of ZA as a way to prevent HCT-associated BMD loss. The first by Ganguly et al initiated ZA before allo-HCT and again at 6 months after to acute leukemia patients [33]. In 17 patients followed over 3 years, no loss of BMD was seen during the study period, and there were no cases of ONJ. Problematic with this trial and with others in the field was the lack of an appropriate control group. While DEXA studies were performed at 6 and 12 months post-HCT, later follow-up BMD measurements were not taken, leaving unanswered the question if the beneficial effects reported really hold once the BP agent is stopped.

Hausman et al report on their use of ZA post-HCT in a cohort of patients given the BP on an every 3 month schedule for 2 years [34]. Initiation of the therapy (pre-HCT or post conditioning) was not well described. BMD measurements of 26 patients were taken at a median of 13 and ~25 months. Their results again showed positive BMD effects at all skeletal sites measured. The major factors associated with an increase in BMD were younger age, female donor, and immunosuppression with CSA/MTX. Interestingly, analyses did not demonstrate a negative effect of corticosteroid use on BMD; however, and as in most studies published to date, small samples sizes may have confounded the ability to detect a true difference.

These recent studies still only present small patient sample sizes with which to draw concrete conclusions regarding BP use and offer no clear-cut guideline as to the appropriate time at which to start these agents. They do highlight the relatively low risk of serious complications of ONJ and the need for well-designed prospective data to help elucidate who will benefit the most from these therapeutics.

Other Agents that may Have a Role

Calcitonin is a Food and Drug Administration (FDA) approved agent for the treatment of OP in postmenopausal women based on data that it increased total body calcium and improved BMD. Its approval was not based on fracture data, though 1 study demonstrated a decrease in vertebral fractures of about 8 % in a large, non-HCT population [35]. In a post-HCT cohort, however, no benefit in BMD was seen adding it to calcium supplementation [12]. Recently a FDA advisory board has joined the European Medicines Agency (EMA) in recommending that calcitonin no longer be used as post-marketing studies showed more malignancies in patients treated with calcitonin [36]. A full decision on the fate of calcitonin is expected in the coming months.

The 2 newest agents for the treatment of OP/osteopenia are teriparatide, a human parathyroid hormone analogue that has an anabolic effect on bone and denosumab, a monoclonal antibody that binds and inhibits RANKL from interacting with RANK precursors of osteoclasts. Both agents are FDA approved for use in postmenopausal women and men at high risk of fracture. We could find no report of either agents' use in HCT patient populations. Part of this is likely due to the association of teriparatide with osteosarcomas in animal models exposed to the drug over long periods of time, though this has not been seen in humans [37, 38]. It is therefore generally avoided in those having received radiation to bones, ie, total body irradiation (TBI), for this same reason. Data on its use, however, suggests that it is more effective than alendronate in reducing incidence of vertebral and hip fractures [39]. Combination trials with anti-resorptive agents (BPs, denosumab) in addition to this anabolic agent are already being reported [40–42]. One such trial demonstrated that using both agents compared with either alone resulted in significantly increased BMD in the lumbar spine ($P=0.0005$), the femoral neck ($P=0.0007$), and hip ($P<0.0001$) [43••]. Whether these agents will fit into the treatment of HCT-associated BMD loss remains to be determined.

Recommendations for Practitioners

In 2006, representatives from the Center for International Blood and Marrow Transplant Research (CIBMTR), the

European Group for Blood and Marrow Transplantation (EBMT), and the American Society of Blood and Marrow Transplantation (ASBMT) came together to provide consensus guidance on screening and preventive practices for autologous and allogeneic HCT patients. This group reconvened in 2011, this time with a broader international contingent, to update these recommendations including those for OP/osteopenia screening. Summary recommendations included screening DEXA at 1 year post-HCT for all adult women, all allogeneic HCT recipients, and patients at highest risk for bone loss. HRT was recommended for those with documented estrogen deficiency. BP use was recommended for those at high risk for fracture by some [44••]. We conducted a review at our own institution and, with input from a panel of adult and pediatric practitioners from transplant and endocrinology, developed guidelines for patients that incorporate much of the above consensus recommendations. However, recognizing that prolonged corticosteroid and immunosuppressive use contributes significantly to the development of OP/osteopenia, the aging of our treatment population, and the substantial pre-treatment burden that many of our patients undergo prior to receiving their HCT, we consider testing BMD sooner if contributing factors exist [45•]. While each center's and each patient's clinical situation may differ, we have used this as a starting point to enable better management of those at highest risk for fracture in our practice until more prospective studies enhance our ability to balance cost and risk of treatment with efforts to reduce the morbidity of this complication.

Compliance with Ethics Guidelines

Conflict of Interest BL McClune declares that he has no conflicts of interest. NS Majhail declares that he has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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