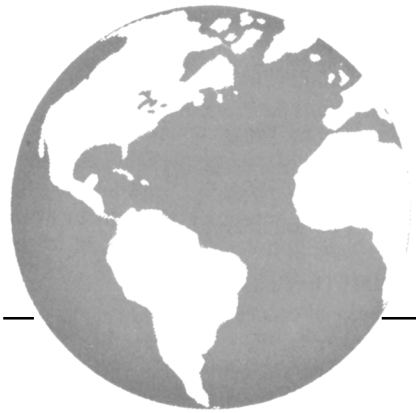

# Cancer treatment–related bone loss: a review and synthesis of the literature

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## ABSTRACT

Cancer therapy can result in significant bone loss and increased risk of fragility fracture. Chemotherapy, aromatase inhibitors, and gonadotropin-releasing hormone analogues contribute to increases in the rate of bone remodelling and reduce bone mineral density. Patients with prostate cancer on androgen deprivation therapy experience an increase in the risk of fracture. New research has demonstrated the key role played by bisphosphonates in preventing declines in bone density and increases in bone remodelling. Novel antiresorptive agents targeting receptor activator of nuclear factor κB ligand have great potential in skeletal protection and prevention of bone loss related to cancer therapy. Early assessment of skeletal health, followed by initiation of calcium, vitamin D, and an exercise program are valuable in the prevention and treatment of osteoporosis. In addition, individuals at increased risk for fracture should be offered antiresorptive therapy. Early data have demonstrated that bisphosphonates are able to prevent the bone loss and increased bone remodelling associated with cancer therapy, including aromatase inhibition and androgen deprivation therapy. The present paper reviews the new research and advances in the management of bone loss associated with both cancer therapy and estrogen deficiency in the postmenopausal female.



## KEY WORDS

Cancer therapy, aromatase inhibition, bone loss, osteoporosis, androgen deprivation, antiresorptive therapy, bisphosphonates, osteonecrosis of jaw


## 1. INTRODUCTION

Osteoporosis is characterized by a decline in bone mineral density (BMD) and an associated deterioration of bone microarchitecture, resulting in increased bone fragility and higher fracture risk [1]. Osteoporotic fractures result in increased morbidity and mortality, with men experiencing higher mortality rates following a hip fracture (close to 40% within the first year of the fracture). Oncology patients are at an increased risk of developing osteoporosis because of the effects of chemotherapy and radiotherapy. Hormonal and non-hormonal treatment options can both also result in hypogonadism, which can further contribute to progressive bone loss.

## 2. DISCUSSION

### 2.1 Aromatase Inhibitors, Gonadotropin-Releasing Hormone Analogues, and Tamoxifen

In premenopausal women with breast cancer, ovarian ablation therapy can be associated with a rate of bone loss as high as 13% within 12 months of treatment [2]. Gonadotropin-releasing hormone (GNRH) analogues result in downregulation of GNRH receptors and ovarian insufficiency within 6 months of therapy [3]. Dramatic decreases in bone density have been observed in patients treated with goserelin as compared with patients treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) adjuvant chemotherapy [4]. In goserelin-treated patients, BMD at the lumbar spine decreased by 10.5%, as compared with 6.5% in CMF-treated patients ($p < 0.001$) [4]. The CMF patients remained estrogen-deficient and had ongoing bone loss, whereas patients in the group treated with goserelin demonstrated bone density recovery 1 year after therapy ended [5].

The aromatase inhibitors (AIS) block conversion of androgens to estrogen and can also contribute to bone loss [6]. As a steroidal AI, exemestane has a structure similar to androstenedione and competitively binds with aromatase. The nonsteroidal AIS anastrozole and letrozole reversibly inhibit the cytochrome P450 moiety of aromatase. All three of these agents have been approved for adjuvant treatment of breast cancer. The major metabolite of exemestane, 17-hydroexemestane, has androgenic effects, and the steroidal and nonsteroidal AIS may differ with respect to their effects on bone loss and fracture. These po-

tential differences have not been evident in clinical trials completed to date.

All three AIs have been associated with increases in markers of bone resorption and bone formation, and no statistically significant differences have been noted between the three agents [7–9]. All three appear to increase the rate of bone turnover and thus may be associated with an increased risk of fracture [7–9]. The clinical trials completed to date have been small in size, and the effect of AIs on fracture risk is not yet clear, partly because in the trials completed to date, the AIs have been compared to tamoxifen. Tamoxifen exerts estrogen agonistic effects at the skeletal level and can reduce the rate of bone remodelling and provide skeletal protection. Thus it is not the ideal standard against which to measure the skeletal effects of AIs.

In postmenopausal women, tamoxifen has been shown to preserve bone density and to reduce the rate of fracture [10–12]. In premenopausal women, tamoxifen is associated with bone loss at the spine and hip because its effects on the skeleton are not as potent as those of estrogen. Tamoxifen is thus acting as a bone antagonist as it competes with the more potent bone agonist 17β-estradiol for the estrogen receptor in the premenopausal female. Small reductions in bone density at the lumbar spine were noted over 3 years in premenopausal women treated with tamoxifen as compared with women receiving placebo [11]. In postmenopausal women, tamoxifen was associated with increases in bone density of 1.17% at the lumbar spine and 1.71% at the hip ($p < 0.001$); the placebo group showed stable bone density [11]. In a primary prevention breast cancer study [13], 5 years of tamoxifen therapy were associated with a 32% reduction in osteoporotic fracture [95% confidence interval (CI) = 0.51 to 0.92].

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) and the Breast International Group (BIG) trials [14,15] confirmed that adjuvant therapy with anastrozole or letrozole was superior to tamoxifen therapy with respect to breast cancer outcome. Eastell and colleagues [8] concluded that anastrozole is associated with significant BMD loss and a small increase in bone turnover, but that tamoxifen or a combination of anastrozole and tamoxifen is associated with increased BMD and decreased remodelling. For anastrozole, significant loss of BMD at the lumbar spine and hip was noted at both year 1 and year 2; with tamoxifen, significant gains occurred at the lumbar spine and the hip at year 1 and year 2 [8]. An inverse correlation was seen between the baseline estradiol level and BMD change: a lower baseline estradiol level was predictive of greater BMD losses.

The ATAC trial included 9366 patients treated for 5 years. In that study, the bone resorption marker urinary N-telopeptide of type 1 collagen (NTX) was measured, as was the resorption marker serum C-telopeptide of type 1 collagen (CTX) and the formation markers procollagen type 1 N-propeptide (P1NP) and serum bone-specific alkaline phosphatase (bone ALP). Patients receiving anastrozole showed increases in bone turnover markers; patients receiving tamoxifen tended to show decreases. At 1 year, the resorption markers CTX and NTX increased by 26% and 15% respectively (95% CI: 3% to 25%) in the anastrozole arm. The formation markers P1NP and bone ALP increased by 18% and 20% respectively (95% CI: 14% to 25%). Tamoxifen, however, was associated with decreases in bone resorption: CTX decreased by 56% and NTX, by 52% (95% CI: –62% to –33%); P1NP decreased by 72% and bone ALP, by 16% (95% CI: –24% to –11%). The combination of anastrozole plus tamoxifen was comparable to tamoxifen alone with respect to changes in bone markers. Anastrozole treatment for 2 years was associated with bone loss at the hip and spine and with increases in bone turnover [8].

The ATAC study demonstrated that the low levels of estrogen present in postmenopausal women are important in preserving bone density and regulating bone turnover. The effects of anastrozole were most notable within the first 4 years after menopause, a period associated with a rapid rate of bone loss. Tamoxifen was associated with skeletal protection and resulted in preservation of bone density and a decrease in bone turnover. However, tamoxifen in combination with anastrozole was less effective in improving disease-free survival than was anastrozole alone. The combination is therefore not recommended in the management of postmenopausal women with breast cancer.

The ATAC trial found that anastrozole had a safer profile than tamoxifen with respect to endometrial cancer, cerebrovascular events, and venous thromboembolic events [14]. However, as compared with tamoxifen, anastrozole was associated with an increase in the overall fracture rate (11% vs. 7.7%, $p < 0.0001$) [16]. In the BIG 1-98 trial, a higher incidence of clinical fractures was noted in the letrozole group as compared with the tamoxifen group (5.7% vs. 4%, $p < 0.001$) [15]. However, these trials make it difficult to confirm the effects of AIs on fracture, because the control group was treated with tamoxifen, which has protective skeletal effects and preserves bone density.

The effect of tamoxifen on fracture has not yet been confirmed. How an agent affects vertebral fracture is best evaluated by serial X-ray of the spine. Unfortunately, the large trials conducted to date have not included serial spinal radiographs as part of the clinical assessment, and therefore the effect of AIs on vertebral fracture is difficult to define.

The use of AIs after tamoxifen therapy has been evaluated. Exemestane was studied in 4742 postmenopausal women with breast cancer who had previously received 2–3 years of tamoxifen therapy [17]. Patients were randomized to switch to exemestane for the remainder of the 5-year treatment program or to complete a full 5 years on tamoxifen. After

30 months of follow-up, a higher, but not statistically significant, clinical fracture rate was noted in the exemestane group as compared with the tamoxifen group (3.1% vs. 2.3%, $p = 0.08$). A new diagnosis of osteoporosis was more common in the exemestane group (7.4% vs. 5.7%, $p = 0.05$) [17].

Anastrozole after tamoxifen has also been associated with a greater number of clinical fractures than has tamoxifen alone (2% vs. 1%, $p < 0.05$) [18]. But the effect of the AI on fracture is difficult to interpret, because tamoxifen, being an estrogen agonist in the postmenopausal female, may have reduced the risk of fracture. The study included premenopausal and postmenopausal women alike, and did not obtain spinal radiographs. These limitations make it difficult to confirm the effect of the AI on the incidence of fracture.

In a 2-year randomized control trial [19], exemestane was compared to placebo in postmenopausal women with early breast cancer. Assessments of spine and hip by dual X-ray absorptiometry were completed on an annual basis. After 1 year, the exemestane group showed declines in bone density at the lumbar spine (2.2%) and the hip (2.7%). The placebo group also experienced declines in bone density (1.8% at the spine, 1.5% at the hip). There was no significant difference between the two groups at the spine; the difference at the hip was statistically significant at $p = 0.023$ [19]. Exemestane-treated patients demonstrated increases in bone remodelling, with an increase of 44% in P1NP and 35% in CTX. The increased rates of bone turnover were consistent with the data obtained from other clinical trials.

Eastell and colleagues evaluated risk factors for fracture in the ATAC study [8]. Older age was associated with a higher risk of fracture. Low bone density T scores of less than –2.5 were also associated with a higher risk of fracture than were bone density T scores greater than –1.5. These authors also noted that use of a statin was associated with a lower risk of fracture.

Androgen deprivation therapy has been evaluated with respect to its effects on bone loss and fracture. Gonadotropin-releasing hormone agonists reduce serum concentrations of testosterone by more than 95% [20]. That decline is associated with dramatic reductions in bone density of about 4%–10% within the first year of treatment [21]. An increased risk of fragility fractures was documented retrospectively with androgen deprivation therapy in men with prostate cancer [22–24]. In a retrospective review of 50,613 men who received a diagnosis of prostate cancer, 19.4% of those who received androgen deprivation therapy had a fracture, as compared with 12.6% of those who did not receive such therapy ($p < 0.001$) [16]. Duration of treatment was an independent predictor for fracture risk. Men who received 9 or more doses of GNRH agonists in the year after diagnosis and men who underwent orchiectomy both had a relative risk of fracture of 1.45 (95% CI: 1.36 to 1.56) [16].

Bicalutamide, an approved agent for prostate cancer, is a nonsteroidal anti-androgen. It competitively binds to the androgen receptors in target tissues, inhibiting the effects of androgen. It can increase serum concentrations of estradiol [25]. As compared with GNRH analogues, bicalutamide has been shown to increase BMD [26].

### 2.2 Prevention and Treatment of Osteoporosis

In addition to adequate calcium, vitamin D, and exercise, options for the prevention and treatment of osteoporosis include antiresorptive and anabolic agents.

Antiresorptive (anticatabolic) agents inhibit osteoclast activity and reduce bone turnover [2], with the various agents having different mechanisms of action. Bisphosphonates reduce the rate of bone turnover, providing a longer time for bone to mineralize. Bisphosphonate therapy is thus associated with modest increases in BMD. Estrogen acts through the estrogen receptors on both osteoblasts and osteoclasts, and results in suppression of receptor activator of nuclear factor κB ligand (RANKL)–induced osteoclast differentiation, thereby decreasing bone remodelling [3]. Raloxifene, a selective estrogen receptor modulator (SERM), can bind to estrogen receptors, with tissue-specific agonist or antagonist effects. Raloxifene decreases bone remodelling, in addition to its other extraskeletal effects. Osteoclastic bone resorption is also inhibited by calcitonin acting on calcitonin receptors.

The antiresorptive agents mentioned above are effective in reducing fracture risk by approximately 30%–50% in the postmenopausal female population. However, fractures still occur, and more effective options are desirable, particularly for severe disease states. Anabolic therapy can make major improvements in the quality and quantity of bone, and anabolic agents are a welcome addition to the antiresorptive options currently available.

Anabolic therapy can increase the production of bone matrix by enhancing osteoblastic function. The resulting reduction in risk of fracture is approximately 65% over 18 months in the postmenopausal female with osteoporosis [27]. The currently approved anabolic agent is teriparatide. Strontium ranelate has been shown to have antiresorptive properties; it may also have anabolic properties. This agent is expected to be approved in Canada for the treatment of postmenopausal osteoporosis before the end of 2008.

#### *2.2.1 Calcium and Vitamin D*

The Scientific Advisory Council of Osteoporosis Society of Canada recommends [28]

- 1500 mg elemental calcium daily and 800 IU vitamin D daily for women and men 50 years of age and older.

- 400 IU vitamin D daily and 1000 mg elemental calcium daily for all adults under 50 years of age.

The effectiveness of calcium and vitamin D in preventing hip fracture was evaluated in the Women's Health Initiative (WHI) trial, which involved 36,282 postmenopausal women who daily received either 1000 mg calcium and 400 IU vitamin D, or a placebo, for an average of 7 years [29]. Patients were allowed to take additional daily supplements of up to 1000 mg calcium and 600 IU vitamin D. Personal use of bisphosphonates, calcitonin, SERMs, and estrogen therapy was also permitted, and approximately 38% of subjects took more than 1200 mg elemental calcium daily. In the WHI, the calcium and vitamin D study arm overlapped with the hormone replacement therapy (HRT) arm, and thus approximately 51% of patients were receiving estrogen.

Treatment compliance was poor: by the end of the study, only 59% of patients were taking more than 80% of their medication. As compared with the patients taking placebo, the patients taking 1000 mg calcium and 400 IU vitamin D daily showed a 1.06% increase in hip BMD ($p < 0.01$). In the treatment-compliant group, the hazard ratio for hip fracture was 0.71 (95% CI: 0.52 to 0.97), representing a statistically significant 29% reduction in hip fracture risk in the individuals taking more than 80% of their calcium and vitamin D supplements. Estrogen use was associated with a 42% reduction in hip fracture risk. A small, but significant, 17% increase in risk of renal stones was noted in the treatment group as compared with the placebo group, with a hazard ratio of 1.17 (95% CI: 1.02 to 1.34) [29]. Clinicians must therefore ensure that patients are not inadvertently taking excessive calcium supplements and that their urinary calcium excretion is normal, particularly when a history of renal stone formation is present.

Vitamin D inadequacy was also noted in the WHI study and may have contributed to the findings. In the nested case–control study, the mean 25-hydroxy vitamin D level was 46 nmol/L in patients who sustained hip fractures as compared with 48.4 nmol/L in control subjects [29]. Vitamin D supplementation of more than 600 IU daily may have reduced the fracture risk, as has been demonstrated in other clinical trials. Ensuring adequate vitamin D supplementation is a key component of therapy in the prevention and treatment of osteoporosis.

### *2.2.2 Antiresorptive Therapy*

***SERMs:*** The SERM class of agents demonstrates tissue-specific estrogen-agonistic or estrogen-antagonistic effects [30]. In the Multiple Outcomes of Raloxifene Evaluation trial, patients treated with either 60 mg or 120 mg raloxifene daily for 4 years demonstrated a 36% and 43% reduction in vertebral fracture risk respectively [31]. However, no significant effect on the risk of non-vertebral fractures was noted [31]. The latter finding may have been the result of multiple factors, including the very low incidence of non-vertebral fractures seen in the placebo arm of this trial, as compared with incidences seen in the randomized clinical trials for other antiresorptives.

In the Study of Tamoxifen and Raloxifene, involving 19,747 postmenopausal women with increased risk of breast cancer, 60 mg raloxifene daily demonstrated breast cancer risk reduction effects equivalent to 20 mg tamoxifen daily over 5 years [32]. (Both drugs reduce the risk of breast cancer by approximately 50%.) Raloxifene was associated with a better overall safety profile than tamoxifen was, with 36% fewer uterine cancers and 29% fewer deep vein thromboses [32].

***Bisphosphonates:*** Nitrogen-containing bisphosphonates (alendronate, risedronate, zoledronic acid) demonstrate antiresorptive effects by binding to the calcium hydroxylapatite crystal at sites of bone resorption where the bone matrix is exposed [33]. The bisphosphonate is buried under the newly formed bone, where it lies inert and has no skeletal effects. During bone resorption, the drug is released from the bone matrix and is ingested by osteoclasts; it inhibits farnesyl diphosphate synthase (FDPS), a key enzyme in the cholesterol synthesis pathway involved in post-translational modification of important signalling molecules (Ras, Rac, Rho, and Rab). The FDPS inhibition disrupts several pathways involved in cytoskeletal organization, cell survival, and cell proliferation, leading to osteoclast deactivation and apoptosis [34]. The result is reduced bone turnover and enhanced bone mineralization because of the extended time available for mineral accumulation. With the normalization of bone remodelling to premenopausal levels, overall bone strength is improved [34,35].

*Alendronate:* Alendronate effectively reduces the risk of vertebral fractures in postmenopausal women with and without baseline vertebral fractures, as has been demonstrated in the Fracture Intervention Trial (FIT) [36–38]. Several trials have shown that alendronate use reduces bone resorption and improves BMD [38,39]. In early postmenopausal women, alendronate for 5 years inhibited bone loss at the spine, hip, and total body [37]. In a separate study involving women below 60 years of age, 5 mg alendronate daily resulted in a 3.5% increase in BMD at the lumbar spine, together with a 1.9% increase at the hip ($p < 0.001$ as compared with baseline at both sites) [39]. It is worth noting that the FIT Long-term Extension study reported that increases in BMD continued at the lumbar spine and hip through 10 years of treatment, with an associated fracture risk reduction [38]. Bone biopsies performed in patients following 10 years of alendronate treatment revealed double fluorescent tetracycline label in all biopsy samples, indicating ongoing bone remodelling and an absence of "frozen" bone [38].

Those data provides reassurance that long-term alendronate therapy can safely reduce vertebral and non-vertebral fractures.

Bisphosphonates may prevent bone loss associated with GNRH-induced hypogonadism, as was first evaluated with etidronate [40]. Clinical trials are currently evaluating the use of alendronate or risedronate in the prevention of bone loss in association with AIs.

*Risedronate:* Risedronate maintains bone mass and preserves bone microarchitecture [41]. A number of studies in postmenopausal women have shown that risedronate significantly reduces the risk of vertebral and non-vertebral fractures alike [42–44]. Analysis of data from the Vertebral Efficacy with Risedronate Therapy trials indicated that 5 mg risedronate daily reduced the incidence of new fractures within 6 months of starting therapy and significantly lowered the risk of new vertebral fractures within 1 year [42–44]. This reduction in fracture risk was maintained for up to 7 years of treatment [45]. Risedronate effectively reduced the risk of hip fractures in a study evaluating 9331 elderly women at high risk of fracture [41].

Risedronate has been shown to effectively reduce the risk of non-vertebral fractures after 3 years of treatment [46]. Another study, involving early postmenopausal women, demonstrated that, as compared with placebo, 5 mg risedronate daily increased BMD at the lumbar spine by more than 5% during 2 years of treatment ($p < 0.05$ as compared with both baseline and placebo) [47]. Other studies have confirmed those findings, showing that risedronate prevents bone loss and preserves trabecular architecture in early postmenopausal women [48]. In addition, key clinical trials have shown that reductions in vertebral fracture risk with risedronate are independent of increases in BMD [41].

The Study of Anastrozole with the Bisphosphonate Risedronate evaluated the effects of risedronate on BMD and bone turnover in postmenopausal women using anastrozole as adjuvant therapy for hormone receptor–positive early breast cancer [49]. The preplanned analysis of markers of bone turnover after 6 months of therapy were presented in June 2007 [49]. Patients were stratified according to baseline fracture risk by lumbar spine and hip T scores, with higher risk defined as including patients with a T score of less than –2 or a history of fracture, or both. "Moderate risk" included patients with a T score of less than –1, but greater than or equal to –2. "Low risk" included patients with a T score of –1 or better. High-risk patients received open-label anastrozole plus risedronate 35 mg once weekly. Moderate-risk patients were randomized in a double-blind manner to receive anastrozole plus risedronate or placebo. Low-risk patients received open-label anastrozole only. All patients were given calcium and vitamin D. Low-risk patients demonstrated a significant increase in serum CTX ($p = 0.05$), but no significant change in P1NP or bone ALP. Significant decreases in all bone markers were noted for the high-risk patients ($p < 0.0001$). In the moderate-risk group, all markers significantly declined in patients receiving anastrozole plus risedronate as compared with patients receiving anastrozole plus placebo ($p < 0.0001$). Risedronate was able to reduce bone turnover in anastrozole-treated postmenopausal women with hormone receptor–positive early breast cancer and a pre-existing moderate or higher risk of fracture [49].

*Zoledronic Acid:* Zoledronic acid is the most potent bisphosphonate currently available [50,51]. It contains two nitrogen atoms in the R2 side chain, and the intravenous administration of 4-mg doses has been approved for the prevention and treatment of metastatic bone disease and hypercalcemia of malignancy. Zoledronic acid 5 mg has been approved in Canada as a treatment for Paget disease.

In a double-blind placebo-controlled dose-ranging trial involving 351 postmenopausal women with low BMD, significant reductions in markers of bone resorption were noted, together with improvements in BMD, in all treatment groups over placebo [52]. In addition, the study noted that zoledronic acid 4 mg annually achieved reductions in bone turnover comparable to those seen with daily oral bisphosphonate therapy [52].

The phase III randomized controlled Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial (PFT) evaluated the effects of zoledronic acid 5 mg annually on fracture incidence in men and women 50 years of age or older who had already sustained a low-trauma hip fracture [53]. Data from that trial demonstrated that zoledronic acid reduced the 3-year risk of vertebral fractures by 70% over placebo (relative risk: 0.30; 95% CI: 0.24 to 0.38). The 3-year fracture risk for hip fractures was reduced by 41% in the zoledronic acid group over placebo. Increases in BMD were significantly higher and height loss was lower in the zoledronic acid group [53].

In another study, 301 patients receiving adjuvant letrozole were randomized to upfront or delayed zoledronic acid given intravenously in doses of 4 mg every 6 months [54]. Zoledronic acid was administered when the lumbar spine or total hip T score dropped below –2 or in the presence of a non-traumatic fracture. At 12 months, lumbar spine BMD was 4.4% higher in the upfront group than in the delayed start group. Bone resorption marker was also 15% lower in the upfront group. Zoledronic acid has been approved for the prevention of osteoporosis in the postmenopausal female population. Further evaluation of this valuable agent in preventing bone loss induced by cancer treatment is planned.

*Bisphosphonate Advantages and Disadvantages:* A major advantage of oral bisphosphonate therapy is ease of administration and an excellent tolerability profile. The side effects most commonly associated

with such therapy are abdominal pain and dysphagia. However, alendronate and risedronate have both demonstrated upper gastrointestinal side effects comparable to placebo in the randomized controlled trials conducted to date [55]. Intravenous administration of bisphosphonates provides a number of advantages, including less frequent dosing and less potential for gastrointestinal side effects as compared with oral bisphosphonates.

Recently, reports of mandibular or maxillary osteonecrosis as a potential rare complication of bisphosphonate use have been published [56]. Osteonecrosis of the jaw (ONJ) is an avascular bone necrosis that may occur in patients at risk for this condition. Most of the reports have been associated with frequent high-dose administration of intravenous pamidronate or zoledronic acid in oncology patients with a history of breast cancer or myeloma. Many of these patients have been on concomitant chemotherapy or radiotherapy (or both), which are risk factors for avascular bone necrosis. The condition has been most commonly reported in high-risk individuals following dental surgery such as dental extraction [57]. The condition has seldom been reported with alendronate and risedronate use [56]. It is important to note that ONJ has not been seen in any of the clinical trials conducted to date, which represent prospective data obtained in more than 100,000 patients treated with aminobisphosphonates for an average of 3 years. All published cases have been anecdotal reports. In a retrospective chart review by the M.D. Anderson Cancer Center of 4000 cancer patients treated with zoledronic acid, pamidronate, or both, ONJ was identified in 0.825% of the patient population [58]. The HORIZON PFT trial found that the incidence of ONJ was similar in the treatment and placebo groups, with 1 case occurring in each group. The cases were validated by an adjudication committee.

Canadian guidelines regarding the diagnosis, prevention, and management of ONJ are expected to be published in early 2008 by a Canadian multidisciplinary task force on ONJ. Current international guidelines recognize ONJ as a very rare condition limited mostly to the oncology population receiving high-dose intravenous bisphosphonates. Prospective data in the oncology and non-oncology population are needed to better understand the underlying pathophysiology of ONJ so that appropriate decisions can be made about prevention, diagnosis, and management.

Administration of potent bisphosphonates has been shown to provide a number of advantages in patients with metastatic disease, such as the ability to effectively control hypercalcemia and to stabilize bone lesions while bypassing the gastrointestinal tract. Thus, intravenous bisphosphonates are of tremendous value in the management of skeletal complications in patients with malignancy, and they are an important component of therapy in those patients. The benefits of intravenous bisphosphonates far outweigh the risks of developing ONJ. Further prospective data are needed for the true incidence and pathophysiology of ONJ to be understood. The exact relationship between ONJ and the use of bisphosphonates also needs to be clarified. It should also be noted that the annual dose of intravenous bisphosphonates used in osteoporosis is significantly lower than that used in cancer patients.

Bisphosphonates are a valuable treatment option for postmenopausal osteoporosis as well as for steroid-induced bone loss. These agents may also be effective in preventing bone loss associated with cancer therapy; however, they have not yet been approved specifically for that indication.

***HRT:*** Hypogonadism may be the result of cancer therapy in non-hormone dependent tumours such as lymphoma. In those circumstances, hypogonadism will be associated with progressive bone loss and is not an intended effect of cancer treatment. Data regarding estrogen replacement in the postmenopausal female has confirmed significant improvements in BMD, reductions in the rate of bone turnover, and reductions in the risk of vertebral and non-vertebral fracture.

Estrogen therapy has significant antiresorptive effects. Specifically, it enhances the osteoblastic production of osteoprotegerin, which has anti-osteoclastic properties because of its ability to bind to RANKL and subsequently to block the RANKL/RANK interaction required for osteoclast recruitment and activation [59,60]. In the WHI, a primary prevention trial, the combined estrogen plus progesterone arm demonstrated an increase in total hip BMD, together with a 34% reduction in hip and vertebral fractures and a 24% reduction in total osteoporotic fractures [61]. The estrogen-only arm presented similar results, with a 30%–39% reduction in fracture rates [62]. This trial therefore confirmed the antifracture effects of HRT suggested by previous clinical trials [63,64]. In early postmenopausal women, combined estrogen–progesterone therapy resulted in increases in BMD of 2%–3% at the hip and spine over 2 years of therapy [63]. A decline in the markers of bone turnover in response to HRT was also seen in early postmenopausal women [64]. The combined estrogen and progesterone arm experienced a 26% increased risk of breast cancer and a 29% increased risk of cardiac events, prompting the early termination of this treatment group after 5.2 years of follow-up [65]. The estrogen-alone arm was also terminated prematurely because of a 41% increased risk of stroke and a doubling of the risk of thromboembolic disease [62]. Because the risks of HRT are significant and appear to outweigh the benefits, HRT is considered a treatment option for select patients unsuited to standard first-line antiresorptive therapies [66].

***RANKL Inhibitors:*** Denosumab is a fully human monoclonal antibody to RANKL; it binds to human

RANKL, thus preventing osteoclast activation and subsequently reducing bone resorption. A phase II study reported by McClung *et al.* demonstrated that denosumab was well-tolerated and had an effect on bone turnover similar to that of alendronate [67]. As compared with patients who received placebo, patients treated with denosumab experienced significantly increased BMD. Subcutaneous administration of the drug in doses of either 30 mg every 3 months, or 60 mg every 6 months, resulted in sustained decreases in urinary N-telopeptide excretion [67].

In addition, denosumab has been shown to effectively reduce bone turnover in patients with metastatic bone disease, with effects comparable to those of intravenous pamidronate [68]. This agent is currently being evaluated further in oncology patients with metastatic skeletal disease and in patients with postmenopausal osteoporosis. It is expected to become a valuable additional option in the management of those conditions.

#### *2.2.3 Anabolic Agents*

Until recently, postmenopausal osteoporosis treatment was limited to antiresorptive therapies. However, the availability of anabolic agents—namely, parathyroid hormone (PTH) and strontium ranelate—represent a major advance. Anabolic agents result in major improvements in the quality and the quantity of bone, significantly increasing bone strength.

***PTH—Teriparatide and Full-Length PTH:*** Teriparatide, a 34-amino acid recombinant fragment of the 84–amino acid human PTH, is administered subcutaneously in doses of 20 μg daily for 18 months. Although exposure to continuously elevated PTH levels is associated with bone loss, intermittent pulse therapy with PTH preferentially stimulates osteoblast activity and is associated with increases in BMD [69]. Teriparatide promotes the differentiation of pre-osteoblasts into bone-forming osteoblasts [70], resulting in a net increase in both the number and activity of bone-forming cells [69]. Several clinical trials have noted impressive effects of teriparatide on BMD and fracture risk [27,71–75].

In a randomized controlled trial involving postmenopausal women with fragility fractures, teriparatide 20 μg daily over 21 months led to a 9% increase in lumbar spine BMD and improved BMD at the femoral neck and whole body [27]. Risks for vertebral and non-vertebral fractures were reduced by 65% and 53% respectively [27]. Evidence for the anabolic effects of teriparatide on bone microarchitecture has been found in bone biopsies of patients treated with teriparatide. These show dramatic increases in the thickness, density, and number of trabeculae and increases in cortical thickness and bone size [71]. A reduction in back pain has also been noted with teriparatide use.

The full-length PTH molecule (1-84) has been assessed in the Treatment of Osteoporosis trial [72]. That 2-year study involved 2532 postmenopausal osteoporotic women who were randomized to receive 100 μg PTH (1-84) or placebo. The PTH was found to reduce the incidence of new vertebral fractures by 66%.

Teriparatide is well-tolerated; however, minor adverse events such as nausea, headaches, and transient mild hypercalcemia have been noted [70]. Preliminary studies in rats, in which the animals received near-lifelong exposure to high doses of teriparatide (5 μg/kg or more daily), found a dose- and duration-dependent relationship between teriparatide and the development of osteosarcoma [76]. However, such doses are much higher than the 20 μg daily dose (approximately 0.28 μg/kg daily) used in humans, and osteosarcoma has not been seen in humans or in studies with monkeys. Furthermore, it is important to note that osteosarcoma does not occur with increased frequency in individuals with primary hyperparathyroidism. To date, 300,000 people have been treated with teriparatide, and 1 case of osteosarcoma has occurred, which is comparable to the background incidence of osteosarcoma of 1 in 250,000.

Teriparatide is contraindicated in individuals who have had metastatic skeletal disease or who have a history of skeletal radiation. It is also contraindicated in patients with renal insufficiency, hypercalcemia, hypercalciuria, or elevated ALP that has not yet been evaluated. Because osteosarcoma is more common in individuals with Paget disease, teriparatide is contraindicated in those patients.

Combination therapies have included teriparatide in combination with HRT or with bisphosphonates [73,74]. Data suggest that pretreatment with alendronate may blunt the anabolic effects of PTH therapy [77]. Long-term fracture risk studies are required to determine if combination therapy is of value.

***Strontium Ranelate:*** Strontium ranelate has demonstrated antiresorptive effects and also appears to have anabolic properties. It has not been associated with an increased risk of osteosarcoma. It is incorporated into bone and accumulates in the skeleton because of its physical and chemical similarities to calcium [78].

Strontium ranelate provides skeletal benefits because it stimulates replication of pre-osteoblasts and synthesis of bone matrix; it also prevents bone resorption by inhibiting osteoclasts [79–83]. In a study involving ovariectomized rats, strontium ranelate prevented bone loss by reducing bone resorption and enhancing bone formation [84]. A phase III trial involving 1649 postmenopausal women demonstrated a 49% reduction in new vertebral fractures at 1 year in subjects administered strontium ranelate 2 g daily as compared with those receiving placebo [85]. A 16% reduction in non-vertebral fractures in the strontium ranelate group was also noted [86]. Subjects at high risk of fracture (74 years of age or older with a femoral neck BMD T score of –3 or lower) demonstrated an even greater reduction in risk of hip fracture (36%, $p = 0.046$) [58]. Side effects associated with strontium

ranelate have been limited to nausea and diarrhea during the first few months of therapy [80]. Current guidelines recommend that intervention be based on the presence of low BMD and planned cancer treatment.

### 2.3 Available Guidelines

International guidelines have been published providing recommendations for skeletal protection in oncology patients, including guidelines from the American Society for Clinical Oncology. A 2007 consensus statement published by the Belgian Bone Club provides recommendations for the management of bone loss induced by cancer treatment in early breast and prostate cancer [87]. Their recommendations include assessment of fracture risk and bone density testing by dual X-ray absorptiometry for all women beginning medical castration therapy or aromatase therapy. All men beginning androgen deprivation therapy should similarly be evaluated for risk of osteoporosis. Monitoring of BMD every 1–2 years for osteoporotic and osteopenic patients is recommended. In individuals with a normal baseline BMD, that assessment is recommended be repeated every 2–5 years, depending on the presence of other risk factors. Lifestyle modification with appropriate calcium and vitamin D supplementation is also recommended. Further evaluation to exclude secondary causes of osteoporosis such as vitamin D deficiency, hyperparathyroidism, or hyperthyroidism is recommended to ensure that no other factors are contributing to bone loss apart from androgen deprivation therapy or induction of hypogonadism.

Bisphosphonate therapy is recommended for osteoporotic individuals with a T score of –2.5 or lower, or a history of a fragility fracture. Bisphosphonates are also recommended for individuals who have important risk factors for fracture and osteopenia with a T score between –1 and –2.5. In the latter case, the recommendations suggest zoledronic acid 4 mg every 6 months for patients receiving AIs and zoledronic acid 4 mg annually or alendronate weekly for patients receiving androgen deprivation therapy.

Ongoing clinical trials evaluating the skeletal protective effects of bisphosphonates will provide further refinement of the existing recommendations.

## 3. SUMMARY

Osteoporotic fractures result in significant morbidity and increased mortality rates. Cancer treatment can dramatically reduce bone density and increase the rate of bone turnover and the risk of fragility fracture. The importance of both quantity and quality of bone in determining bone strength and fracture risk has been recognized. Bisphosphonates are being evaluated for their skeletal protective effects, and they offer great promise in the prevention of fragility fracture for patients receiving cancer treatment. Clinical research is also evaluating RANKL inhibitors, and other antiresorptive options and anabolic therapies are expected to possibly play a future role in the prevention of fracture in the patient with cancer. Early diagnosis and treatment of osteoporosis will contribute to improved health and wellbeing for the patient receiving cancer treatment.

## 4. DISCLOSURE

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