Bone Loss and Fracture Risk Associated with Cancer Therapy

THERESA A. GUISE
Department of Medicine, University of Virginia, Charlottesville, Virginia, USA

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Abstract
Background. Cancer patients experience osteoporosis resulting from accelerated loss of bone mineral density (BMD) caused by their treatment. Such bone loss greatly increases the risk for fracture and can have other serious effects on quality of life.

Methods. In the current report, the author focuses on studies of cancer therapy-associated bone loss, its prevalence and pathogenesis, and resulting clinical impact. Options for management and prevention are also reviewed, including treatment guidelines where available.

Results. A variety of cancer therapies, including hormonal therapy, chemotherapy, and glucocorticoids, affect gonadal hormone production, which increases bone resorption and decreases BMD. Such bone loss occurs more rapidly and to a greater degree than normal age-related osteoporosis, increases the risk for fracture and other morbidities, and decreases survival. Regular BMD screening and early intervention can prevent further decline in bone density and bone quality. Pharmacologic therapy with oral and i.v. bisphosphonates has been shown to slow bone loss in patients receiving cancer therapy, and the i.v. bisphosphonate zoledronic acid can increase BMD in patients with cancer treatment-related bone loss. Lifestyle changes, including supplementation with calcium and vitamin D, diet, and proper exercise, can also slow the rate of bone loss.

Conclusions. Bone loss associated with various cancer therapies significantly affects bone health. Early initiation of bisphosphonates, when indicated, and lifestyle modification can improve patient outcomes. Education of patients and health care professionals regarding the importance of this complication and effective treatment options is essential. The Oncologist 2006;11:1121–1131

Introduction
Patients with cancer are at increased risk for developing osteoporosis as a result of complications from their anti-cancer therapy. A variety of hormonal and nonhormonal treatments have the potential to promote bone loss by inducing hypogonadism, which increases bone resorption.

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and bone turnover. Examples include endocrine therapies for breast cancer (e.g., selective estrogen-receptor modulators [SERMs] and aromatase inhibitors [AIs]), androgen deprivation therapy (ADT) for prostate cancer, various chemotherapeutics, and glucocorticoids (Table 1) [1]. Surgical gonadal ablation, such as bilateral orchiectomy in prostate cancer and oophorectomy in breast cancer, also results in hypogonadism and bone loss in patients with hormone-sensitive tumors. Such bone loss can lead to osteoporosis, which is associated with an increased fracture risk, decreased bone strength, diminished quality of life, and increased mortality [2–4].

A significant proportion of men and women in the U.S. are at increased risk for fracture from bone loss. It is estimated that nearly one third of postmenopausal Caucasian women suffer from osteoporosis, and 25% have at least one vertebral deformity [5]. While the actual incidence of fracture is not known, the estimated lifetime risk of developing a fracture is 40% in women >50 years of age and 13% for men >50 years of age [5]. As many as two thirds of all vertebral fractures go undiagnosed (so-called “silent fractures”). Individuals with a history of fracture are at increased risk for subsequent fractures.

Fractures can have a significant impact on health care costs, because many patients require hospitalization followed by rehabilitation in long-term care facilities. Between 2001 and 2003, Medicare expenditure on fractures among older women with osteoporosis was estimated to be nearly $13 billion [6]. For 80-year-old individuals, it was estimated that hip fracture resulted in a longer time in a nursing facility, by 237 days, and a 25% lower life expectancy compared with age- and sex-matched controls [7]. The estimated lifetime cost attributed to hip fracture was $81,300, much of which was related to nursing facility costs. Another study found that hip fractures resulted in average hospital stays of 16.3 days in the orthopedic ward, higher health care costs, and higher 1-year mortality rates compared with the general population [8]. Other investigators have found a similar negative impact of fracture on survival. Hip or vertebral fracture was associated with a 20% greater expected mortality rate after 5 years [5]. These studies demonstrate the substantial negative effects of osteoporosis and fracture on morbidity, mortality, and overall health care costs. Thus, diagnostic methods that can identify cancer patients at risk for osteoporosis and approaches to halt or reverse bone loss are of prime concern for oncologists.

### Unique Aspects of Cancer Therapy-Associated Bone Loss

Bone loss that occurs with cancer therapy is generally more rapid and severe than postmenopausal bone loss in women or normal age-related osteoporosis in men. Rates of bone loss occurring with cancer therapy can be up to tenfold higher than normal (Fig. 1) [4, 9–14]. In normal men, bone mineral density (BMD) decreases at a rate of 0.5%–1.0% per year starting in midlife [4]. Women have higher rates of bone loss around menopause—an average of 2% loss in bone mass per year for 5–10 years—which then declines over time [9]. Patients receiving cancer therapy, however, can experience bone loss at significantly higher rates. For example, bone loss in men with prostate cancer on ADT can occur at a rate of 4%–5% per year. Marked changes are detectable at 6 months after initiation of hormonal therapy in men with prostate cancer [13].

Significant bone loss can occur in women with breast cancer who are treated with AIs or other endocrine therapies. Results of recent trials such as the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, the MA-17 trial, the Breast International Group 1-98 (BIG 1-98) trial, and the Intergroup Exemestane Study (IES) have demonstrated that adjuvant therapy with an AI (e.g., anastrozole, letrozole, or exemestane) is superior to treatment with tamoxifen in women with hormone receptor–positive disease [15–18].

The ATAC trial compared 5 years of adjuvant therapy with anastrozole, tamoxifen, or the combination in postmenopausal women with early-stage breast cancer. Women who received anastrozole lost 4% and 6.1% of bone mass in the lumbar spine after 2 years and 5 years, respectively. Notably, four of the five women with baseline osteopenia who went on to develop osteoporosis on study received anastrozole; however, no women with normal

<table>
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<tr>
<th>Therapy</th>
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<td>Bilateral orchiectomy</td>
<td>Prostate cancer</td>
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<td>Oophorectomy</td>
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<td>Androgen deprivation therapy</td>
<td>Prostate cancer</td>
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<td>Chemotherapy</td>
<td>Various malignancies</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Breast cancer</td>
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<tr>
<td>Methotrexate/ifosfamide</td>
<td>Osteosarcoma</td>
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<td>Alkylating agents</td>
<td>Hodgkin’s/non-Hodgkin’s lymphoma</td>
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<td>Selective estrogen-receptor modulators</td>
<td>Breast cancer</td>
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<td>Aromatase inhibitors</td>
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<td>Glucocorticoids/cyclosporine</td>
<td>Stem cell transplantation for various malignancies</td>
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<td>Radiation therapy</td>
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BMD at study entry developed osteoporosis, regardless of treatment [19]. This suggests that women at highest risk for progressing to osteoporosis on an AI are those with preexisting low BMD. Patients receiving anastrozole had a >1.5-fold higher risk for fracture compared with those not treated with an AI [20].

Women in the MA-17 trial also experienced more fractures with letrozole after tamoxifen than placebo, although this difference was not significant. However, they were significantly more likely to be diagnosed with new-onset osteoporosis [16]. The recent bone substudy of MA-17 demonstrates a decrease of 5.4% in lumbar spine BMD after 2 years of letrozole [21]. Similarly, the BIG 1-98 study reported a significantly higher risk for fracture in postmenopausal women treated with letrozole for 5 years compared with those who received tamoxifen [17].

This question was also studied in the IES of 4,742 postmenopausal women with primary breast cancer who had received 2–3 years of prior tamoxifen therapy and were then randomized to exemestane or remained on tamoxifen [18]. After a median follow-up of >30 months, patients treated with exemestane had a higher incidence of osteoporosis (7.4%) than those who remained on tamoxifen but did not switch to exemestane (5.7%) and bone loss at the lumbar spine was 3.6% [18, 22].

The overall effects on bone health of the nonsteroidal AIs (anastrozole and letrozole) compared with the steroidal AI exemestane are controversial. Osteoporosis was more frequent in patients receiving exemestane but the fracture rate was only slightly higher than with tamoxifen and did not reach statistical significance [18]. It has been hypothesized that the partial androgenic activity of exemestane and its major metabolite may mitigate the bone loss occurring during treatment with this AI. Although bone fracture rates differ among these trials with distinct treatment arms and patient populations, it appears that all AIs result in bone loss of approximately 4%–5% over the first 2 years of treatment [19, 21, 22].

Similarly, bone loss commonly occurs in men with prostate cancer who are treated with ADT, with annual BMD declines of 2%–8% [23, 24]. Maillefert et al. found that, after 1 year of ADT, there was a 4.6% decrease in BMD at the lumbar spine and a 3.9% decrease at the femoral neck [13]. Orchietomy also resulted in substantial changes, with a 15% decrease in trochanter BMD after 1 year reported in one study [25]. After 1 year of ADT, 15 men with adenocarcinoma of the prostate had significantly lower BMD at the total hip and ultradistal radius than age- and sex-matched controls. The mean bone loss was 3.3% at the total hip and 5.3% at the ultradistal radius, an area rich in trabecular bone [26]. Collectively, these results indicate that substantial loss of BMD occurs in patients with breast and prostate cancer treated with a variety of cancer therapies, causing significant morbidity and mortality.

Screening for Bone Loss

Osteoporosis often remains undetected in patients with cancer until bone fracture occurs. Consequently, detection and prevention of bone loss are important clinical goals of therapy. Yet bone density testing is performed in only 3%–32% of high-risk patients [27, 28]. Several organizations, therefore, have developed clinical guidelines for screening cancer patients for bone loss. The U.S. Surgeon General's office recommends BMD screening for all patients at increased risk for osteoporosis. This includes postmenopausal women >65 years of age, younger women with multiple risk factors, women with fragility fractures, and those taking medications that can increase fracture risk [29]. The American Society of Clinical Oncology (ASCO) has established guidelines for breast cancer patients, recommending that all women considered at high risk for osteoporosis be evaluated for BMD. This includes: all women >65 years of age; women 60–64 years of age with a family history of fractures, body weight <70 kg, prior nontraumatic fracture, or other risk factors; postmenopausal women receiving AI therapy; and premenopausal women with ovarian failure.
Cancer-Related Bone Loss and Fracture Risk

Secondary to treatment [30]. Clinical practice guidelines for patients with breast cancer issued by the Guidelines from the U.S. Preventive Services Task Force are broader, recommending BMD screening for all women >65 years of age [31]. Similarly, National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend BMD screening for men with prostate cancer who undergo surgical or chemical castration [32]. All patients with prostate cancer who receive ADT should undergo BMD screening at baseline and at yearly intervals to monitor for further bone loss [23, 33].

Subsequent monitoring for bone loss is recommended based on baseline T-score and the presence of confounding risk (Table 2) [30, 34]. The T-score reflects the number of standard deviations (SDs) by which a patient’s bone mass varies from the mean value for sex-matched young adults (see below) [2]. Although professional guidelines recommend only high-risk breast cancer patients with T-scores between −1 and −2.5 undergo monitoring on an annual basis for changes in BMD, it is the opinion of this author that all patients receiving therapy that depletes estrogen should have regular assessment of BMD. These same guidelines recommend bisphosphonate or raloxifene therapy, along with annual BMD testing, only for those with scores ≤–2.5. The practice of this author differs in that patients with T-scores between −1 and −2.5 are treated with bisphosphonates to prevent the development of osteoporosis, unless such drugs are contraindicated. All patients should receive guidance regarding lifestyle changes, such as proper exercise, supplementation with calcium and vitamin D, and dietary modification, as discussed later. Finally, patients with existing osteopenia and osteoporosis should be evaluated for conditions that further insult skeletal health, such as vitamin D deficiency, hyperthyroidism, hyperparathyroidism, and hypercalciuria. Markers of bone resorption, such as cross-linked N-telopeptide of type I collagen (NTx), may be useful to predict bone loss in those patients with osteopenia.

No similar consensus exists for BMD testing in men with prostate cancer, although an expert panel recently issued screening recommendations [23]. The panel proposed that all men at increased fracture risk (i.e., those on ADT and/or with a history of fracture) should have routine BMD assessment. Patients with a score ≥−1 should be monitored and rescreened every 2 years. Those with a T-score of −1 to −2.5 should have BMD testing repeated after 6–12 months. Recent clinical practice guidelines call for intervention with i.v. bisphosphonates in men with prostate cancer who are osteopenic/osteoporotic or are being treated with androgen ablation [32].

The standard approach for measurement of bone loss relies on a technique known as central dual-energy x-ray absorptiometry (DXA). DXA has been widely used for quantifying bone loss in the spine, proximal femur, and total body. In addition to diagnosing osteoporosis, DXA can aid in treatment decisions and monitoring response to therapy. This test can be performed rapidly in the outpatient setting and allows use of lower doses of radiation than with conventional x-rays or quantitative computed tomography (QCT). Changes in BMD in peripheral sites, such as heel, forearm, and finger, are more accurately measured using peripheral DXA or single-energy x-ray absorptiometry (SXA) [35]. These techniques may be useful for predicting fracture risk.

### Table 2. Management of bone loss in patients with breast cancer [30, 34]

<table>
<thead>
<tr>
<th>Risk level</th>
<th>T-Score</th>
<th>T-Score</th>
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<tr>
<td></td>
<td>&gt; −1 (normal BMD)</td>
<td>−1 to −2.5 (osteopenia)</td>
<td>&lt; −2.5 (osteoporosis)</td>
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<tr>
<td>Low risk</td>
<td>Lifestyle modifications</td>
<td>Lifestyle modifications</td>
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<td>Daily calcium, vitamin D supplementation</td>
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<td>Annual assessment of risk factors</td>
<td>Annual assessment of risk factors</td>
<td>Annual assessment of risk factors</td>
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<tr>
<td>High risk</td>
<td>Annual BMD testing</td>
<td>Annual BMD testing</td>
<td>Annual BMD testing</td>
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<tr>
<td></td>
<td>Lifestyle modifications</td>
<td>Lifestyle modifications</td>
<td>Initiate therapy with bisphosphonate or raloxifene&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Daily calcium, vitamin D supplementation</td>
<td>Daily calcium, vitamin D supplementation</td>
<td>Lifestyle modifications</td>
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<td>Annual assessment of risk factors</td>
<td>Annual assessment of risk factors</td>
<td>Daily calcium, vitamin D supplementation</td>
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<tr>
<td></td>
<td>Consider therapy with bisphosphonates or raloxifene</td>
<td>Consider therapy with bisphosphonates or raloxifene</td>
<td>Annual assessment of risk factors</td>
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<sup>a</sup>Raloxifene is indicated for patients who are not receiving aromatase inhibitors and who have not received tamoxifen.

Abbreviation: BMD, bone mineral density.
in patients, but do not exclude osteoporosis at central sites. These modalities are less precise than DXA and cannot be used to follow fracture [36]. Other newer methods such as quantitative ultrasonography (QUS) [37] and peripheral QCT may provide additional information on bone strength and quality but are not routinely used in the clinical setting.

Results of BMD testing as reported in T-scores reflect bone density but do not reflect bone loss, unless measured in a serial fashion. A T-score of at least –1 indicates BMD within normal limits, whereas a value of –1 to –2.5 (i.e., at least 1 SD below the mean) indicates low bone mass or osteopenia. A T-score ≤–2.5 defines clinically significant osteoporosis, and in the presence of a fracture is considered severe. Patients with T-scores ≤–2.5 and patients with T-scores revealing osteopenia in the presence of risk factors are candidates for bisphosphonate therapy. In the appropriate populations, such as postmenopausal women, T-scores are predictive of fracture risk, with larger changes in T-score reflecting greater bone loss and higher fracture risk [38]. Moreover, there is an exponential relationship between decline in BMD and increased fracture risk (Fig. 2) [39]. A 10%–15% decrease in BMD approximately doubles the risk for fracture. Consequently, small increases in BMD can have a significant impact on bone health and reduction in fracture risk. It is important that BMD measurements of the spine and hip be standardized to ensure accurate and reproducible DXA measurements [40]. Daily quality control measures using a spine phantom and calibration against models simulating different amounts of body fat are essential to ensure accuracy and precision [41].

The true incidence of bone fracture in older cancer patients (e.g., postmenopausal women) is likely underestimated as a result of the occurrence of undetected or “silent” fractures. Up to two thirds of all vertebral fractures may not be clinically diagnosed since they do not produce any obvious symptoms. These may be caused by simple falls rather than severe trauma, and often go unrecognized by patients and physicians [42]. In addition to pain, these can affect posture, height, and quality of life, and increase the risk for additional vertebral and hip fracture. Routine BMD screening of at-risk patients can help detect inapparent fractures and allows initiation of therapy as indicated.

In cases where DXA is not informative, definitive analysis of bone quality and diagnosis of osteoporosis can be achieved through a bone biopsy, which is considered to be the gold standard [43]. This approach, however, is invasive and costly, and provides only a two-dimensional histologic assessment. Newer, less invasive diagnostic methods such as high-resolution magnetic resonance imaging (MRI) are being developed that may offer significant advances over biopsy and DXA. There is also growing interest in the use of biochemical markers of bone turnover to monitor response to treatment of osteoporosis and these surrogate markers are being evaluated in clinical trials (see Future Directions section).

**Managing Bone Loss**

Existing treatment guidelines recommend that men and women who are osteoporotic should be strongly considered for bisphosphonate therapy [30–32]. Bisphosphonates may be used in conjunction with chemotherapy and endocrine therapy. Currently, the bisphosphonate alendronate is approved in the U.S. for the treatment and prevention of osteoporosis in men and postmenopausal women. Risedronate and ibandronate (oral and i.v.) are also approved for use in postmenopausal women, and alendronate and risedronate are approved for glucocorticoid-related osteoporosis in both men and women. Numerous studies have been conducted with these and other bisphosphonates that demonstrate a beneficial effect on inhibiting bone loss and, in some cases, reducing fracture risk.

Bisphosphonate therapy is designed to prevent or slow the rate of bone loss in patients receiving cancer treatment to reduce fracture risk. Initiation of therapy earlier, prior to the occurrence of severe osteoporosis or fracture, rather than later may therefore be more effective. This is supported by results from the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) in which zoledronic acid was evaluated for prevention of cancer therapy-related bone loss in 602 postmenopausal women with early breast cancer who were receiving adjuvant letrozole therapy. Zoledronic acid
(4 mg i.v. infusion every 6 months) was administered either upfront or delayed (until postbaseline T-score declined <–2 SD or occurrence of fracture). Upfront treatment with this bisphosphonate increased BMD as early as 6 months after initiation of therapy, whereas delayed administration resulted in decreased BMD (Fig. 3) [44].

While both oral and i.v. bisphosphonates can slow or prevent bone loss accompanying cancer therapy in patients with breast or prostate cancer, there are significant differences in activity [45]. Some agents can reduce skeletal-related events (SREs), prolong time to first SRE, and alleviate pain in women with metastatic breast cancer receiving chemotherapy or endocrine therapy and men with metastatic prostate cancer receiving ADT. The i.v. bisphosphonate pamidronate prevented bone loss at the hip and lumbar spine in patients treated with ADT for advanced/recurrent, nonmetastatic prostate cancer [46]. However, only zoledronic acid has been shown to significantly increase BMD over baseline in this patient population (Fig. 4) [47]. Longer survival has not been demonstrated with any bisphosphonate.

Effective management of bone loss is key for patients who experience osteoporosis resulting from their malignancy and cancer therapy. This can be divided broadly into two categories: improving bisphosphonate therapy by increasing compliance and reducing toxicity, and lifestyle modifications that help reduce bone loss and fracture risk.

Safety
The toxicity profile of oral bisphosphonates differs from that of their i.v. counterparts. Oral bisphosphonates are often limited by their pharmacodynamics and toxicity in the gut. As a result of poor gastrointestinal (GI) absorption (<5% of administered dose), larger amounts of drug must be given. Absorption can be further decreased if these agents are not taken exactly as prescribed. High doses can cause significant GI toxicities, including esophageal and gastric ulcers, esophagitis, and nausea. However, oral bisphosphonates can be administered at home in weekly or monthly formulations, offering convenience for patients [48].

Figure 3. Upfront administration of zoledronic acid to premenopausal women with breast cancer increased bone mineral density (BMD) in the lumbar spine and hip at 6 months after initiating therapy compared with delayed administration. From data in Brufsky A, Harker G, Beck T et al. Zoledronic acid (ZA) for prevention of cancer treatment-induced bone loss (CTIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (Let): preliminary results of the Z-FAST trial. Presented at the 27th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, December 8–11, 2004, with permission.

Figure 4. Change from baseline in bone mineral density at the lumbar spine, femoral neck, trochanter, and total hip in men with nonmetastatic prostate cancer receiving androgen deprivation therapy.

*Statistically significant difference for zoledronic acid compared with placebo (p <.001).

Intravenous bisphosphonates are generally well tolerated, although transient flu-like symptoms, such as nausea, myalgia, arthralgia, and low-grade fever, and increased bone pain can occur [48]. Approximately one third of patients experience such symptoms, usually following the first infusion. These typically resolve over several hours to days, and may respond to acetaminophen or low-dose steroids.

Acute renal toxicity has occurred following rapid infusion of i.v. bisphosphonates for the treatment of multiple myeloma and Paget’s disease [49, 50] as well as after inadvertent overdose [51], but this is rare if drugs are administered as indicated. Increases in serum creatinine levels are usually not of clinical significance. Given the potential for renal toxicity, monitoring of serum creatinine levels is recommended at baseline and prior to drug infusions [30, 48]. For patients with significantly elevated serum creatinine, dosing should be withheld until levels return to within 10% of baseline. Pamidronate and zoledronic acid are not indicated for cancer patients with severe renal impairment (i.e., creatinine clearance <30 ml/min).

The safety of bisphosphonates in patients with pre-existing renal insufficiency has not been fully evaluated. Multiple cycles of therapy could lead to progressive renal deterioration and renal failure with the need for subsequent dialysis. Physicians should consider the potential risks and benefits of continuing bisphosphonate therapy in patients with hypercalcemia of malignancy who exhibit severe renal impairment. Other risk factors that may affect renal toxicity of bisphosphonates include dehydration and the use of other nephrotoxic drugs [52]. Dose adjustment of zoledronic acid is not necessary for patients with hypercalcemia and mild-to-moderate renal impairment (serum creatinine <400 μmol/l or <4.5 mg/dl) prior to initiating therapy with zoledronic acid [53].

Osteonecrosis of the jaw (ONJ) was first reported in 2003 as a complication in patients with metastatic cancer or multiple myeloma treated with containing bisphosphonates [54]. The following year a retrospective chart review of 124 patients at Memorial-Sloan Kettering Cancer Center identified 13 patients with these diseases who had been treated with i.v. bisphosphonates and developed ONJ [55]. The only prospective study of ONJ in 252 patients with multiple myeloma or metastatic breast or prostate cancer was published in 2005 by Bamias et al. [56]. These authors reported an overall incidence of 6.7% and concluded that the incidence increased with longer duration of i.v. bisphosphonate exposure—from 1.5% after 4–12 months of therapy to 7.7% after 37–48 months of therapy. ONJ was significantly more common in patients receiving zoledronic acid than in those treated with pamidronate. Most patients presenting with ONJ in these three studies had been treated with chemotherapy, radiation therapy, or steroids, had experienced oral trauma, or had experienced recent or existing periodontal problems such as extraction or infection [54–56].

A large chart review at the MD Anderson Cancer Center recently estimated the incidence of ONJ to be 0.73% among approximately 4,000 patients treated with i.v. bisphosphonates [57]. Of note, all affected patients had either multiple myeloma or metastatic breast cancer, with no ONJ occurring in the settings of other metastatic solid tumors, osteoporosis, or hypercalcemia of malignancy. Higher doses and longer duration of treatment, dental extractions, and periodontal disease were identified as risk factors. Older age was also found to be a significant risk factor in a retrospective review of 90 patients with multiple myeloma [58].

An expert panel of oral and maxillofacial surgeons, endocrinologists, and medical oncologists was convened to identify risk factors and propose clinical guidelines for managing ONJ [59]. The report of this group, and a similar position paper of the American Academy of Oral and Maxillofacial Pathology [60], concluded that its true incidence cannot be accurately determined from the retrospective reviews and case reports published to date. This information, as well as causal factors related to this adverse event, is the subject of large ongoing prospective trials.

To safeguard against ONJ, patients should alert dental professionals that they are initiating bisphosphonate therapy. A thorough oral exam is recommended prior to initiating treatment, and good oral hygiene should be stressed. Any dental procedures and major debridement surgeries should be postponed if possible. ONJ is best managed through conservative measures such as antibiotics and chlorhexidine mouth rinses. Increased awareness of this risk during bisphosphonate therapy and early diagnosis of ONJ may reduce the morbidity associated with such complications [59, 60].

**Compliance**

Compliance is a potential barrier to effective use of oral bisphosphonates. Long-term, consistent adherence to prescribed therapy is essential for patients to realize the full benefits of treatment. Poor compliance is not uncommon, however, and can result in early discontinuation of therapy and reduced efficacy. Lower adherence (<80% of prescribed dose) or early discontinuation of these agents was shown to result in lower BMD and higher fracture risk compared with patients having good compliance [61].

Poor compliance may result from drug-related GI adverse effects, resulting in missed doses and/or drug discontinuation [48]. Tosteson et al. [62] reported that 20% of patients on oral bisphosphonates discontinued therapy after...
less than 1 year because of toxicity or not fully understanding the significance of their bone density testing results [62]. Additionally, some patients have difficulty swallowing the capsules or following complex dosing procedures required to minimize GI toxicity (e.g., remaining upright after swallowing medication) and maximize efficacy (e.g., waiting 30 minutes before consuming food or beverage). Despite these potential barriers, oral bisphosphonates are successfully taken by many women and men with postmenopausal or age-related osteoporosis. Better education of patients and health care professionals regarding the importance of good compliance with oral bisphosphonate therapy and its impact on efficacy and toxicity will help to maximize patient outcomes.

**Lifestyle Modifications**

In addition to bisphosphonate therapy, other nonpharmacologic interventions can help improve bone health with the aim of reducing fracture risk in patients receiving cancer therapy. A proper diet will ensure that protein consumption is sufficient for maintaining muscle strength and body weight, and that intake of essential vitamins and minerals is adequate. Because calcium and vitamin D are key for bone formation and maintenance, patients should be counseled (possibly by a registered dietitian) to obtain foods rich in these nutrients and have adequate sunlight exposure for vitamin D production [29]. For patients unable to reach the daily target levels of calcium and vitamin D, bioavailable supplements are an option. The total recommended calcium intake is 1,200 mg/day. Any supplemental calcium should be taken in divided doses to improve absorption. Vitamin D intake should range from 400–800 IU daily; older patients (>60 years of age) may require the higher level (800 IU/day) to reduce fracture risk [63]. Routine monitoring of serum levels of 25-hydroxyvitamin D (25OHD; the primary metabolite of vitamin D) may identify vitamin D deficiencies and facilitate prompt intervention [64]. A 25OHD concentration of 30 ng/ml or higher is optimal for skeletal health. All patients on bisphosphonate therapy should have routine assessment of their vitamin D status.

A regular exercise program can help improve bone strength and mobility in cancer patients at risk for bone loss. Both weight-bearing aerobic exercise (e.g., walking, stair climbing) and muscle-strengthening exercise (weight lifting, exercise machines) should be performed 4–5 times per week for ≥30 minutes a day [4]. Such a program will increase bone health and strength, improve overall wellbeing and quality of life, and decrease the incidence of falls that may lead to fracture. Other lifestyle changes that can improve bone health include smoking cessation and avoidance of excessive alcohol and caffeine [65].

**Future Directions**

Current studies are investigating new avenues for improving diagnosis, prognosis, and treatment for patients experiencing bone loss related to cancer therapy. These include analysis of circulating biomarkers of bone metabolism, high-resolution MRI, and alternate bisphosphonate dosing schedules.

**Bone Biomarkers**

Changes in levels of biochemical markers associated with bone metabolism may have prognostic utility in the management of osteoporosis for patients with cancer. Therapies that cause hypogonadism result in increased bone turnover, and biochemical markers of bone formation and bone resorption can be detected in the serum and urine of cancer patients with bone metastases [26, 66, 67]. Several studies in malignant bone disease have demonstrated that high urinary levels of the bone resorption marker NTXs are correlated with poorer outcome, including a higher risk for fracture and other SREs, greater risk for disease progression, as well as a four- to sixfold greater risk for death [68–70]. Bone biomarkers, therefore, may be useful for predicting skeletal complications, although their value in the diagnosis of bone metastases or other SREs has not yet been determined. Several markers of bone resorption and formation are currently being evaluated as useful surrogate markers for monitoring response to bisphosphonates in the premetastatic setting.

Another novel approach to assessing osteoporosis and fracture risk is through use of high-resolution MRI (μMRI). This noninvasive technique (a “virtual bone biopsy”) allows qualitative imaging and quantitative analysis of bone trabecular microarchitecture [71]. In men with hypogonadism, μMRI could detect deterioration of bone architecture before any detectable BMD changes. This powerful method is being developed to provide three-dimensional imaging of bone, providing full tissue disclosure rather than information based on a limited tissue sample.

**Alternate Bisphosphonate Dosing Regimens**

As a result of the complexity of oral dosing regimens, poor compliance, and toxicity that can limit daily or weekly administration of oral bisphosphonates, other schedules relying on intermittent or extended dosing are being investigated [72]. Monthly or intermittent administration of oral ibandronate was shown to be at least as effective as daily therapy in women with postmenopausal osteoporosis, with similar gains in BMD [73, 74]. Extending this further, the effects of once-yearly zoledronic acid on BMD and bone turnover were found to be equivalent to an every-3-month regimen [75]. A recent study demonstrated that a single
injection of zoledronic acid was superior to daily treatment with risedronate for Paget’s disease, characterized by high bone turnover [76]. Ongoing trials are evaluating whether this yearly dosing regimen can also reduce fracture risk in patients with osteoporosis.

**Conclusions**

Patients with cancer are at significant risk for bone loss and fracture, not only from their disease and age-related osteoporosis but also from therapy for their malignancy. A variety of anticancer treatments induce or exacerbate bone loss, which has been shown to occur in hormone-sensitive tumors and other cancers. This loss of bone density has serious clinical consequences, increasing the risk for fracture and other morbidities that can in turn decrease survival. Unfortunately, low awareness of this problem and infrequent screening result in many cancer patients with undiagnosed bone loss. Thus, significant decreases in BMD may occur well before osteoporosis per se is manifested or before fracture is detectable. Recognition of the magnitude of this problem and early identification of patients at risk for bone loss are key to effective management.

Because cancer therapy-associated bone loss is largely preventable, an aggressive approach to bone health is critical. Preserving BMD should be an important concomitant goal of cancer therapy and not simply considered as supportive care. High-risk patients should have early and regular assessment of BMD and risk factors for bone loss, with implementation of bisphosphonate therapy where indicated. Patients also need to be educated and empowered to take an active role in promoting bone health through better diet, supplementation, exercise, and other positive lifestyle changes. Such a proactive rather than reactive approach to bone health will help to maintain BMD, minimize fracture risk, and improve outcomes and quality of life in patients receiving cancer therapy.

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**Disclosure of Potential Conflicts of Interest**

T.A.G. has acted as a consultant for Novartis, Amgen, and Scios.
Cancer-Related Bone Loss and Fracture Risk


