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Cancer Therapies and Bone Health

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Abstract Cancer patients are at risk for adverse events involving bone. Metastasis of cancer to bone and primary bone tumors can compromise the integrity of bone. Various cancer therapies cause long-term skeletal disorders, particularly bone loss, osteomalacia, and avascular necrosis. Cancer therapies that include chemotherapy, glucocorticoids, hormonal agents, and newer targeted therapies can affect bone in several ways. With the improved effectiveness of cancer treatment, more cancer patients are surviving longer and may experience fractures as a long-term complication of bone loss. Prevention of bone loss through early detection and appropriate use of anti-osteoporosis treatment may decrease bone loss and fractures. This article reviews causative risk factors, mechanisms, and prevention and treatment strategies for cancer therapy-related bone loss in hematologic and specific solid malignancies.

Keywords Osteoporosis · Cancer · Chemotherapy · Hormonal therapy · Adverse drug effect · Survivor · Bone

Clinical Trial Acronyms

ABCSG	Austrian Breast and Colorectal Cancer Study Group
ATAC	Arimidex, Tamoxifen, Alone or in Combination
BIG 1–98	Breast International Group 1–98 Collaborative Group—A Comparison of Letrozole and Tamoxifen in Postmenopausal Women With Early Breast Cancer
IES	Intergroup Exemestane Study
MA.17	National Cancer Institute of Canada Clinical Trials Group MA.17
REBBeCA	Prevention of Osteoporosis in Premenopausal and Newly Postmenopausal (Up to 8 Years) Women With Breast Cancer Following Chemotherapy
Z-FAST	Zometa-Femara Adjuvant Synergy Trial

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Introduction

The past two decades have been witness to progressive improvement in cancer outcomes, with current survival rates approaching 80% for many cancers. This translates into approximately 10.8 million cancer survivors in the United States. Cancer survivors frequently face challenging long-term complications of cancer treatment that involve their musculoskeletal, cardiopulmonary, gastrointestinal, and endocrine systems. Osteoporosis is generally recognized as one of the most common cancer therapy-related effects and leads to increased vertebral and hip fractures that compromise quality of life. Bone loss is aggravated by therapeutic regimens for treatment of cancer that take advantage of tumoral dependence upon hormonal stimulation, as is the case for breast and prostate cancer. In addition, exposure to glucocorticoids and various chemotherapeutic agents can lead to significant deterioration of bone health.

Bone is a metabolic tissue with an ongoing remodeling process initiated by osteoclast-mediated bone resorption followed by osteoblast deposition of collagen into the resorption lacuna; mineralization completes the cycle. The dynamic process of bone resorption and formation is tightly regulated by multiple factors, including hormones, cytokines, and growth factors that influence not only osteoblast and osteoclast cell lineages but also the microenvironment of the bone marrow [1]. Peak bone mass is generally achieved by early adulthood; it subsequently declines at a rate of 0.5% to 1% per year [2••]. With increasing age, the rate of bone resorption exceeds bone deposition, and a net loss of bone mass occurs. Bone loss can be accelerated at any age. For example, during the first 5 to 10 years after normal menopause and associated estrogen deficiency, women experience a rapid loss of bone mass approximating 2% per year [3]. Men lose bone mass at a rate of about 0.5% to 1% per year starting at midlife [3].

Hypogonadal states leading to estrogen and testosterone deficiencies are associated with abnormally increased marrow production of interleukin-1, interleukin-6 and tumor necrosis factor-α, as well as reduced bone synthesis of transforming growth factor-β1 [4]. Moreover, estrogen-deficient bone marrow is associated with reduced expression of osteoblast-specific transcription factors RUNX2 and osterix in osteoblast precursors, leading to lower bone formation rates. In hypogonadal individuals without cancer, estrogen and testosterone deficiencies translate into abnormalities in bone microarchitecture. Patients treated with estrogen or androgen deprivation therapy for breast or prostate cancer, respectively, may exhibit an abnormally increased RANKL (receptor activator for nuclear factor-κB ligand)/OPG (osteoprotegerin) ratio [5]. As RANKL plays a critical role in osteoclast formation, an effect that is blocked by OPG, patients treated with agents that lower estrogen or testosterone levels may have a marked increase in bone resorption, leading to microarchitectural abnormalities, osteoporosis, and/or fractures.

Hormonal Therapy

Bone loss associated with breast cancer therapy is usually more rapid and severe (2.6%–7.7% in the spine within the first year of various treatments) than that associated with natural menopause (averaging 2% per year for 5–10 years). Even more importantly, the annual incidence of vertebral insufficiency fractures is higher in patients with early-stage breast cancer than in the general population [6]. Results from the large observational study in the Women's Health Initiative showed that breast cancer survivors had a 15% higher rate of all fractures—regardless of the treatment they received—than women without any cancer history [7].

Androgen deprivation therapy (ADT) (bilateral orchiectomy, leuprolide, or other gonadotropin-releasing hormone [GnRH] analogues) for prostate cancer patients, alone or in combination with an antiandrogen (e.g., flutamide, bicalutamide), causes profound hypogonadism characterized by loss of libido, muscle mass, and bone. Significant bone loss can be seen in men within a year of castration or 6 months after initiating treatment with a GnRH analogue [8]. Accelerated bone loss in prostate cancer survivors is similar to that observed in women who have undergone bilateral oophorectomy and greater than that observed in healthy postmenopausal women. The annual incidence of osteoporotic fractures is higher in prostate cancer patients treated with surgical or medical castration than in those who receive nonhormonal treatment or in healthy men [9]. Fractures occur within 2 years of beginning ADT treatment and increase in frequency with longer duration therapy. Importantly, skeletal fractures in patients with prostate cancer may be associated with shorter survival, independent of the pathological stage of the cancer [10].

Selective Estrogen Receptor Modulators

In patients with breast cancer-expressing estrogen or progesterone receptors, adjuvant endocrine treatment blocks estrogen action on target organs (selective estrogen receptor modulators [SERMs]) or suppresses estrogen levels (aromatase inhibitors [AIs], or ovarian ablation or suppression). The SERMs, tamoxifen and raloxifene, have differential effects on various organs, with antagonist effects in breast tissue. SERMs have antagonist and agonist effects on the bone, depending on menopausal status. Premenopausal women taking a SERM can experience loss in bone mineral density (BMD) attributed to antagonism of the effects of endogenous estrogen on bone. In contrast, postmenopausal women, who have extremely low levels of bioavailable estrogen, typically exhibit increased BMD with a SERM, as its estrogen-like effect is sufficient to positively influence bone density [11]. Vehmanen et al. [11] treated premenopausal women with early-stage breast cancer with tamoxifen 6 months after they began adjuvant chemotherapy. After 3 years of follow-up, significant bone loss in the lumbar spine (−4.6% from baseline) was noted in the tamoxifen-treated patients who continued to menstruate, but not in the menstruating control patients (+0.6% from baseline). In patients who became amenorrheic after chemotherapy, those treated with tamoxifen demonstrated less bone loss in the spine than control patients (−6.8% vs. −9.5%) [11]. Postmenopausal women who cease taking tamoxifen experience rapid bone loss within 12 months. Besides reducing the rate of breast cancer development in healthy women, tamoxifen use led to a 32% reduction in the incidence of osteoporotic fractures at the hip, spine, and radius [12].

Aromatase Inhibitors

AIs, introduced in the mid-1990s, have changed the paradigm of breast cancer management. Three AIs have been approved for the treatment of estrogen-dependent breast cancer in postmenopausal women: two reversible nonsteroidal agents (anastrozole and letrozole) and one irreversible steroidal agent (exemestane). Aromatase mediates the peripheral conversion of androgenic precursors (testosterone and androstenedione) of predominant adrenal origin to estradiol and estrone within the ovaries, adipose tissue, liver, muscle, and brain and is an important component of estrogen produced in the postmenopausal period. Thus, already low levels of estrogen in postmenopausal breast cancer patients can be diminished further by use of AIs, exacerbating bone loss and fracture risk in postmenopausal patients.

Within the bone substudy of the ATAC trial evaluating changes in BMD and bone turnover markers after treatment with anastrozole or tamoxifen, patients treated with anastrazole alone experienced significant decreases in BMD after 5 years, whereas the BMD of tamoxifen-treated patients increased from baseline (Table 1). In this study, which excluded osteoporotic patients, four of the five women treated with anastrozole who were osteopenic at baseline became osteoporotic at 5 years; however, no patients with normal baseline BMD became osteoporotic during the course of the study [13•]. The incidence of fractures at the wrist, humerus, and spine was significantly higher in the anastrazole group than in the tamoxifen group [14].

Similar losses in bone density were seen in postmenopausal breast cancer patients treated with letrozole in the MA.17 and BIG 1–98 studies (Table 1). Patients with osteopenia at baseline experienced a greater decline in BMD than those with normal baseline BMD, indicating higher susceptibility to bone loss when baseline BMD is low [15]. Letrozole given for 5 years conveyed a statistically greater fracture risk than tamoxifen.

Exemestane is a steroidal AI with a structure similar to that of androstenedione, an androgen precursor. It was presumed to have more bone-protective qualities than anastrazole or letrozole because of the increased bone formation seen with androgen excess. Although some preclinical studies have supported this hypothesis, clinical evidence is less convincing. Results of the bone substudy of the IES trial identified significantly decreased BMD in patients who were switched from tamoxifen to exemestane than in those who continued with tamoxifen after 1 and 2 years of treatment (Table 1) [13•]. The final analysis of all patients (median follow-up, 58 months) revealed that patients treated with exemestane had a significantly greater incidence of clinical fractures than those treated with tamoxifen.

Gonadotropin-releasing Hormone Agonist

For premenopausal women, complete estrogen suppression via ovarian ablation is a treatment modality for hormone-sensitive breast cancer. This can be accomplished by bilateral oophorectomy, radiation-induced ovarian ablation, or administration of an agonist of GnRH. Goserelin, the only GnRH agonist approved for use in breast cancer in the United States, is safe, its effects are reversible, and it does not cause permanent ovarian dysfunction. After an initial increase in production of luteinizing and follicle-stimulating hormones by the pituitary gland, long-term administration of goserelin desensitizes the pituitary gland and down-regulates pituitary GnRH receptor expression, resulting in sustained suppression of gonadotropin release and estrogen production. Combination therapy with tamoxifen and ovarian suppression is preferred over either treatment alone in premenopausal women with hormone-sensitive breast cancer. Significant suppression of endogenous estrogen levels in premenopausal women, however, can decrease BMD substantially; one study demonstrated a loss of 5% of total body BMD after 2 years of goserelin therapy [16]. Bone density recovers partially (1.5% increase) 1 year after cessation of goserelin.

Prostate cancer treatment can include the use of GnRH agonists. Significant losses in BMD can occur in men treated with leuprolide or goserelin. The rate of bone loss in prostate cancer survivors is similar to that observed in women who have undergone bilateral oophorectomy and is greater than that observed in healthy postmenopausal women. Fracture incidence increases with longer duration of ADT.

Bilateral Orchiectomy

Significant reduction of BMD (distal radius, femoral neck, or spine) in trabecular and cortical bone occurs in patients with prostate cancer 1 to 2 years after bilateral orchiectomy [17]. Fracture incidence is higher in patients treated with bilateral orchiectomy compared with healthy, noncastrated cohorts (40% vs. 19%) [9].

Chemotherapy

Chemotherapeutic agents have direct (effects on bone cells) or indirect (loss of normal hormonal function) adverse effects on bone. A large, population-based cohort study of older adult patients with non-Hodgkin's lymphoma (NHL), identified from the nationwide Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data with up to 11 years of follow-up, demonstrated a significantly higher risk of osteoporosis and fractures associated with chemotherapy [18•]. Studies of childhood acute lymphoblastic

Table 1 Bone mineral density changes and fracture rates in response to use of aromatase inhibitors

Trial	Treatment arms	Change in BMD from baseline (AI vs comparator)	Follow-up, *y* (patients in bone study)	Clinical fracture rate (AI vs comparator); median follow-up interval
ATAC	Anastrozole vs tamoxifen[a]	Spine: −6.1% vs +2.8% ($P<0.0001$) Hip: −7.2% vs. +0.7% ($P<0.0001$)	5 ($n=308$)	11% vs. 8% ($P<0.0001$; $n=6,286$); 68 mo
MA.17	Letrozole vs. placebo	Spine: −5.35% vs. −0.7% ($P=0.008$) Hip: −3.6% vs. −0.71% ($P=0.044$)	2 ($n=226$)	5.3% vs. 4.6% ($P=0.25$; $n=226$); 30.6 mo
IES	Exemestane vs. tamoxifen[b]	Spine: −2.97% vs. −0.02% ($P<0.0001$) Hip: −1.57% vs. −0.5% ($P<0.0001$)	1	7% vs. 5% ($P=0.003$; $n=4,724$); 58 mo
		Spine: −4% vs. −0.6% (P value not available)	2 ($n=206$)	

[a] Analysis of monotherapy arms, with a total of 167 patients evaluable at 5 years

[b] Exemestane compared with continued tamoxifen treatment after all patients treated with tamoxifen for 2–3 years

AI aromatase inhibitor; *ATAC* Arimidex, Tamoxifen, Alone or in Combination; *BMD* bone mineral density; *IES* Intergroup Exemestane Study; *MA.17* National Cancer Institute of Canada Clinical Trials Group MA.17

leukemia (ALL) have shown significant morbidity related to osteoporotic fractures in adult life, attributable to a failure to reach a normal peak bone mass in early adulthood [19]. Factors that contribute to this failure include chemotherapy, glucocorticoids, vitamin D deficiency, effects on gonadal function, and chronic illness during the peak years of bone accretion.

Chemotherapy-induced Hypogonadism

Effects of chemotherapeutic agents on gonadal function are the most common mechanism by which chemotherapy causes bone loss. Chemotherapy-induced menopause is more important for the development of osteoporosis than the direct effects of cytotoxic agents or glucocorticoids. A study by Holmes et al. [20] of male Hodgkin's lymphoma survivors found that BMD was negatively affected by and correlated well with the degree of hypogonadism. Another study of young female patients with adult-onset Hodgkin's lymphoma showed significant bone loss attributable to chemotherapy-induced premature ovarian failure [21].

Systemic chemotherapy can induce ovarian failure in premenopausal patients with early-stage breast cancer and exacerbate bone loss in postmenopausal patients. Ovarian failure develops within 1 year of initiating adjuvant chemotherapy (cyclophosphamide/methotrexate/5-fluorouracil or 5-fluorouracil/doxorubicin/cyclophosphamide) in 63% to 96% of premenopausal women [22]. Patients with ovarian failure lose about 7% of BMD in the lumbar spine and 4.6% in the femoral neck during the first 12 months. In contrast, no significant bone loss is observed in patients who maintained normal ovarian function [23]. Chemotherapy-induced amenorrhea is dependent on age, medication type, and cumulative dose [24]. Cyclophosphamide is the major cause of hypogonadism in these patients, through its metabolite, phosphoramide mustard, as the cause of ovarian toxicity [25]. Testicular cancer patients treated with cisplatinum also experience gonadal toxicity [26]. Other chemotherapies reported to be associated with ovarian failure include L-phenylalanine mustard, busulfan, chlorambucil, and mitomycin-C.

Direct Chemotherapy Effects on Bone

Methotrexate

Methotrexate treatment of pediatric patients with ALL is associated with an increased frequency of osteoporotic fractures [27], and combined therapy with methotrexate, ifosfamide, and bleomycin is associated with a reduction in BMD at the spine [19]. In a retrospective study, insufficiency fractures, mainly at the distal tibia, were reported in about 9% of children who received high-dose methotrexate for osteosarcoma and were substantially more likely to occur in younger patients [28]. Methotrexate lowers bone mass by a dual effect: enhanced resorption and inhibition of formation, leading to a reduction in bone volume [29]. There may be synergistic effects of combined methotrexate and glucocorticoids on bone, as they are often used in the same regimen in the treatment of leukemia. The inhibitory effect of methotrexate on bone formation is dose dependent, with the greatest effects on bone seen at cumulative doses exceeding 40,000 mg/m^2 [30].

Cyclophosphamide

Besides the aforementioned effect on gonadal function, animal studies suggest cyclophosphamide has direct effects

on bone cells. Cyclophosphamide treatment of young rats reduces osteoblast and osteoclast populations by arresting the cell division, leading to osteopenia [31]. The long-term effects of cyclophosphamide on human skeletal function are unclear.

Ifosfamide

Ifosfamide, widely used in the treatment of solid tumors such as pediatric osteosarcoma, causes more sex hormone-independent negative effects on bone than any alkylating agent [32]. At higher doses, alone or in combination with cisplatin, it causes injury to the proximal renal tubule and reduces the threshold for phosphate reabsorption. This leads to metabolic acidosis, renal phosphate loss, hypophosphatemia, and hypercalciuria [33]. Hypophosphatemic osteomalacia with associated radiologic signs was observed in 5 of our of 44 children with Wilms' tumors [34]. In addition, serum levels of osteocalcin were found to be low in children treated with ifosfamide-based chemotherapy, suggesting an inhibitory effect of this agent on bone formation [35].

Platinum

Platinum compounds are used to treat leukemia, lymphoma, and solid tumors. Pediatric ALL patients treated with cisplatin and 6-mercaptopurine were found to have reduced hip BMD [19]. Direct effects of platinum on bone have been difficult to demonstrate, as it is often used in combination with other cytotoxic agents. Cisplatin also causes hypomagnesemia, which can lead to the suppression of osteoblast activity and inhibition of bone formation [36].

Doxorubicin

Doxorubicin, an anthracycline antibiotic, is used in the treatment of multiple solid tumors, including lymphoma, sarcoma, and breast cancer. Doxorubicin's effects on bone have been examined primarily in animal and in vitro studies. In rodents, doxorubicin caused diminished bone formation and decreased trabecular bone volume in proximal rat tail vertebrae [37]. In other studies, doxorubicin inhibited the differentiation and proliferation of osteoblasts and selectively inhibited parathyroid hormone-mediated stimulation of cyclic adenosine monophosphate formation in isolated bone cells [38, 39]. These studies suggest doxorubicin may inhibit bone formation through several different mechanisms.

Stem Cell Transplantation

Hematopoietic stem cell transplantation (SCT) has been used to treat a broad range of diseases. Advances in the use of alternative donors, stem cell sources, reduced-intensity preparative regimens, and better supportive care after transplant have greatly expanded the use of this technique. Significant reduction in early transplant-related mortality rates during the past decade has focused attention on long-term toxicity, such as chronic graft-versus-host disease (GVHD) and other transplant-associated late effects. Most bone loss in SCT patients occurs during the first 3 to 6 months after the procedure and is most severe at the femoral neck [40]. In addition to raising the risk for hip fracture, lower femoral neck BMD in transplant patients has been associated with avascular osteonecrosis, a condition associated with significant pain and immobility [41].

Osteoporosis that develops after SCT is complex. Not only are there effects of immunosuppressive agents on bone, but compelling evidence indicates that interaction between immunologic cells (T cells) and stromal bone cell precursors is impaired during the transplant process. In a study that examined 22 patients an average of 12.2 months following allogeneic SCT, the ability of marrow mesenchymal stem cells to produce bone was suppressed as measured by the in vitro colony-forming unit fibroblast (CFU-F) assay. Interestingly, treatment with zoledronate for 12 months yielded a significant increase in the CFU-F growth, whereas CFU-F growth in the control group remained suppressed. In this same study, there was a significant increase in BMD in the zoledronate treatment group and continued bone loss in the control group [42]. In general, more than 50% of patients with allogeneic SCT develop GVHD, necessitating prolonged use of glucocorticoid therapy and other forms of immunosuppression. In this setting, use of inhibitors of nuclear factor of activated T cells, such as cyclosporine, combined with glucocorticoids was associated with bone loss [43, 44]. In addition, bone loss after SCT correlates well with myeloablative conditioning, higher doses of infused stem cells, higher grades of acute GVHD, and the use of glucocorticoids for chronic GVHD [45••].

Other Conditions

Adverse skeletal effects of radiation therapy may occur as a result of direct osteoblast damage or indirectly from loss of one or more hormonal substances. Pediatric cancer patients treated with cranial irradiation for ALL and for nasopharyngeal carcinoma can suffer from low bone mass. In these patients, cranial radiation can lead to decreased secretion of growth hormone and gonadotropins, yielding a reduction in insulin-like growth factor-1 (IGF-1) and gonadal steroids, respectively, and leading to a reduction in bone accretion during the critical (for bone accretion) second decade of life. In children treated with cranial radiation, replacement

of growth hormone and, at puberty, sex steroids will increase BMD [46]. For patients with low BMD despite hormonal treatment and for those with severely low BMD but without evidence of pituitary dysfunction, bisphosphonates have been used to prevent fractures, although only limited evidence suggests that that such therapy has benefit. Radiation therapy after surgical resection for breast, prostate, or gynecologic cancers can lead to a higher incidence of rib or pelvic insufficiency fractures. Patients monitored long term after radiation therapy for breast cancer have a higher incidence of rib fractures (0.3%–2.2%) than controls [47].

Glucocorticoids are used commonly in the treatment of hematologic malignancy and the prevention of chemotherapy-induced emesis for solid tumors. Glucocorticoids can cause rapid bone loss by directly decreasing bone formation via glucocorticoid-induced apoptosis of both osteoblasts and osteocytes, and increasing bone resorption by prolonging the life span of preexisting osteoclasts [48]. Glucocorticoids negatively affect calcium balance by inhibiting gastrointestinal calcium absorption and renal tubular reabsorption of calcium. In addition, systemic suppressive effects of glucocorticoids on gonadal dysfunction and interference with the growth hormone/IGF-1 axis contribute to bone loss [49].

The degree of influence that comorbid conditions such as physical inactivity and vitamin D deficiency have on bone loss and fracture rate in cancer patients is unclear but may be substantial. Decreased physical activity and prolonged bed rest during cancer treatment are powerful stimulants to bone resorption. Vitamin D deficiency is prevalent in healthy older adults, as well as in those with a history of hip fractures or osteoporosis treatment. At our cancer center, a survey of vitamin D levels in the cancer population showed 25-hydroxy-vitamin D levels below 30 ng/mL in more than 50% of patients (Gagel, unpublished observation). Although there are no reports on the bone-protective effects of calcium and vitamin D used alone in cancer patients, supplementation with vitamin D has been shown to reduce the risk of hip fractures in healthy ambulatory women [50]. It is recommended that any evaluation of low bone mass in an oncologic population include vitamin D assessment.

Prevention and Management of Bone Loss in Cancer Patients

A critical element in the prevention of bone loss in cancer patients is appropriate surveillance of bone health. Recent guidelines for bone health surveillance from the American Society of Clinical Oncology have been published for breast cancer survivors [51], but not for prostate cancer patients. However, Diamond et al. [52] recommended that patients with prostate cancer undergoing ADT should have bone mass assessed by dual x-ray absorptiometry scans. The Children's Oncology Group Long-term Follow Up guidelines (2006) recommend a BMD evaluation at baseline for survivors of childhood malignancies at the time of entering long-term follow-up, usually 2 years after completion of cancer therapy. The National Comprehensive Cancer Center Network's recently published guidelines on bone health in cancer patients describe an algorithm incorporating fracture risk analysis by FRAX (World Health Organization Fracture Assessment Risk Tool), BMD, and risk factors for bone loss to guide pharmacologic therapy for low BMD or osteoporosis [53].

Bone loss related to chemotherapy, tamoxifen, and AIs in breast cancer patients has been addressed by multiple studies. Until recently, the number of studies evaluating chemotherapy-induced bone loss was limited, and study populations were small, making the findings difficult to interpret. Bisphosphonates have been shown to increase BMD in various trials. The recently published REBBeCA study by Greenspan and colleagues [54•] evaluated the efficacy of once-weekly oral risedronate as prevention of bone loss in women who recently became menopausal after undergoing chemotherapy for breast cancer. In contrast to the placebo group, which demonstrated significant decreases in BMD, the risedronate-treated women demonstrated increases in BMD at 24 months. Bone turnover markers were suppressed in patients on active therapy and elevated in the placebo group, indicating a therapeutic effect of risedronate to lower bone turnover. Conversely, risedronate treatment of premenopausal women recently initiated on chemotherapy did not significantly prevent bone loss compared with placebo, reinforcing the premise that bone loss is primarily related to estrogen deficiency [55].

The ABCSG trial evaluated the effect of combining goserelin with tamoxifen or anastrazole in premenopausal women naïve to cytotoxic chemotherapy [56]. A bone substudy assessed the effects of zoledronate (4 mg intravenously every 6 months) on bone health over 5 years. The groups that did not receive zoledronate had significant overall bone loss. In contrast, zoledronate stabilized BMD regardless of the type of hormone treatment. After discontinuation of therapies at 3 years, the zoledronate-treated group demonstrated an increase of BMD at 5 years compared with baseline; the group without zoledronate had a lower BMD than the baseline value. No fractures occurred during the course of this trial, which may reflect the lower risk in younger women enrolled and the short duration of the trial.

The Z-FAST study reported the results of zoledronate (4 mg every 6 months) given at the time of initiating letrozole, when the T score fell below −2.0 SD, or when a nontraumatic fracture occurred. The group treated with bisphosphonate at the time letrozole was initiated had a

significantly higher BMD than the delayed treatment group at 3 years. The study was not powered for fracture prevention [57].

Very few trials have evaluated the effect of antiresorptive agents in other cancer populations besides breast malignancy. Although several small studies have been conducted, they were not powered to examine fracture reduction. Intravenous or oral bisphosphonate therapy lowers bone loss in prostate cancer survivors treated with various hormonal therapies. Surrogate markers of osteoporosis (eg, BMD, markers of bone resorption) are positively affected by an orally or intravenously administered bisphosphonate in these patients [54•, 58]. Intravenous bisphosphonates initiated near the time of stem cell transplantation decrease bone loss significantly [45••, 59].

Although there is no disagreement regarding the benefit of preventing osteoporosis-related fractures during and after pediatric cancer treatment, the clinical trials published thus far are limited to small patient populations with diagnoses of ALL and NHL. In one of these studies, alendronate given to 15 children with ALL with osteoporosis/osteopenia was shown to improve BMD and had no adverse effects on height velocity [60]. Available studies provide no guidance regarding long-term use of bisphosphonates in the pediatric population, although experience with use of bisphosphonate is growing in children with osteogenesis imperfecta, and this experience may provide guidance regarding safety.

Estrogens play an important role in regulating normal bone metabolism in women and men. Raloxifene, approved for the prevention and treatment of postmenopausal osteoporosis, has been shown to prevent the development of invasive breast cancer, with a more favorable side effect profile than that observed with tamoxifen; thus, the American Society of Clinical Oncology recommends consideration of raloxifene in postmenopausal women at high risk for invasive breast cancer [61]. Raloxifene could be considered in postmenopausal breast cancer survivors for prevention and treatment of osteoporosis. The efficacy of estrogens in preventing bone loss has been evaluated in patients undergoing ADT. Besides significantly reducing bone markers, treatment with estrogen for 1 year has been shown to preserve BMD. Smith et al. [62] evaluated the efficacy of raloxifene in preventing bone loss in males treated with ADT. After 12 months, BMD was preserved in raloxifene-treated patients, whereas those in the placebo group experienced significant bone loss [62]. It must be noted, however, that estrogen-based therapies have been associated with higher rates of adverse cardiovascular events in males.

Anabolic therapy with teriparatide or parathyroid hormone 1–84 induces bone formation and prevents fractures in men and women with severe osteoporosis. However, anabolic therapy induces production of growth factors that may theoretically induce tumor growth or tumor activation. Prior skeletal irradiation therapy often precludes the use of teriparatide because of the perceived increased risk for osteosarcoma in irradiated patients. Whether this is a real risk is unclear. These agents have not been investigated in cancer patients; therefore, the risks and benefits of the use of anabolic agents should be considered carefully in cancer survivors.

Finally, there have been various clinical investigations of a fully human monoclonal antibody, denosumab, in the settings of postmenopausal osteoporosis, cancer-related bone loss, and metastatic bone disease. Denosumab binds to RANKL, preventing its interaction with the RANK receptor. Disruption of RANKL-RANK interaction blocks osteoclast formation and is a potent inhibitor of bone resorption. A recent study in prostate cancer showed an increase in BMD and reduction of fractures at 12, 24, and 36 months in denosumab-treated patients [63•]. Advantages of denosumab use include the lack of nephrotoxicity and the reversibility of the suppressive effect on osteoclast formation and bone resorption. There may be some reluctance to use this agent in immunosuppressed cancer or SCT patients during active therapy, as one side effect is a small but significant increase in infections in denosumab-treated patients [62]. More studies will be required to define its role in the prevention or treatment of cancer-related bone loss.

Conclusions

Although patients with cancer are living longer because of treatment advances, this success has uncovered other health issues, including bone loss, which can lead to clinically significant and highly morbid outcomes. The preservation of bone health in these patients throughout treatment and long-term follow-up should be emphasized from the beginning of therapy. Patients should be educated and encouraged to participate actively in the treatment plan by implementing management strategies such as diet modification, calcium and vitamin D supplementation, exercise, and lifestyle changes. Early initiation of bisphosphonate therapy in patients with malignancies who are at high risk for severe bone loss (i.e., undergoing treatment with AI, GnRH agonist, high-dose steroids, or several chemotherapeutic regimens) may be beneficial in preventing or delaying bone loss. The clinical value of this practice will need to be validated, however, by demonstration of diminished fracture rates in longer follow-up studies of these patients. As awareness of the problem of bone loss in cancer increases, we can expect improved surveillance protocols and treatment modalities for clinically relevant

bone loss in cancer survivors, thus leading to improvement in quality of life.

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- •• Of major importance

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