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Osteoporosis Related to Disease or Therapy in Patients With Cancer: Review and Clinical Implications

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Osteoporosis is a major public health issue in the general population, particularly in postmenopausal women. Patients with cancer may not only be at risk for primary osteoporosis, but for secondary osteoporosis related to cancer therapies—particularly therapies that impair gonadal function, lead to loss of serum estrogen, and negatively affect bone turnover. Normal bone remodeling is influenced by the receptor activator for nuclear kappa-B ligand pathway, calcium, vitamin D, and other nutrition factors, as well as modifiable and nonmodifiable factors. Identifying which patients with cancer are at risk for bone mineral density loss is important and may include patients with breast or prostate cancer, some survivors of pediatric malignancies, and adults with other tumors. Nurses play a major role in identifying those patients and their risk for low-impact fractures, which can have a significant effect on patient morbidity and mortality. Counseling and teaching are central nursing functions, as well as safely administering therapies, particularly bisphosphonates and denosumab.

Bone health and the loss of bone density are important clinical concerns for patients with cancer who may be at risk for primary osteoporosis because of aging and other risk factors. They may have the added risk for cancer treatment-induced bone loss (CTIBL), which also could be termed secondary osteoporosis related to therapy and cancer. Patients with either of those conditions will be the focus of this article.

Increased understanding of normal bone physiology has led to a greater appreciation of the multiple factors affecting bones and regulating bone remodeling, as well as the importance of recognizing and managing individuals at risk for bone loss. Recognition and understanding are important for all oncology nurses because of their role in assessing patients at risk of bone loss, teaching and counseling patients, translating (and possibly ordering) laboratory and other diagnostic tests, safely administering antiresorptive therapies, and conducting long-term follow-up, particularly for cancer survivors.

At a Glance

- Patients with cancer may be at risk for bone mineral density loss secondary to aging and hereditary factors or to cancer therapies.
- Bone loss is asymptomatic until a low-impact fracture occurs.
- Oncology nurses must identify patients at risk for bone mineral loss to collaborate for additional workup, to counsel and teach patients, and to avoid potential adverse effects related to bisphosphonate treatment.

Maintaining Healthy Bones

Bones consist of a collagen and mineralized calcium hydroxyapetite matrix that surrounds osteocytes (Seeman & Delmas, 2006). Outer cortical bone is hard, stiff, and strong, whereas

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inner trabecular bone is lightweight and flexible because of its architecture of connecting plates and bars (trabeculae) that allows it to withstand great compressive forces. Maximum bone mass and strength are achieved by ages 18–20, a fact that may be important to survivors of childhood cancers.

Bone remodeling—lysis and resorption of damaged bone and replacement with newly synthesized bone—continues throughout life to maintain bone strength and integrity. Sites of greatest stress (vertebrae, femoral head, hip, and long bones) undergo the most frequent remodeling. About 25% of trabecular bone and 3% of cortical bone are replaced each year in adults (Rude, Singer, & Gruber, 2009). Bone resorption equals synthesis in young adults (i.e., bone remodeling is coupled). After age 35, slightly less bone is formed than is resorbed each year, which leads to gradual and continuous loss of bone density (Borovecki, Pecina-Slaus, & Vukicevek, 2007; Guise, 2006). Uncoupled bone turnover increases dramatically in perimenopausal women who lose 2%–4% of bone mass per year because of sudden estrogen loss. Five to 10 years after menopause, bone loss wanes to 0.5%–1% per year, the same as that seen men older than age 55.

Bone Remodeling

Bone remodeling occurs in three phases: initiation, transition, and termination (Li, Kong, & Qi, 2006). Initiation begins with microcracks in trabecular or cortical bone, or after loss of mechanical loading secondary to inactivity, hormone changes, or other events. Monocytes congregate, differentiate into preosteoclasts, and then fuse into large multinucleated osteoclasts with abundant lysosomes, mitochondria, and free ribosomes. Osteoclasts have a ruffled border and sealing zone that tightly attach to mineralized bone where intracellular lysosomes demineralize and resorb damaged bone in the course of about three weeks (Matsuo & Irie, 2008; Michaud & Goodin, 2006). Transition begins when osteoclasts stimulate local mesenchymal stem cells to differentiate into preosteoblasts and then osteoblasts. Simultaneously, osteoclasts undergo apoptosis (programmed cell death) and stop resorbing bone. Termination continues for three to four months as osteoblasts form layers of new bone until the excavated cavity fills in. Osteoblasts ultimately differentiate into osteocytes encased in hydroxyapetite, but new bone is not as highly mineralized or strong as older bone for several months. Any sustained increased rate of bone remodeling results in bone loss because of the large difference in the duration of initiation and of termination.

Mediators of Bone Remodeling

The key regulator of bone turnover is the receptor activator for nuclear kappa-B ligand (RANKL) pathway, and hormones (particularly estrogen) play critical roles (Borovecki et al., 2007; Li et al., 2006). Other influences of bone remodeling include gene transcription factors, cytokines (i.e., macrophage–colony-stimulating factor and interleukin-6), peripheral neuro-osteomediators, calcium, vitamin D, and magnesium.

Osteocytes induce nearby osteoblasts to express RANKL, a transmembrane-bound protein, in response to mechanical forces or micro damage. Osteoblasts also synthesize osteoprotegerin, a decoy receptor. RANKL binding to the receptor activator for nuclear kappa-B (RANK) receptor on osteoclast precursors promotes recruitment and differentiation of mature osteoclasts and extends osteoclast lifespan (Sambrook & Cooper, 2006). Conversely, RANKL binding to osteoprotegerin inhibits osteoclasts and blocks bone resorption. RANKL thereby maintains balanced bone remodeling. T cells, B lymphocytes, and tumor cells also synthesize RANKL, which may have roles in immunity, tumor cell migration and signaling, and osteoclastic (lytic) bone metastasis (Murthy, Morrow, & Theriault, 2010).

Both osteoclasts and osteoblasts have estrogen receptors. In osteoclasts, estrogen binding promotes down regulation of RANKL and apoptosis, whereas osteoblast binding upregulates osteoprotegerin and extends osteoblast lifespan (Murthy et al., 2010). Estrogen, therefore, suppresses the rate of bone turnover and maintains coupled bone remodeling. Estrogen may be lost secondary to menopause, chemotherapy-induced ovarian failure, or by inhibited aromatization of androgen precursors to estrogens. Rapid loss has the greatest effect by increasing the number and lifespan of osteoclasts and impairing osteoblast synthesis and function, which leads to markedly decreased bone mass and altered bone architecture (Michaud & Goodin, 2006; Zallone, 2006).

Optimal bone mineralization requires adequate dietary protein, calcium, magnesium, phosphorus, vitamin D, and other trace elements (Palacios, 2006; Tucker, 2009). More than 99% of calcium is bound in hydroxyapetite, and it confers hardness and strength to bones and teeth. The remaining amount has multiple critical physiologic roles in the circulation and in numerous tissues. Calcium homeostasis is regulated by vitamin D and parathyroid hormone (PTH). Vitamin D deficiency leads to reduced calcium absorption from the gut and increased PTH, which, in turn, enhances calcium resorption from bone and in the kidney. Diets in the United States often are calcium deficient and average intake is about 600 mg per day rather than the 1,000–1,500 mg recommended daily allowance for adolescents and adults to prevent calcium loss from bones (Institute of Medicine [IOM], 2011; National Osteoporosis Foundation [NOF], 2010).

After age 35, slightly less bone is formed than is resorbed each year, which leads to gradual and continuous loss of bone density.

Magnesium, which has many direct and indirect effects on bone quality and neuromuscular functioning, is the most abundant intracellular cation and an enzyme cofactor in virtually every biologic process (Abed & Moreau, 2009). Fifty percent to 60% of magnesium is stored in bone, and patients with osteoporosis may be deficient (Rude et al., 2009; Sahota, Mundey, San, Godber, & Hosking, 2006). Hypomagnesemia also may accompany chronic diarrhea, chronic use of some drugs (i.e., cisplatin, carboplatin, amphotericin B, and loop diuretics), diabetes, alcoholism, and hypercalcemia of malignancy (Swaminathan, 2009). Diets in the United States often are low in magnesium, which is available in green leafy vegetables, nuts, grains, cereals, and legumes. Even moderate magnesium deficiency may lead to increased RANKL expression and decreased osteoprotegerin, decreased osteoblast numbers and integrity, altered osteoblast and osteoclast activity, trabecular bone loss, low serum vitamin D levels, and impaired

PTH secretion, resulting in hypocalcemia (Abed & Moreau, 2009; Rude et al., 2009). Greater magnesium intake has been associated with significantly higher bone mineral density (BMD) in older adult Caucasians (but not African Americans), and magnesium supplements may increase BMD in menopausal and postmenopausal women and reduce bone turnover in men (Palacios, 2006; Ryder et al., 2006).

Vitamin D, a prohormone, has been the subject of debate in the past several years. The newest recommended daily allowances set by IOM (2011) address *only* the amount of vitamin D that will prevent rickets in children and osteomalacia in adults—600 IU for children and most adults and 800 IU for people older than age 70. However, controversy arises about the strength of the evidence regarding the roles of vitamin D in numerous tissues and organs, and whether greater intake may be important to preventing diseases (including some cancers) and optimizing extraskeletal health (IOM, 2011).

Vitamin D itself has no bioactivity; it first undergoes hepatic hydroxylation to a measurable intermediate metabolite (25OHD [calcidiol]) and then is transported to the kidney and other tissues, where it is further hydroxylated to its nonmeasurable, short-lived, active metabolite (1,25[OH]2D [calcitriol]). Calcitriol directly facilitates dietary calcium absorption and metabolism, inhibits PTH synthesis, has other hormone actions, and is a powerful regulator of cellular growth in normal and cancer cells (Raisz, 2005; Stechschulte, Kirsner, & Federman, 2009). In bone, vitamin D, along with PTH and interleukin-6, indirectly increases RANKL (Murthy et al., 2010).

About 50% of the population in the United States is vitamin D insufficient or deficient and, therefore, at risk for diminished bone mineralization, abnormal calcium-phosphorus structure formation, and increased likelihood of osteoporosis and fractures (Raisz, 2005; Stechschulte et al., 2009). In addition, unrecognized vitamin D deficiency can lead to painful osteomalacia misdiagnosed as bone metastases or exacerbate bisphosphonate-related adverse effects (Khokhar, Brett, & Desai, 2009; Wang-Gillam, Miles, & Hutchins, 2008; Zuradelli et al., 2009).

In general, Americans ingest only 150–200 IU of vitamin D per day from fortified foods, oily fish, and egg yolks (Holick & Chen, 2008). The primary source of vitamin D for humans is ultraviolet B sunlight, which causes cutaneous photoconversion of 7-dehydrocholesterol in the skin to cholecalciferol (vitamin D_3). Synthesis is highly variable and depends on ultraviolet B sunlight occurring from 10 a.m. to 3 p.m. from late spring to early fall at latitudes north of 35°; blockage of sun rays with sunscreen use, clothing, or sun avoidance; aging, which dramatically decreases synthesis; and darker skin (melanin is an effective sun block).

Osteoporosis Versus Cancer Treatment-Induced Bone Loss

BMD loss with aging occurs because of hypogonadism and may progress to primary osteoporosis, whereas secondary osteoporosis, including CTIBL, results from chronic diseases, nutritional deficiencies, drugs, and other factors that negatively alter bone remodeling (see Figure 1). The results in either case are increased PTH levels, greater bone resorption than synthesis, impaired neuromuscular functioning, and increased risk for falls and fractures (Heaney, 2007; Joint Commission, 2009; Rude et al., 2009).

General

- Age: women 65 and older, men older than 70
- Caucasian or Asian ethnicity
- Family history of osteoporosis
- Has experienced a low-impact fracture
- Maternal or parental hip fracture
- Postmenopausal status

Lifestyle

- Cannot rise from a chair for extended time
- Cigarette smoking (active or passive)
- High alcohol intake (three or more drinks per day)
- Sedentary lifestyle; low physical activity

Nutrition

- High caffeine consumption
- Low calcium intake
- Vitamin D deficiency
- Thin: weight less than 127 lbs; BMI lower than 19

Medications (Long-Term Therapy)

- Aluminum (in antacids)
- Anticonvulsant therapy (phenobarbital, phenytoin)
- Aromatase inhibitor for breast cancer
- GnRH analog for prostate cancer
- Immunosuppressant agents
- Long-term corticosteroid use (5 mg prednisone per day for three months or longer)
- Long-term heparin use
- Parenteral progesterone
- Proton pump inhibitors
- Supraphysiologic doses of thyroxine
- Tamoxifen (premenopausal women)
- Total parenteral nutrition

Medical Conditions

Cancer-related

- Leukemia or lymphoma
- Multiple myeloma
- Solid organ or allogeneic stem cell transplantation

General

- Amyloidosis
- Ankylosing spondylitis
- Celiac disease
- Cerebral vascular accident
- Chronic obstructive pulmonary disease
- Congenital porphyria
- Cushing syndrome
- Dialysis
- Eating disorder (e.g., anorexia, bulimia)
- Gastric bypass
- Gastrointestinal surgery
- Gaucher disease
- Hemochromatosis
- Hemophilia
- HIV
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism
- Hypophosphatasia
- Idiopathic scoliosis
- Inflammatory bowel disease
- Insulin-dependent diabetes
- Malabsorption syndrome, including gastrectomy or bariatric surgery
- Mastocytosis
- Multiple sclerosis
- Pernicious anemia
- Rheumatoid arthritis
- Severe liver disease
- Spinal cord transaction
- Thalassemia
- Weight loss

BMI—body mass index; GnRH—gonadotropin-releasing hormone

Figure 1. Risk Factors for Low Bone Mass and Osteoporosis

Note. Based on information from Joint Commission, 2009; Khan et al., 2007; National Osteoporosis Foundation, 2010; Sweet et al., 2009.

More than 10 million people in the United States, most commonly postmenopausal women and men older than age 50, have primary osteoporosis, and 33.6 million have low bone density (formerly termed osteopenia) (Khosla & Melton, 2007; NOF, 2010). Men have low rates of osteoporosis because they have no menopause equivalent, have larger bones, and have a shorter life expectancy than women (Khan et al., 2007). Patients at risk for CTIBL include women with breast cancer, men with prostate cancer, adult survivors of childhood cancers (who may not achieve maximal bone development after treatment), and some older adult individuals treated for other tumors. Older adult patients with cancer may have a greater risk for bone loss because of primary osteoporosis or cancer itself. Risks for significant bone loss may be chemotherapy, hormone therapy, surgical castration, or radiation therapy to the gonads or brain.

The hallmarks of osteoporosis from any cause are asymptomatic decreased bone mass and BMD, deterioration of bone micro-architecture, and increased risk for fragility (low-impact) fractures of the spine, hip, wrist, or other sites (see Figure 2). Fragility fractures result from falls no greater than standing height or occur with coughing, sneezing, abrupt movement, or even spontaneously (Institute for Clinical Systems Improvement [ICSI], 2008). Such fractures often lead to a diagnosis of osteoporosis, but 66% of vertebral fractures are "silent" and go undiagnosed. Sustaining one osteoporotic fracture is the greatest risk factor for subsequent fractures, which are immensely burdensome to patients, caregivers, and the healthcare system (Guise, 2006). About 50% of Caucasian women and 20% of Caucasian men suffer a fragility fracture, most commonly of the spine, but hip fractures are most devastating (Sambrook & Cooper, 2006). Each year, 300,000 Americans sustain a hip fragility fracture; 14% (42,000) die within one year and only 40% regain their prefracture level of independence (Joint Commission, 2009; NOF, 2010). Postmenopausal women in the United States have a greater risk for a hip fragility fracture than their *combined* risk for developing breast, ovarian, and uterine cancers. Men experience fewer fractures, but are more likely to die after a hip fracture (Khosla, Amin, & Orwoll, 2008).

Risk Factors for Bone Density Loss

Risk factors for BMD loss are nonmodifiable or modifiable. Nonmodifiable risks include aging, genetic predisposition (i.e., personal family history of osteoporosis or fragility fracture, congenital diseases, and Caucasian or Asian ethnicity) and previous low-impact fracture (ICSI, 2008; Joint Commission, 2009; NOF, 2010; Sweet, Sweet, Jeremiah, & Galazka, 2009). Osteoporosis is less common in African Americans, but those with low bone mass have the same fracture risk as Caucasians and Asians.

Modifiable lifestyle risk factors are cigarette smoking, excessive alcohol or caffeine consumption, low exercise or activity level, and inadequate calcium and vitamin D intake. Although the link between smoking and osteoporosis has been recognized for many years, determining if smoking has a direct effect on bones or if an interaction between smoking, low activity level, and poor diet leads to an effect on bones is unknown. However, a study by Ajiro, Tokuhashi, Matsuzaki, Nakajima, and Ogawa (2010) showed a significant direct effect on BMD, osteocyte size, and osteoblast number in rats exposed to passive smoke not found in control animals. Other chronic illnesses and long-term use of some drugs add to the total risk for accelerated bone loss (Camacho et al., 2008). Corticosteroids are the most common drug-related cause of osteoporosis, particularly in patients who take large doses (5 mg or higher of a prednisone equivalent per day) for a long period (three months or longer) or when their total cumulative dose is greater than 10 g (NOF, 2010).

Cancer-specific risk factors for secondary osteoporosis include receiving antineoplastic agents and hormones known to cause CTIBL, undergoing stem cell transplantation, or having multiple myeloma (see Figure 3). Some drugs (i.e., cyclophosphamide, doxorubicin, high-dose ifosfamide, and methotrexate) have direct, dose-dependent, toxic effects on bone (Michaud & Goodin, 2006). Other chemotherapy agents and hormones induce gonadal failure, which leads to more rapid and dramatic bone loss than what occurs with normal aging (Body et al., 2007; Guise, 2006). Primary ovarian failure and premature menopause occur in 20%–90% of women with breast cancer; those older than 40 or receiving higher cumulative doses of cyclophosphamide are at greatest risk for ovarian failure and significant CTIBL (Fornier, Modi, Panageas, Norton, & Hudis, 2005; Hirbe, Morgan, Uluckan,

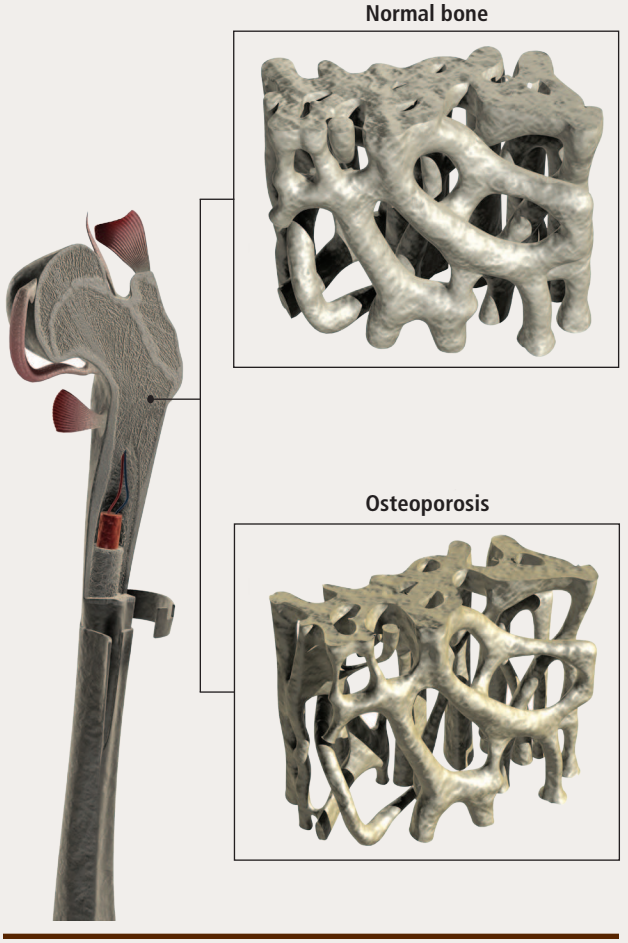

Figure 2. Trabecular (Spongy) Bone of Healthy Individuals and Those With Osteoporosis

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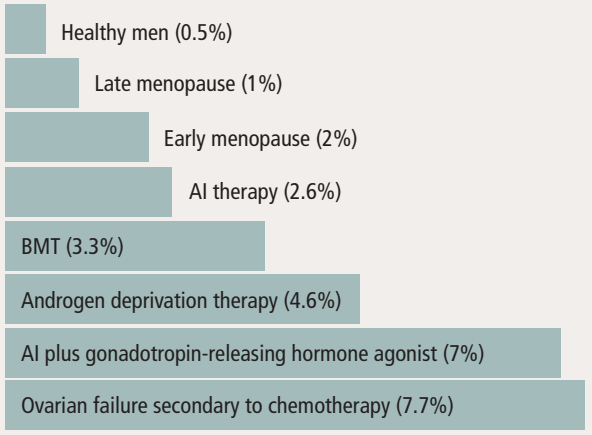


AI—aromatase inhibitor; BMT—bone marrow transplantation

Note. Percentages indicate lumbar spine bone mineral density loss at one year.

Figure 3. Estimated Annual Bone Loss in Aging Adults and With Cancer Therapies

Note. From "Bone Loss and Fracture Risk Associated With Cancer Therapy," by T.A. Guise, 2006, *Oncologist, 11,* p. 1123. Copyright 2006 by Alphamed Press, Inc. Adapted with permission.

& Weilbaecher, 2006). Adding a taxane or irinotecan to a regimen including cyclophosphamide or anthracycline increases the risk for ovarian failure (Pfeilschifter & Diel, 2000; Sterns, Schneider, Henry, Hayes, & Flockhart, 2006; Tanaka, Utsunomiya, Utsunomiya, & Umesaki, 2008; Tham et al., 2007). Busulfan, melphalan, chlorambucil, nitrogen mustard, and procarbazine are considered highly toxic to gonadal function, whereas paclitaxel and cisplatin are moderately toxic (Oktay & Sonmezer, 2008). Amenorrhea generally is reversible in women younger than age 40, but having no menstrual periods for one year after chemotherapy ends usually signifies menopause.

Survivors of pediatric cancers (i.e., leukemia, lymphoma, sarcomas, Wilm's tumor, or other malignancies) may attain low stature and suboptimal maximal bone mass secondary to cancer treatment that predisposes premature ovarian failure, CTIBL, and increased fracture rates (Cicognani et al., 2004; Sala & Barr, 2007; Siebler, Shala, & Robson, 2002; Sklar et al., 2006; Teinturier, Hartmann, Valteau-Counet, Benhamou, & Bougneres, 1998; van der Sluis & van den Heuvel-Eibrink, 2008; Vassilopoulou-Sellin et al., 1999). Treatment-related risk factors in children and adolescents include chemotherapy administered (i.e., an alkylating agent, high-dose methotrexate, or high-dose busulfan [plus or minus concomitant corticosteroid]), pelvic or cranial irradiation, or autologous stem cell transplantation.

Adults treated with alkylating agents and mediastinal radiotherapy for Hodgkin lymphoma also may be at risk for CTIBL. For instance, 37% of treated women in one study experienced ovarian failure before age 41 (Haukvik, Dieset, Bjøro, Holte, & Fossa, 2006). Median time to ovarian failure was related to age at diagnosis—15 years, 6 years, and 2 years in those diagnosed when they were younger than 25, ages 25–29, or ages 30–40, respectfully. Similarly, adults older than age 65 treated with high-dose chemotherapy, allogeneic bone marrow transplantation, and long-term corticosteroids for non-Hodgkin lymphoma experienced significant BMD loss despite daily supplemental calcium and vitamin D compared to patients who did not receive chemotherapy (Cabanillis, Lu, Fang, & Du, 2007; Schulte & Beelen, 2004).

Patients with breast or prostate cancer treated with selective estrogen receptor modulators, aromatase inhibitors, or gonadotropin-releasing hormone (GnRH) analogs are at greatest risk for CTIBL because those hormonal agents deplete circulating estrogen levels (Brufsky, 2008; Guise, 2006). Tamoxifen is an antagonist in the bones of premenopausal women and increases bone loss, but is an agonist and is bone sparing in postmenopausal women (Bjarnason, Hitz, Jorgensen, & Vestergaard, 2008; Michaud & Goodin, 2006). Aromatase inhibitors (anastrozole, exemestane, and letrozole) antagonize aromatase and almost totally block conversion of adrenal androgens to estrogen, causing greater bone loss than tamoxifen, particularly during the first two years of use (Doggrell, 2008; Eastell et al., 2008).

GnRH analogs (also known as leutenizing hormone-releasing hormone agonists) are used to treat some patients with premenopausal breast or prostate cancer; they rapidly decrease circulating estrogen by stimulating the pituitary and inducing down regulation of GnRH receptors, decreasing luteinizing hormone secretion, and inducing ovarian insufficiency in women (Body et al., 2007; Michaud, 2010). Bone loss accelerates to 4%–10% in the first year of use and to 4%–5% per year with sustained use (Guise, 2006; Mittan et al., 2002). Adding a GnRH analog to chemotherapy (cyclophosphamide, methotrexate, and fluouracil) led to significantly greater bone loss in the spine and hip than with chemotherapy alone (10.5% and 6.4% versus 6.5% and 4.5%; $p < 0.001$) (Jonat et al., 2002).

Low bone mass or osteoporosis occurs in 33%–60% of patients with prostate cancer before treatment and in more than 50% of those receiving any anticancer therapy, but is most common with androgen deprivation therapy secondary to surgical castration or GnRH agonist (buserelin, goserelin, histrelin, or leuprolide) therapy (Berruti et al., 2002; Srinivas & Colocci, 2006). For instance, surgical castration results in profound loss of testosterone, decreased BMD, and a risk for fractures that increases from about 10% three years after orchiectomy to 50% nine years after surgery; fracture rate in men not undergoing castration is consistently at less than 4% (Daniell, 1997). Similarly, androgen deprivation therapy eliminates circulating testosterone that normally is converted to estrogen by aromatase, which results in increased BMD loss (Body et al., 2007). In one sample of men with prostate cancer undergoing androgen deprivation therapy, the incidence of osteoporosis was 50% after four years and more than 80% after 10 years (Morote et al., 2007). Vitamin D deficiency is another cause of secondary osteoporosis in women with breast cancer receiving an aromatase inhibitor and in men on androgen deprivation therapy (Bjarnason et al., 2008; Brufsky, 2008; Camacho et al., 2008; Wang-Gillam et al., 2008).

Management Issues

No consensus or evidence-based guidelines exist that are specific to screening and managing bone health in all patients with cancer. Earlier recommendations from the American Society

of Clinical Oncology (ASCO) (Hillner et al., 2003) focused on bisphosphonates (for women with breast cancer with bone metastases, those with extra-skeletal metastases, or those receiving adjuvant bisphosphonate); however, the new ASCO guidelines discuss *only* the use of bone-modifying agents for women with metastatic breast cancer (Van Poznak et al., 2011). In addition, the National Comprehensive Cancer Network (NCCN) guideline (2011) focuses on men with prostate cancer receiving androgen deprivation therapy. Those recommendations are consistent with the NOF (2010) screening and management recommendations that propose postmenopausal women and men older than age 50 should be screened for risks of osteoporosis and fragility fractures, and that other individuals also may warrant screening (see Figure 4).

The World Health Organization fracture risk assessment tool (FRAX®) is a computerized fracture assessment algorithm that should be used to aid decision-making regarding additional diagnostic procedures and pharmacologic management (Shuler, Conjeski, & Hamilton, 2011). FRAX was developed from large population-based studies and estimates the absolute 10-year probability for hip or other fractures from decreased BMD (Kanis et al., 2009). Cost analyses have confirmed the effectiveness of starting antiresorptive therapy if a patient's 10-year risk for a hip fracture is 3% or greater (Gralow et al., 2009; Tosteson et al., 2008). FRAX can be downloaded at no cost from http://www.sheffield.ac.uk/FRAX/tool.jsp?country=9. If a particular patient's femoral neck BMD is unknown, specific osteoporosis risks (i.e., gender, age, body mass index, prior fragility fracture, and cigarette smoking) can be incorporated into the FRAX calculation (Dawson-Hughes et al., 2008). Calculations are available for Caucasian, Asian, African American, and Hispanic men and women ages 40–90.

Dual x-ray absorptiometry (DXA) uses two x-ray beams to measure BMD and is indicated for people at high risk for osteoporosis (particularly women age 65 and older) and for postmenopausal women ages 60–64 with two or more other risk factors (NOF, 2010). Recommendations for younger women and for men are controversial but may be justifiable for people with other risk factors, including CTIBL, if the acquired information influences treatment decisions. That includes many patients with cancer who frequently do not have DXA scans prescribed (Tanvetyanon, 2005; Tham et al., 2007). Peripheral DXA (forearm, heel, or finger) can be used to screen for bone loss, but a central DXA (femoral neck, total hip and spine, or total body) is necessary to confirm baseline low BMD and to evaluate response to therapy (Brufsky, 2008; ICSI, 2008; NOF, 2010). BMD can vary at different sites, so DXA of one location may not confirm osteoporosis.

DXA is relatively inexpensive, easily and rapidly conducted, can evaluate several sites, and uses a low radiation dose (Srinivas & Colocci, 2006). Conversely, results can vary depending on the machine used and differing calibration and reference standards (Gralow et al., 2009). Disadvantages are minimized by repeat scanning with the same sites with the same machine and reference standards. The optimal interval for repeat DXA after initiation of antiresorptive therapy is every two to three years because BMD changes can vacillate and DXA measurement is imprecise. Small increases in BMD may be attributable to measurement error and must be 2%–4% in the vertebral spine and 3%–6% in the hip to predict a decreased risk for fracture of 30% and 50%, respectively (Bergmann et al., 2009).

DXA results are reported as t and z scores, which are standard deviations in a patient's BMD from the mean value of a comparison group. T scores are compared to BMD of healthy young adults (ideally of the same gender and ethnicity), and z scores are compared to the BMD of same-age adults (Sala & Barr, 2007; Sweet et al., 2009; Yamamoto & Viale, 2009). T scores are almost always used; t scores of greater than –1 are considered normal, –1 to –2.5 are considered low bone mass (osteopenia), and lower than –2.5 leads to a diagnosis of osteoporosis (Brufsky, 2008). Bone density is the best single predictor for hip fracture risk, which increases by 1.5–2.6 times for each standard deviation decrease in hip BMD (Khosla & Melton, 2007). However, 50% or more of low intensity fractures occur in women who have t scores of –1 to –2.5 (Siris et al., 2004). T scores are not applicable to children, adolescents, and adults younger than age 50; z scores are more appropriate (Sala & Barr, 2007). A low z score reflects lower BMD than would be expected in a person of the same age, gender, and ethnicity.

Other diagnostic tests, such as quantitative ultrasound densitometry of the heel, quantitative computed tomography, and bone formation biomarkers are not widely used.

- Screen for secondary causes of osteoporosis.
- Counsel and educate.
- DXA (BMD) testing is indicated for women aged 65 and older, men 70 and older, and may be recommended to
  - Postmenopausal women and men aged 50–69 years based on concerns regarding risk factor profile
  - Patients with vertebral deformity consistent with fracture on radiograph
  - Patients who have sustained a vertebral, hip, or other fracture to determine severity of BMD loss
  - Men with hypogonadism for more than five years
  - Patients receiving drugs for cancer known to increase risk of CTIBL
  - Solid organ or allogeneic stem cell transplantation
- Monitor BMD (DXA center that uses accepted quality assurance measures).
  - Normal baseline (t score greater than –1): every two to five years, depending on risk factors
  - Low bone mass (t score of –1 to –2.4) or osteoporosis (t score –2.5 or lower): every one to two years
  - Response to pharmacologic management: every two years
- Initiate pharmacologic treatment in
  - Patients with hip or vertebral fracture
  - Patients with t score of –2.5 or lower in the femoral neck or spine
  - Postmenopausal women and men older than age 50 who have low bone mass at femoral neck or spine and a 10-year probability of hip fracture of 3% or higher, or major osteoporosis-related fracture of 20% or higher based on the World Health Organization's fracture risk assessment tool

BMD—bone mineral density; CTIBL—cancer treatment-induced bone loss; DXA—dual x-ray absorptiometry

Figure 4. Major Clinical Recommendations Regarding Osteoporosis in Postmenopausal Women, Men Aged 50 Years and Older, and Patients With Cancer at Risk for CTIBL

Note. Based on information from Body et al., 2007; Gralow et al., 2009; Institute for Clinical Systems Improvement, 2008; National Comprehensive Cancer Network, 2011; National Osteoporosis Foundation, 2010.

Quantitative ultrasound densitometry is rapid, inexpensive, does not use radiation, and is a good predictor of hip fractures (Kazakia & Majumdar, 2006). However, quantitative ultrasound densitometry is not very sensitive and cannot be used to monitor spinal BMD or response to treatment. Quantitative computed tomography is highly sensitive for three dimension views of cortical and trabecular bone in vertebrae, but is more expensive than DXA and uses a higher radiation dose (Griffith & Genant, 2008). Bone formation biomarkers include serum bone-specific alkaline phosphatase and amino-terminal peptide of type 1 procollagen, and bone resorption markers include urine or serum telopeptides of collagen crosslinks. Bone biomarkers change rapidly and are useful to monitor efficacy of antiresorptive therapy before evaluable DXA changes can be observed in postmenopausal women (Bergmann et al., 2009; Sambrook & Cooper, 2006; Szule, Kaufman, & Delmas, 2007). Little data exist about biomarkers in men.

Table 1. Pharmacologic Agents for Osteoporosis

CLASS OR DRUG	DOSE OR SCHEDULE	ESTIMATED COST ($)[a] PER MONTH	ESTIMATED COST ($)[a] PER YEAR
Bisphosphonates			
Alendronate	**Treatment**		
	• 10 mg per day (oral)	70.50	846
	• 70 mg per week (oral)	33	396
	Prevention		
	• 35 mg per week (oral)	50	600
Ibandronate	**Treatment**		
	• 150 mg per month (oral)	116.33	1,396
	• 3 mg IV every three months	473.37 (per dose)	1,893[b]
Risedronate	**Treatment in postmenopausal women**		
	• 5 mg per day (oral) or 35 mg per week (oral)	118.61	1,423
	• 150 mg per month (oral)	113.84	1,366
	• 75 mg on two days	119.75	1,437
	Treatment in men		
	• 35 mg per week	113.80	1,366
Zoledronic acid	• 5 mg IV every 12 months	–	1,137[b]
Receptor Activator for Nuclear Kappa-B Ligand Antibody			
Denosumab	• 60 mg subcutaneous every six months	–	1,650[b]
Other Agents			
Calcitonin	• 100 IU subcutaneous or intramuscular every other day or 200 IU spray (nasal) every day	476.93 109.99	5,723 1,320
Teriparatide	• 20 mcg subcutaneous per day	948.27	11,379

[a] Cost information obtained from www.drugstore.com.
[b] Does not include administration costs
Note. Based on information from Drake et al., 2008.

Pharmacologic Management of Osteoporosis

Few osteoporosis studies include men, so management recommendations are largely based on research of postmenopausal women. U.S. Food and Drug Administration-approved agents to prevent or treat osteoporosis include bisphosphonates, denosumab, estrogen, selective estrogen receptor modulators, calcitonin, and teriparatide (see Tables 1 and 2).

Bisphosphonates

Bisphosphonates have high affinity for bone, bind to hydroxyapetite crystals, and inhibit farnesyl diphosphate synthase to block osteoclasts from resorbing bone (Boonen et al., 2009). Bisphosphonates also inhibit differentiation of preosteoclasts and induce osteoclastic apoptosis, as well as stimulate osteoblasts to release osteoclast inhibitory factor (Tanvetyanon & Stiff, 2006). Nitrogen-containing bisphosphonates (i.e., alendronate, ibandronate, risedronate, and zoledronic acid [ZA]) are the mainstay of osteoporosis management and have other cancer-related indications (i.e., Paget disease, bone metastases, and hypercalcemia). Bisphosphonates, such as ZA and pamidronate, also may have direct and indirect antitumor effects (Brufsky et al., 2008; Colemen, 2007; Gnant et al., 2009; Green & Clézardin, 2010). For instance, ZA 4 mg every 3, 6, or 12 months may be used to decrease skeletal-related events in patients with breast or prostate cancer (Bhoopalam et al., 2009; Saad et al., 2008). Bisphosphonates are superior to placebo to decrease fragility fractures in postmenopausal women, but none of those agents have demonstrated superiority over the others (MacLean et al., 2008). The durations of physiologic activity of bisphosphonates is unknown, but they may remain in bone for decades and suppression of bone markers persists for five years or longer.

Oral bisphosphonates are for first-line treatment or prevention of osteoporosis. Bioavailability of oral bisphosphonates is less than 2% and food decreases absorption, so they must be taken with water on an empty stomach. Patients must be able to sit or stand for at least 30 minutes after oral doses because of adverse gastrointestinal effects (Boonen et al., 2009; Roelofs, Thompson, Gordon, & Rogers, 2006). Bisphosphonates are excreted by the kidneys and doses must be decreased in patients with mild to moderate renal impairment (creatinine clearance of 30–60 ml per minute), and are contraindicated for patients with severe renal impairment (creatinine clearance of less than 30 ml per minute), particularly because bisphosphonates can cause acute and chronic renal failure (Perez & Weilbaecher, 2006; Tanvetyanon & Stiff, 2006). Because of a possible increased risk for esophageal cancer, oral bisphosphonates are contraindicated for patients with Barrett's esophagus (Wysowski, 2009).

As many as 50%–60% of patients discontinue prescribed daily oral bisphosphonates within one year, possibly because osteoporosis is asymptomatic or because of adverse effects,

Table 2. Adverse Effects of Antiresorptive Agents

CLASS OR DRUG	POTENTIAL ADVERSE EFFECTS
Bisphosphonates	
Alendronate, ibandronate, risedronate, and zoledronic acid	**For oral agents:** esophageal and gastric irritation, ulceration, nausea, reflux, heartburn; hypersensitivity reaction; arthralgia and myalgia (may be severe); arrhythmias (men); headache; depression; atypical stress fracture (rare); and osteonecrosis of the jaw (rare with oral agents). **For IV agents:** acute reactions, low-grade fever, myalgias, and arthralgias; renal impairment and failure; and hypocalcemia
Receptor Activator for Nuclear Kappa-B Ligand Antibody	
Denosumab	Fatigue, asthenia, dyspnea, cough, headache, hypocalcemia, hypophosphatemia, and osteonecrosis of the jaw
Other Agents	
Calcitonin	Hypersensitivity reaction, anaphylaxis, bronchospasm, nausea, increased appetite, abdominal pain, diarrhea, flushing, rash, and nocturia
Teriparatide	Transient hypercalcemia, arthralgias, muscle spasms, nausea, dyspepsia, constipation, pneumonia, and orthostatic hypotension

Note. Based on information from Drake et al., 2008; Gralow et al., 2009; Roelofs et al., 2006; Sambrook & Cooper, 2006; Smith et al., 2009.

regimen complexity, or costs (Badamgarov & Fitzpatrick, 2006; Boonen et al., 2009). Adherence (and benefit) may improve with weekly or monthly dosing. IV bisphosphonates (ibandronate or ZA) are useful for patients who cannot tolerate an oral bisphosphonate. Once yearly IV ZA 5 mg is convenient and leads to faster and greater reduction in bone turnover markers than weekly oral alendronate (Woodis, 2008). However, 10%–50% of patients experience an acute phase reaction with flu-like symptoms that start about 24–36 hours after the first infusion of ZA and resolve in two or three days (Bertoldo et al., 2010). Acute phase reactions, which are a nonspecific immune reaction accompanied by increased levels of circulating acute-phase proteins (C-reactive protein and serum amyloid A), are more common in patients with vitamin D deficiency. Vitamin D deficiency or hypomagnesemia also can cause symptomatic hypocalcemia and decreased creatinine clearance for several days after ZA administration (Chennuru, Koduri, & Baumann, 2008). Patients also may experience severe bone, joint, and muscle pain starting 12 hours after bisphosphonate administration (independent of acute phase reactions) that may require holding or stopping oral or IV agents (Solomon, Rekadal, & Cadarette, 2009; Tanvetyanon & Stiff, 2006).

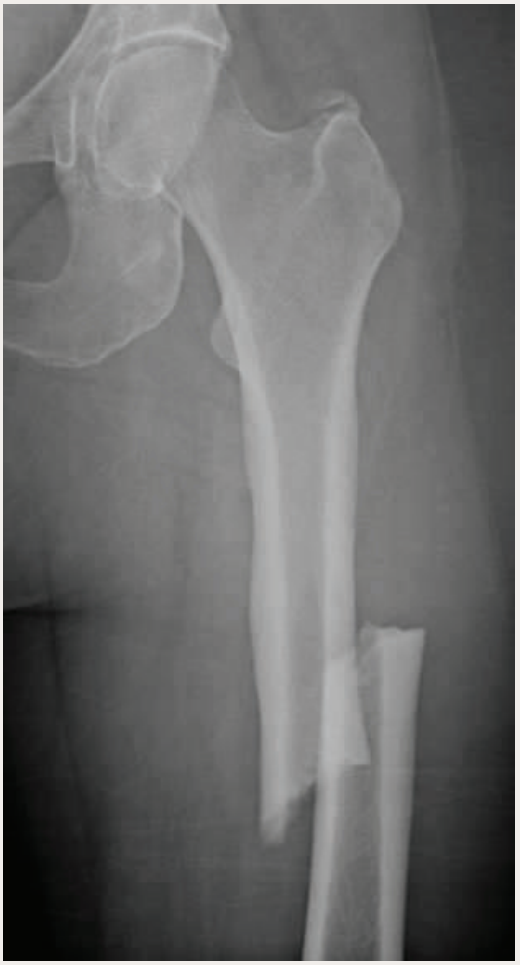
Serious but relatively rare complications of bisphosphonates are osteonecrosis of the jaw and atypical stress fractures. Osteonecrosis of the jaw (exposed and necrotic bone persisting for more than eight weeks, with or without pain or infection) is more frequent in the mandible than the maxilla (Agbaloo, Felsenfeld, & Tetradis, 2010). Osteonecrosis of the jaw is most common after long-term administration of IV bisphosphonates, particularly in patients with metastatic breast cancer or myeloma (Fehm et al., 2009), and has been reported in 1%–1.4% of patients receiving ZA (Drake, Clarke, & Khosla, 2008; Fizazi et al., 2011; Henry et al., 2011; Stopeck et al., 2010). Pathogenesis may be related to high bone turnover with excessive bisphosphonate deposition in the mandible and maxilla, compromised healing secondary to chemotherapy, and actinomyces infection (Naik & Russo, 2009). Risk factors include tooth extractions or other causes of dental trauma (i.e., dentures, oral infection), poor dentition, diabetes, age, smoking, monthly bisphosphonate administration for more than 12 months, and cumulative dose of ZA (Dickinson et al., 2009; Vahtsevanos et al., 2009).

Another concern of bisphosphonates is that long-term inhibition of bone turnover may cause accumulation of microdamage that leads to brittle bones and contributes to the pathogenesis of atypical, nontraumatic, transverse or oblique fractures of the femoral shaft or subtrochanteric region (more rarely the pelvis, sacrum, or metatarsals) (Sambrook & Cooper, 2006). Atypical fractures are rare, and have most often been reported in 0.13%–0.22% of patients taking oral bisphosphonates for longer than five years (Lenart et al., 2009; Park-Wyllie et al., 2011; Schilcher & Aspenberg, 2009; Shane et al., 2010; Visekruna, Wilson, & McKiernan, 2008). A retrospective review by Puhaindran et al. (2011) identified 4 atypical fractures in 327 patients with cancer (1.2%) who had received at least 24 doses of IV ZA or pamidronate for bone metastases. Patients typically have local pain for weeks to months before a fracture that occurs with minimal trauma and usually require surgical repair, and x-rays show characteristic cortical thickening (see Figure 5). The risk for atypical stress fractures is extremely small compared to the risk for osteoporosis-related fractures (Park-Wyllie et al., 2011). However, this has still led to questions about how long bisphosphonates should be taken.

Denosumab

Denosumab is a fully human, highly specific immunoglobulin G2 monoclonal antibody for RANKL. Binding prevents RANKL interaction with RANK, thereby mimicking the action of osteoprotegerin to inhibit osteoclasts and prevent bone breakdown. Serum denosumab is detectable shortly after administration, and decreased bone turnover markers persist for at least 84 days (Burkiewicz, Scarpace, & Bruce, 2009). Several large randomized, placebo-controlled studies have analyzed denosumab for osteoporosis, CTIBL, or the prevention of skeletal-related events. Denosumab is approved for second-line therapy of postmenopausal osteoporosis to increase BMD, as well as to decrease fracture risk in men with nonmetastatic prostate cancer receiving androgen deprivation therapy and women with breast cancer receiving adjuvant aromatase inhibitors. Denosumab also is indicated to prevent skeletal-related events in patients with bone metastases from solid tumors (excluding multiple myeloma).

In the pivotal study of denosumab, 7,868 women with confirmed postmenopausal osteoporosis were randomized to subcutaneous denosumab 60 mg or placebo every six months for 36 months (Cummings et al., 2009). Denosumab was superior in terms of improved BMD and fewer fractures—vertebral (2.3% versus 7.2%, $p < 0.001$) and non-vertebral(6.5% versus 8%, $p = 0.01$), and was not more likely to cause adverse events.



Note. Lateral fracture and cortical thickening are visible.

Figure 5. Transverse Stress Fracture in a Patient Treated With a Bisphosphonate

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Results were similar in patients with nonmetastatic breast or prostate cancers and CTIBL treated with subcutaneous denosumab 60 mg every six months for 24 or 36 months. Women receiving aromatase inhibitor therapy and with low BMD were randomized to denosumab or placebo. After 12 months, denosumab-treated women had greater decreases in bone resorption biomarkers ($p < 0.0001$) and greater increases in lumbar spine BMD (4.9% versus –0.7%, $p < 0.0001$) (Ellis et al., 2008). Men with nonmetastatic prostate cancer on androgen deprivation therapy and with low bone mass or osteoporosis also were randomized to denosumab or placebo. Lumbar spine BMD increased 5.6% in men on denosumab, but decreased 1% in placebo-treated men ($p < 0.001$), and the denosumab group had fewer vertebral fractures (1.5% versus 3.9%, $p = 0.006$) (Smith et al., 2009).

Three published studies compared denosumab and ZA in patients with bone metastases. In a study of men with metastatic prostate cancer and another of women with metastatic breast cancer, denosumab was superior to delay the time to first skeletal-related event by 18% ($p = 0.008$) and 23% ($p = 0.01$), respectively (Fizazi et al., 2011; Stopeck et al., 2010). In the third study of patients with other solid tumors or multiple myeloma, denosumab was superior to ZA in patients with solid tumors but equivalent for those with myeloma (Henry et al., 2011). No differences were noted in time-to-disease progression or in survival in any of the studies. Osteonecrosis of the jaw occurred in 2% of patients with cancer receiving denosumab and 1.4% of those given ZA.

Potential advantages of denosumab for osteoporosis and CTIBL are that every six months of dosing may increase adherence over daily, weekly, or monthly oral bisphosphonate dosing, and subcutaneous administration is easier, less time consuming, and less expensive than IV infusions of ZA. Denosumab is not taken up and stored in bone, so long-term effects may reverse more rapidly than with bisphosphonates. Denosumab does not cause acute phase reactions and does not require dose adjustment for impaired renal function, but hypocalcemia is more frequent after denosumab than ZA.

Other Approved Agents for Osteoporosis

Other agents indicated for osteoporosis generally are not used for individuals with cancer. For instance, estrogen maintains BMD by inducing osteoclast apoptosis and extending osteoblast lifespan, down regulating RANKL, and up regulating osteoprotegerin (Murthy et al., 2010). Hormone replacement therapy with estrogen increases BMD and reduces the incidence of hip fractures. However, hormone replacement therapy also increases the risks for deep venous thrombosis, myocardial infarction, stroke, and pulmonary embolus (Rossouw et al., 2002). Estrogen is not recommended for osteoporosis or CTIBL in patients with breast cancer because of an increased risk for metastatic disease or second malignancies.

Raloxifene is the only selective estrogen receptor modulator approved to prevent or treat osteoporosis, but is not as potent as bisphosphonates are in preventing fragility fractures of the hip or other non-vertebral fractures (Gralow et al., 2009). In addition, raloxifene is contraindicated in patients who have been treated with tamoxifen (Hillner et al., 2003). Raloxifene increases the risk for fatal stroke but not heart attack, and also can cause hot flushes, peripheral edema, and leg cramps.

Calcitonin binds to calcitonin receptors on osteoclasts, decreases osteoclast formation and activity, and leads to down regulation of calcitonin receptors (Chestnut et al., 2008). Calcitonin is not used as first-line treatment for osteoporosis because, although it decreases the risk for vertebral compression fractures, other antiresorptive agents are more effective for fragility fractures (Sweet et al., 2009). Calcitonin nasal spray usually is administered once a day in alternating nares and may be useful in palliative care to decrease bone pain. Transient local nasal irritation with stinging or itching, rhinitis, sneezing, and minor bleeding is rare.

Teriparatide (recombinant PTH 1–34) is the only anabolic antiresorptive agent and can be used alone or in combination with another resorptive agent to restore bone mass. Teriparatide is approved for postmenopausal women with persistent osteoporosis despite bisphosphonate therapy and men with osteoporosis and previous or future risk for fragility fractures. PTH 1–34 causes larger increases in spinal and hip bone mass than other antiresorptive agents and improves macro- and microarchitechture of trabecular and cortical bone (Cosman, 2008). PTH 1–34 (20 mcg

subcutaneous) is administered daily for no longer than 18–24 months. Osteosarcoma is a concern because long-term, very high-dose PTH 1–34 induced tumors in rats (Vahle et al., 2004). Only one reported case exists of osteosarcoma in more than 700,000 humans given PTH 1–34 (Cosman, 2008; Harper, Krege, Marcus, & Mitlak, 2007). However, PTH 1–34 is contraindicated in patients with prior radiation therapy to the bone, possible micrometastases or occult cancer, and Paget disease (Gralow et al., 2009). Adverse effects include transient hypercalcemia, nausea, leg cramps, arthralgias, and orthostatic hypotension (Sweet et al., 2009).

Nonpharmacologic Interventions

Nurses have essential roles caring for and counseling patients with cancer who are at risk for or are experiencing low bone mass or osteoporosis, including safe administration of antiresorptive therapies. Another important nursing implication is patient education that addresses unmet knowledge deficits about bone health, particularly about modifiable risk factors, lifestyle choices, and self-care measures to enhance bone health (McKean et al., 2008; Panju et al., 2008). Education begins with a focused bone health history to elicit information on usual daily activities, exercise, cigarette smoking, alcohol intake, nutrition, medication history, and risk for falls (ICSI, 2008; NOF, 2010).

Exercise has modest effects on BMD, but improves posture, muscle strength, coordination, balance, and agility; all of which decrease the risk for falls (Swenson et al., 2009; Vondracek, 2010). Nurses should encourage patients to avoid a sedentary lifestyle and incorporate regular exercise (weight bearing and muscle strengthening) at least twice a week as age, physical condition, and health permit. Those considerations may be particularly important when helping patients with cancer develop realistic exercise plans. Weight-bearing exercise (i.e., walking, jogging, tai chi, dancing, tennis, and stair climbing) stimulates bone formation and improves bone health. Muscle strengthening or resistance exercises (i.e., free weights and elastic bands) also can decrease the risk for falls and fractures.

Correspondingly, nurses should identify patients' risk factors for falls such as frailty, poor balance, impaired gait or function, lower-extremity weakness, poor vision, peripheral neuropathy (secondary to diabetes or chemotherapy), or other home safety issues. A medication review is important to identify drugs that might increase the risk for falls, such as sedatives, antidepressants, opioid analgesics, antipsychotics, anticonvulsants, and drugs with anticholinergic properties, including benzodiazepines and other anxiolytics (Fosnight, Zafirau, & Hazelett, 2008; Vondracek, 2010). Polypharmacy (taking four or more prescription drugs), orthostasis, depression, cognitive impairment, and arthritis also can increase the risk of falls in older adults.

Cigarette smoking, as well as alcohol and caffeine intake, may influence bone health, so nurses should inquire about patients' social habits. Helping patients quit smoking is particularly important for women smokers; smoking puts them at greater risk for early primary or therapy-induced menopause, increases their risk for rapid bone loss, and puts them at greater risk for fractures than nonsmokers (North American Menopause Society, 2006). In addition, women should be advised to limit alcohol to one drink per day and men to two because alcohol affects bone health and may increase fall risk (Vondracek, 2010). Similarly, high caffeine (four or more cups of coffee or caffeinated soft drinks per day) may increase urinary calcium excretion and decrease BMD, particularly in individuals whose calcium intake is less than 700 mg per day.

Nutrition considerations include calcium and vitamin D, as well as magnesium and other trace elements. Calcium absorption is greatest with doses of 500 mg or less, so supplemental doses of calcium (carbonate or citrate) should be divided (Gralow et al., 2009). Calcium carbonate must be taken with food for adequate absorption. Calcium citrate is preferable because it is equally absorbed on an empty stomach or with food, is better absorbed in patients with hypochlorhydria, and is best for patients taking a proton pump inhibitor (Gralow et al., 2009). Calcium is somewhat constipating, which may be problematic for patients taking opioid analgesics or anticholinergic medications. Higher vitamin D intake and corresponding higher serum calcidiol has a calcium-sparing effect for optimal bone mineralization. About 600 mg of calcium per day may be sufficient for women whose serum calcidiol is at least 20 ng/ml (Bischoff-Ferrari, Kiel, et al., 2009), whereas women whose calcidiol is less than 20 ng/ml require a greater daily calcium intake.

The two available forms of vitamin D are D_3 (cholecalciferol), an over-the-counter product that is more potent and has a longer duration of action, and D_2 (ergocalciferol), which must be medically prescribed. Some clinicians and scientists propose larger doses of vitamin D (Bischoff-Ferrari, Dawson-Hughes, et al., 2009) than the current recommended daily allowances of 600–800 IU (IOM, 2011). For instance, Zarowitz (2008) recommended supplemental vitamin D_3 doses of 800–1,000 IU or greater plus dietary intake to increase serum calcidiol and decrease fall risk.

Serum calcidiol more accurately reflects vitamin D status than daily intake; 30–100 ng/ml is considered the normal range, whereas lower levels are classified as vitamin D insufficiency (20–29 ng/ml) or deficiency (less than 20 ng/ml) (Bordelon, Ghetu, & Langan, 2009). Serum calcidiol also is an important consideration in safely administering bisphosphonates. Routine assessment of vitamin D status is the norm when bisphosphonates are prescribed for osteoporosis but often not the case when they are given to patients with cancer (Wang-Gillam et al., 2008). The issue is that patients with low serum calcidiol are more likely to experience acute phase reactions as well as disastrous hypocalcemia after bisphosphenate administration. In one sample, 70% of acute phase reactions after ZA occurred in patients whose serum calcidiol was lower than 30 ng/ml, whereas 76% of patients whose calcidiol was greater than 30 ng/ml did not experience an acute phase reaction (Bertoldo et al., 2010). Similarly, bisphosphenate administration to patients with cancer with undiagnosed vitamin D deficiency led to severe hypocalcemia accompanied by exacerbated secondary hyperparathyroidism, osteopenia, and fractures (Wang-Gillam et al., 2008). Suboptimal calcidiol levels (less than 32 ng/ml) have been documented in 67%–75% of patients with cancer (Everett, 2008; Vashi, Trukova, Lammersfeld, Braun, & Gupta, 2010; Wang-Gillam et al., 2008). The *optimal* serum calcidiol level has not been established, but Bertoldo et al. (2010) recommend assessing and maintaining levels at more than 40 ng/ml before infusing bisphosphonates.

Despite the fact that magnesium and other micronutrients also play a role in RANKL expression, bone loss, and osteoporosis, no information exists regarding optimal dietary intake.

However, data indicate that short-term magnesium supplementation decreases urinary and serum markers of bone turnover and may be more important to bone health than previously thought (Aydin et al., 2010). Oncology nurses should be aware of patients at risk for hypomagnesemia and collaborate with oncologists and nurse practitioners to correct the problem.

Conclusions

Unrecognized primary osteoporosis or secondary CTIBL can profoundly affect patients diagnosed with and undergoing cancer treatment as well as cancer survivors. Nurses have critical roles in identifying patients at risk for primary or secondary BMD loss, to decrease risk factors, and to prevent fractures that often have immense effects on quality and duration of life. Those risks are significant in the general population and may be magnified in patients with cancer treated with antineoplastic or hormone agents, radiation therapy, or surgery. Nurses should also keep abreast of new knowledge about optimal calcium, vitamin D, and possibly magnesium intake to maximize bone health and prevent complications of antiresorptive therapy, including the doses, intervals, and duration of antiresorptive therapies for patients with cancer.

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