CONTINUING EDUCATION

Cancer Treatment-Induced Bone Loss in Patients With Breast or Prostate Cancer

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Purpose/Objectives: To review the prevalence, consequences, pathophysiology, diagnosis, and treatment of cancer treatment-induced bone loss (CTIBL) in patients with breast or prostate cancer.

Data Sources: Published articles, abstracts, book chapters, electronic resources, and manufacturer information.

Data Synthesis: CTIBL is a long-term complication associated with cancer therapies that cause hypogonadism in patients with breast or prostate cancer. Early diagnosis and treatment of CTIBL is essential to prevent bone fractures. CTIBL treatment includes modification of lifestyles that increase the risk of developing bone loss and fractures and includes the use of bone loss therapies (e.g., bisphosphonates, selective estrogen receptor modifiers, calcitonin).

Conclusions: CTIBL is becoming more common as patients with breast or prostate cancer survive longer. Identifying and treating CTIBL early are important because once bone is lost, damaged bone becomes more difficult to repair; early diagnosis and treatment also may prevent fractures.

Implications for Nursing: Nurses must be knowledgeable about CTIBL to identify high-risk patients and educate patients and their families about CTIBL, bone loss therapies, and lifestyle modifications.

Key Points . . .

➤ Cancer treatment-induced bone loss (CTIBL) commonly occurs in patients with breast cancer with chemotherapy-induced menopause; some patients with breast cancer receiving hormonal therapy, such as aromatase inhibitors; and patients with prostate cancer receiving androgen deprivation therapy.

➤ Patients at risk for CTIBL should adopt lifestyles that preserve bone health, including smoking cessation, moderate alcohol consumption, weight-bearing exercise, adequate calcium and vitamin D intake, and measures to prevent falls.

➤ Bisphosphonates are the most effective therapies for patients with CTIBL. IV bisphosphonates are more potent, better tolerated, and less frequently administered than oral bisphosphonates.

Goal for CE Enrollees:

To enhance nurses' knowledge about cancer treatment-induced bone loss (CTIBL) in people with breast or prostate cancer.

Objectives for CE Enrollees:

1. Describe factors that can place a person with breast or prostate cancer at risk for CTIBL.
2. Outline the assessment and diagnostic measures used to evaluate a person with CTIBL.
3. Discuss interventions that should be included in a plan of care for a person with CTIBL.

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Osteoporosis, a disease characterized by low bone mass and deterioration of bone that can lead to bone weakness and increased susceptibility to fracture, with or without trauma, is a common health problem in aging men and women (Brown & Josse, 2002; Follin, 2003). In 2002, approximately two million men and eight million women older than 50 years were estimated to have osteoporosis (National Osteoporosis Foundation [NOF], 2004a). Additionally, approximately 34 million men and women were estimated to have osteopenia—low bone mass not yet at the deficient level of an osteoporosis diagnosis—placing them at risk for developing the more pronounced bone loss associated with osteoporosis (NOF, 2004a).

Patients with breast or prostate cancer are particularly at risk for developing bone loss because their cancer therapies, such as chemotherapy or hormonal therapy, may cause or accelerate bone loss. With improved survival times in both diseases, long-term toxicities such as cancer treatment-induced bone loss (CTIBL) are beginning to have a negative impact on the quality of life of cancer survivors (Berruti, Tucci, et al., 2002; Mincey, Moraghan, & Perez, 2000). Thus, an understanding of CTIBL is necessary to determine which patients may benefit from an early assessment of risk factors and complications associated with bone loss and early intervention with bone loss therapies.

Prevalence of Cancer Treatment-Induced Bone Loss

Bone Loss and Related Fractures in Healthy Adults

Bone undergoes a continual process of loss and formation (i.e., bone remodeling) throughout its life to maintain its structural and mineral integrity (Gholz, Conde, & Rutledge, 2002). Because of the natural aging process and reduction of gonadal hormone production over time, bone loss occurs much more rapidly than bone formation in older men and women, resulting in an overall net loss of bone and an increased risk of fractures (Higano, 2003). With the cessation of estrogen production that characterizes menopause, women initially experience a sharp decrease in bone mass (as much as 30% of bone mass within five years after menopause); the loss of bone mass then becomes more gradual (Higano, 2003; Twiss et al., 2001). Men, however, experience a more gradual loss of testosterone and estrogen production and, thus, a more gradual loss of bone mass; at about 60 years of age, men and women have a similar rate of bone loss (Higano, 2003). Unless bone loss prevention or treatment strategies are implemented, many patients will progress from normal bone mass to osteopenia and, eventually, osteoporosis (Follin, 2003).

The incidence of fractures is increased in men and women who experience bone loss (Cummings & Melton, 2002). In the United States, Caucasian women older than 50 years have a 40% estimated lifetime risk of experiencing a spine, hip, or distal radius fracture; Caucasian men aged 50 years or older have a 13% lifetime risk of a fracture (Messinger-Rapport & Thacker, 2002). Additionally, adults with a history of a fracture are 50%–100% more likely to experience a second fracture (Cummings & Melton). Figure 1 lists the risk factors for developing bone loss and an increased susceptibility to fractures (Hillner et al., 2003; Messinger-Rapport & Thacker; NOF, 2004b).

Modifiable Risk Factors
Excessive alcohol consumption
Excessive caffeine consumption
Existing low bone mass and poor bone quality
Low calcium or vitamin D intake
Low body weight or excessive weight loss
Low estrogen or testosterone levels
Sedentary lifestyle
Tobacco use
Use of certain medications[a]

Unmodifiable Risk Factors
Chronic diseases[a]
Female gender
Height
History of fracture
History of late menarche
Impaired mental status
Impaired vision
Maternal history of fractures
Older age
Skeletal hip formation
Caucasian or Asian race

[a] Those that affect absorption or production of calcium or vitamin D or decrease the production of estrogen or testosterone

Figure 1. Risk Factors for Developing Bone Loss and Fractures

Note. Based on information from Hillner et al., 2003; Messinger-Rapport & Thacker, 2002; National Osteoporosis Foundation, 2004b.

Cancer Treatment-Induced Bone Loss in Patients With Breast Cancer

Patients with breast cancer are at increased risk for developing CTIBL. These patients often experience menopause, either temporary or permanent, as an adverse effect of their chemotherapy, and menopause is associated with a higher rate of bone loss than bone formation (Ramaswamy & Shapiro, 2003; Twiss et al., 2001). Significant bone loss as a result of chemotherapy-induced menopause has been reported in premenopausal patients with breast cancer as early as six months after initiation of some types of adjuvant chemotherapy, and the loss continues for several years (Ramaswamy & Shapiro). The results of two studies evaluating the effect of adjuvant chemotherapy-induced menopause on bone loss showed that bone mineral density—the average concentration of bone mineral in a defined section of bone that is used to diagnose and monitor bone loss—decreased by 4%–7% in the spine and 2% in the femur 12 months after the initiation of adjuvant chemotherapy (Saarto et al., 1997; Shapiro, Manola, & Leboff, 2001). Additionally, bone loss continued for the next two to five years in women with permanent menopause (Saarto et al.; Vehmanen et al., 2001).

Some patients with breast cancer receiving hormonal therapy, such as tamoxifen (Nolvadex®, AstraZeneca, Wilmington, DE), also may be at increased risk for developing CTIBL. The effect of tamoxifen on bone differs in postmenopausal and premenopausal women. In postmenopausal women, tamoxifen preserves bone mineral density, increasing spine bone mineral density by 0.6%–1.2% and hip bone mineral density by 1.7% for each year of therapy (Love et al., 1992; Powles, Hickish, Kanis, Tidy, &

Ashley, 1996). In premenopausal women receiving tamoxifen, however, spine bone mineral density decreases by approximately 1.4% for each year of therapy (Powles et al.).

The effects of other hormonal therapies, such as fulvestrant and aromatase inhibitors, on the development of CTIBL have been studied less. The results of preclinical trials evaluating fulvestrant (Faslodex®, AstraZeneca) have shown varying effects on bone (Ramaswamy & Shapiro, 2003). Likewise, results of preclinical trials and preliminary results of clinical trials evaluating aromatase inhibitors have suggested that nonsteroidal aromatase inhibitors, such as anastrozole (Arimidex®, AstraZeneca) and letrozole (Femara®, Novartis Pharmaceuticals, East Hanover, NJ), do not prevent loss of bone mineral density, whereas the steroidal aromatase inhibitor exemestane (Aromasin®, Pfizer Inc., New York, NY) prevents bone mineral density loss (Ramaswamy & Shapiro). However, the results of clinical trials evaluating aromatase inhibitors in postmenopausal women with breast cancer have shown trends toward increased bone loss following nonsteroidal and steroidal aromatase inhibitor therapy (Coombes et al., 2004; Eastell, Hannon, Cuzick, Clack, & Adams, 2002; Goss et al., 2003). The results of a study evaluating 80 postmenopausal women who received anastrazole as adjuvant treatment for early breast cancer showed that these patients experienced a bone mineral density loss of 2.6% in the lumbar spine and 1.7% in the total hip after one year of therapy, which is similar to the average yearly loss of bone mineral density in postmenopausal women (Eastell et al.; Finkelstein, 2000). The other two clinical trials evaluating letrozole and exemestane did not measure bone mineral density but reported the incidence of newly diagnosed osteoporosis (8% and 7.4%, respectively) (Coombes et al.; Goss, 2004). In the letrozole study, osteoporosis was significantly more common in patients who received aromatase inhibitors than those who did not (8% versus 6%, p = 0.0003), but in the exemestane study, the difference was not significant (Coombes et al.; Goss). Short follow-up periods and the lack of an objective measurement of bone loss in both of these studies may have contributed to an underestimation of the incidence of bone loss that occurs with these drugs (Coombes et al.; Goss et al.). Therefore, careful monitoring of patients receiving aromatase inhibitors is warranted until the severity of bone loss that occurs with these drugs in patients with breast cancer is determined (Ramaswamy & Shapiro).

The incidence of fractures caused by chemotherapy-induced bone loss in patients with breast cancer has not been reported, but the results of three clinical trials have revealed the incidence of fractures caused by hormonal therapy-induced bone loss. In the Arimidex, Tamoxifen Alone or in Combination (ATAC) Trialists' Group study that evaluated 9,366 postmenopausal patients with breast cancer, a higher incidence of fractures was reported in patients receiving anastrozole compared with patients receiving tamoxifen only (5.9% and 3.7%, respectively; p < 0.0001) (Baum et al., 2002). The combination of anastrozole and tamoxifen resulted in a fracture incidence of 4.6%. The results of a randomized study comparing letrozole and placebo in postmenopausal women who had received five years of tamoxifen for early-stage breast cancer showed a higher incidence of clinical fractures in patients receiving letrozole (5.3%) compared with placebo (4.6%), but the difference was not significant (p = 0.25) (Goss, 2004). Preliminary results of the randomized study evaluating exemestane after two to three years of tamoxifen therapy in postmenopausal women

with primary breast cancer ($\overline{X}$ age = 64 years) suggested that patients treated with exemestane following tamoxifen therapy were more likely to have fractures than patients treated only with tamoxifen (3.1% and 2.3%, respectively, p = 0.08), but again this difference was not significant (Coombes et al., 2004). These clinical trial results suggested that all aromatase inhibitors may be associated with an increased risk for fracture; however, further evaluation is warranted. Patients receiving aromatase inhibitors should be monitored closely for fracture-related risk factors.

Cancer Treatment-Induced Bone Loss in Patients With Prostate Cancer

Patients with prostate cancer receiving androgen deprivation therapy, which is the mainstay of treatment for patients with metastatic prostate cancer or locally advanced prostate cancer accompanied by a rising prostate-specific antigen level, are at risk for developing CTIBL (Basaria et al., 2002; Berruti, Tucci, et al., 2002; Eriksson, Eriksson, Stege, & Carlstrom, 1995; Smith et al., 2001). Androgen-deprivation therapy options include the use of gonadotropin-releasing hormone agents, such as goserelin (Zoladex®, AstraZeneca) or leuprolide (Lupron®, Tap Pharmaceutical, Inc., Lake Forest, IL; Viadur®, Alza Corporation, Mountain View, CA) with or without an antiandrogen (e.g., flutamide [Eulexin®, Schering-Plough, Kenilworth, NJ], bicalutamide [Casodex®, AstraZeneca], nilutamide [Nilandron®, Aventis Pharmaceuticals, Bridgewater, NJ]), or surgical castration (Berruti, Tucci, et al.; Smith et al., 2001).

Androgen-deprivation therapy significantly decreases bone mineral density. In patients with nonmetastatic prostate cancer undergoing surgical castration, femoral neck bone mineral density decreased by 2%–10% one year after surgery (Daniell et al., 2000; Eriksson et al., 1995). Patients with nonmetastatic prostate cancer undergoing gonadotropin-releasing hormone therapy, with or without an antiandrogen, experienced spine or femoral neck bone mineral density decreases of 1%–5% within nine months to one year after initiation of androgen-deprivation therapy (Berruti, Dogliotti, et al., 2002; Higano, Jiang, Miller, Pitzel, & Jensen, 2003; Maillefert et al., 1999; Mittan et al., 2002; Smith et al., 2001, 2003). Similarly, patients with metastatic prostate cancer undergoing gonadotropin-releasing hormone and antiandrogen therapy experienced bone mineral density decreases of 2%–7% during the first year of therapy (Diamond, Campbell, Bryant, & Lynch, 1998; Diamond et al., 2001). The loss of bone mineral density associated with androgen-deprivation therapy is greater than that associated with menopause (Smith, 2002). Furthermore, bone mineral density tends to progressively decrease and the risk of fracture increase with longer duration of androgen-deprivation therapy (Kiralti, Srinivas, Perkash, & Terris, 2001; Oefelein et al., 2001).

Although the exact incidence of fractures associated with CTIBL in patients with prostate cancer is unknown, the results of several retrospective studies evaluating 59–224 patients have shown an osteoporotic fracture rate of 5%–14% after androgen-deprivation therapy initiation (Daniell, 1997; Hatano, Oishi, Furuta, Iwamuro, & Tashiro, 2000; Oefelein et al., 2001; Townsend, Sanders, Northway, & Graham, 1997). These rates are two to five times higher than those in healthy men (Oefelein et al.; Smith, 2002; Townsend et al.). Fracture risk also is increased after surgical castration. The results of a

recent retrospective study reported a twofold increased risk of osteoporotic fracture in patients with prostate cancer undergoing bilateral orchiectomy compared with expected rates in the general community (Melton et al., 2003).

Consequences of Cancer Treatment-Induced Bone Loss

Although bone loss occurs more rapidly and tends to be more severe in patients with CTIBL, the clinical consequences of CTIBL are similar to those observed with osteoporosis (see Table 1 and Figure 2) (Begerow et al., 1999; Center, Nguyen,

Table 1. Clinical Consequences of Cancer Treatment-Induced Bone Loss

Consequence	Comments
Abdominal protrusion	Result of multiple vertebral fractures
Acute pain	Result of fracture; in vertebral fractures, pain caused by vertebral collapse may worsen with standing or sudden movement. May require inactivity or immobilization and treatment with analgesics. Typically resolves in weeks to months.
Chronic pain	Result of fracture May continue for several years.
Decreased functional capability	Result of fracture Most severe with hip fracture: 80% of patients are unable to perform at least one activity of daily living after one year; 33% of older adult patients with a hip fracture require nursing home care. Approximately 40% of patients with wrist fractures have long-term weakness that limits performing activities of daily living. Quality of life often is compromised.
Fracture	Result of increased bone fragility Occurs with relatively mild trauma[a] Most common in vertebrae, hip, and wrist Hip fractures often require surgical intervention (see Figure 2). Vertebral fractures often occur without symptoms. Wrist fractures resulting from a fall on an outstretched hand are common in postmenopausal women. Risk of subsequent fracture is increased.
Height loss	Result of multiple vertebral fractures Loss of > 1.5 inches from mature height suggests vertebral fractures.
Increased mortality rate	Particularly with hip and vertebral fractures 12-month mortality rate after hip fracture varies from 12%–35%; risk of death from a hip fracture is higher in older adults and men. Mortality rate after vertebral fracture is 23% higher than in healthy population.
Kyphosis	Result of multiple vertebral fractures If severe, may cause respiratory problems because of compression of thoracic region and poor nutrition because of abdominal compression.

[a] Vertebral fractures can occur with minimal activity, such as bending or lifting.

Note. Data are from healthy adults with osteoporosis. Based on information from Begerow et al., 1999; Center et al., 1999; Cooper, 1997; Cummings & Melton, 2002; Delmas, 2002; Follin, 2003; Miller & Lane, 2001; Smith, 2003b.

Figure 2. Radiograph of Bilateral Hip Prostheses Inserted After a Hip Fracture in an Osteoporotic Woman

Schneider, Sambrook, & Eisman, 1999; Cooper, 1997; Cummings & Melton, 2002; Delmas, 2002; Eastell et al., 2002; Finkelstein, 2000; Follin, 2003; Kaufman et al., 2000; Maillefert et al., 1999; Miller & Lane, 2001; Shapiro et al., 2001; Smith, 2003b). CTIBL, like osteoporosis, increases bone fragility, and fractures may occur when the bone is subjected to only relatively mild trauma (Cooper; Pfeilschifter & Diel, 2000). Fragility fractures resulting from CTIBL most commonly occur in the vertebrae, hip, and wrist and often have clinical sequelae.

Pathophysiology of Cancer Treatment-Induced Bone Loss

The primary etiology of CTIBL in patients with breast or prostate cancer is hypogonadism caused by chemotherapy, hormonal therapy, or surgical castration (Pfeilschifter & Diel, 2000). Because estrogen and testosterone have a fundamental role in maintaining bone mass by directly or indirectly suppressing bone resorption, decreases in the levels of these hormones—as occurs with hypogonadism—results in accelerated bone loss (Hofbauer & Khosla, 1999; Oursler, Landers, Riggs, & Spelsberg, 1993; Pfeilschifter & Diel). Unless bone formation rates increase, continual loss of bone will occur, leading to osteopenia and, eventually, osteoporosis (Follin, 2003). Direct effects of chemotherapy on bone metabolism, such as decreased bone formation or increased bone resorption, also may be responsible for some bone loss, but these effects are not well described (Mincey et al., 2000; Pfeilschifter & Diel).

Breast Cancer

Patients with breast cancer who receive cyclophosphamide-containing regimens (e.g., cyclophosphamide, methotrexate, 5-fluorouracil [5-FU] [CMF]; 5-FU, doxorubicin, cyclophosphamide [FAC]; doxorubicin, cyclophosphamide [AC]) are at high risk for developing hypogonadism (Bines, Oleske, & Cobleigh, 1996; Bruning et al., 1990; Saarto et al., 1997; Twiss et al., 2001). The use of the alkylating agent cyclophosphamide induces hypogonadism by causing menopause as a result of ovarian damage, with ovarian damage ranging from a decreased number of secondary ovarian follicles to the total loss of follicles with accompanying ovarian fibrosis (Bines et al.; Ramaswamy & Shapiro, 2003). Cyclophosphamide-induced menopause occurs in 63%–96% of premenopausal patients with breast cancer receiving adjuvant CMF or FAC, with older patients and patients receiving higher doses of

cyclophosphamide at highest risk (Bines et al.; Pfeilschifter & Diel, 2000; Ramaswamy & Shapiro). Use of adjuvant taxane-containing regimens (e.g., AC followed by paclitaxel) also may cause menopause, the extent and prevalence of which are unknown (Hillner et al., 2003). During menopause, an increase in osteoclast bone resorption resulting from low estrogen levels causes more bone loss than bone formation (Pfeilschifter & Diel).

Hormonal therapies used to treat breast cancer are designed to further reduce circulating estrogen levels, and some of these therapies have been shown to induce bone loss (Pfeilschifter & Diel, 2000). Tamoxifen has been shown to cause and prevent bone loss in pre- and postmenopausal women, respectively (Ramaswamy & Shapiro, 2003). The exact mechanism for the different effects is unknown, but tamoxifen may act as an estrogen agonist in postmenopausal women because of their low estrogen state but as an antagonist on the bone in premenopausal women with higher estrogen levels (Ramaswamy & Shapiro).

The bone mineral density effects of other commonly used breast cancer hormonal therapies, including selective estrogen receptor downregulators (SERDs) and aromatase inhibitors, are not as well defined. However, the mechanism of action of these drug classes suggests that both may cause bone loss in some patients. SERDs lack estrogen agonist activity; therefore, some women may experience an accelerated bone loss similar to that observed in women with early menopause (Pfeilschifter & Diel, 2000; Ramaswamy & Shapiro, 2003). Aromatase inhibitors, which decrease circulating and tissue levels of estrogen by decreasing aromatase activity and inhibiting conversion of adrenal androgens to estrogen, also may accelerate bone loss (Pfeilschifter & Diel; Ramaswamy & Shapiro). A trend toward increased bone loss and an increased incidence of fractures has been reported with each of the commercially available aromatase inhibitors (Coombes et al., 2004; Eastell et al., 2002; Goss et al., 2003; Ramaswamy & Shapiro).

Another class of hormonal drugs that induces ovarian insufficiency is gonadotropin-releasing hormone agents, such as leuprolide, in premenopausal patients with advanced breast cancer. Gonadotropin-releasing hormone agents suppress the release of luteinizing hormone, which reduces estrogen production in the ovaries (Jonat et al., 2002; Pfeilschifter & Diel, 2000). Ovarian insufficiency predisposes women to the development of accelerated bone loss.

Prostate Cancer

As previously discussed, one of the primary therapies for patients with prostate cancer is androgen-deprivation therapy, either by surgical castration or the administration of gonadotropin-releasing hormone, which causes hypogonadism. Although the exact mechanism whereby hypogonadism induces CTIBL is unknown, one hypothesis suggests that androgens increase bone formation directly by binding to androgen receptors on osteoblasts (Chen et al., 2002). Additionally, evidence suggests that aromatization of testosterone into estrogens also is crucial in maintaining appropriate bone remodeling (Hofbauer & Khosla, 1999; Leder, LeBlanc, Schoenfeld, Eastell, & Finkelstein, 2003). Thus, in patients with prostate cancer receiving androgen deprivation therapy, circulating testosterone and estrogen levels are reduced, resulting in decreased osteoblastic bone formation activity,

increased osteoclastic bone resorption activity, and, ultimately, accelerated bone loss (Gholz et al., 2002; Leder et al.). Androgen deprivation therapy-induced hypogonadism also causes a loss of muscle mass, which promotes bone mineral density loss by decreasing mechanical stretch and pressure on the bone (Chen et al.).

Diagnosis of Cancer Treatment-Induced Bone Loss

A diagnosis of low bone mass before the occurrence of a first fracture is important because bone loss therapies are likely to be most effective in the early stages of bone loss in patients with cancer, just as these therapies are most effective in postmenopausal women when bone loss is diagnosed at an early stage (e.g., osteopenia) (Pfeilschifter & Diel, 2000). Historical and lifestyle bone loss risk factors alone do not identify patients with low bone mass (Miller & Lane, 2001). Therefore, some practitioners suggest that patients at risk for CTIBL should receive baseline and serial bone mass assessments; however, the optimal timing of bone mineral density assessments is unknown (Diamond, Higano, Smith, Guise, & Singer, 2004; Pfeilschifter & Diel). Although no technology measures bone mass specifically, bone mineral density is calculated because bone mineral density levels directly correlate with bone strength (Cummings, Bates, & Black, 2002).

Current clinical practice guidelines and recommendations for diagnosing CTIBL in patients with breast or prostate cancer are based on the World Health Organization (WHO) guidelines for diagnosing osteopenia or osteoporosis in Caucasian postmenopausal women (see Table 2). These guidelines are used widely to diagnose bone loss in many patient groups (Berruti, Tucci, et al., 2002; Diamond et al., 2004; Hillner et al., 2003; Kanis, 2002). The WHO defined four diagnostic categories of bone loss: normal bone mineral density, osteopenia, osteoporosis, and severe osteoporosis.

Techniques to Measure Bone Mineral Density

Many techniques can be used to measure bone mineral density, including dual-energy x-ray absorptiometry (DEXA), peripheral DEXA, quantitative computed tomography, radiographic absorptiometry, and quantitative ultrasonography (Cummings et al., 2002). Bone mineral density measurement devices can assess either the central skeleton (e.g., spine, hip) or peripheral skeleton (e.g., finger, heel, tibia, wrist, forearm) (Miller & Lane, 2001). Because hip bone mineral density

Table 2. World Health Organization Diagnostic Categories of Osteopenia and Osteoporosis

Diagnostic Category	T Score[a]
Normal bone mineral density	≥ -1.0
Osteopenia	-1.0 to -2.5
Osteoporosis	≤ -2.5
Severe osteoporosis	≤ -2.5 with fragility fractures

[a] T scores represent the difference between the number of standard deviations in an individual's bone mineral density and the average, peak bone mineral density for a group of young adults of same gender.

Note. Based on information from Berruti, Tucci, et al., 2002; Gholz et al., 2002; Kanis, 2002.

is the best predictor of hip fractures and hip bone mineral density and spine bone mineral density have similar value in predicting vertebral fractures, measuring bone mineral density at these sites is important to obtain an accurate assessment of risk (Cummings et al.). The preferred or gold-standard technique is the DEXA because of its ability to measure the bone mineral density at several different anatomic sites, including the hip and spine, and the total amount of mineral in the whole skeleton with minimal radiation exposure (Cummings et al.; Follin, 2003). DEXA results are reported as T scores, which represent the difference in the number of standard deviations between an individual's bone mineral density and the mean value for a group of young adults of the same gender (Cummings et al.).

Other Diagnostic Evaluations

A thorough review of a patient's history and bone loss risk factors, including previous and current cancer therapies, by a healthcare professional is important in diagnosing CTIBL and determining fracture risk (Berruti, Tucci, et al., 2002; Pfeilschifter & Diel, 2000). Additionally, a thorough physical examination, including assessment of vertebral deformities, height loss, abdominal protrusion, and paraspinal muscle pain, should be performed to rule out asymptomatic vertebral fractures (Miller & Lane, 2001). If any of these symptoms are present, vertebral radiography should be performed (Pfeilschifter & Diel).

Finally, laboratory tests should be performed to exclude any secondary causes of bone loss (Pfeilschifter & Diel, 2000; Smith, 2002). For example, serum chemistries should be measured to exclude kidney or liver disease, which may cause osteoporosis as a result of reduced vitamin D production or calcium or vitamin D malabsorption, respectively (Finkelstein, 2000; Smith, 2002). Additionally, serum levels of parathyroid hormone, thyroid-stimulating hormone, and 25-dihydroxyvitamin D should be measured to evaluate for hyperparathyroidism, hyperthyroidism, and vitamin D deficiency, respectively, each of which increases bone resorption (Finkelstein; Lips et al., 1996; Pfeilschifter & Diel). Generally, serum calcium, phosphorus, and alkaline phosphatase levels, which represent key constituents of bone, are within a normal range in patients with osteoporosis because normal feedback mechanisms are regulating these levels continually (Finkelstein; O'Connell, 1999). Fractures, however, may cause a transient increase in alkaline phosphatase levels (Smith, 2002).

Prospective studies designed to validate the clinical usefulness of measuring biochemical markers of bone turnover—enzymes or proteins secreted during bone formation (e.g., bone-specific alkaline phosphatase, osteocalcin, procollagen type I propeptides) or resorption (e.g., hydroxypyridinium crosslinks of collagen pyridinoline and deoxypyridinoline, C-terminal crosslinking telopeptide of type I collagen, N-terminal crosslinking telopeptide of type I collagen)—in the urine or blood of patients with CTIBL have not been performed (Follin, 2003; Higano, 2004). Additionally, these markers are associated with numerous sources of biologic variability (e.g., age, gender, menopausal status), require comparison with reference ranges, and require standardization of timing and sampling conditions (Delmas, Eastell, Garnero, Seibel, & Stepan, 2000). Therefore, determining biochemical markers of bone turnover along with bone mineral density measurement to identify patients with an accelerated rate of bone turnover,

and thus, at high risk for fracture, is not routinely recommended for patients with CTIBL at this time (Diamond et al., 2004; Follin; Hillner et al., 2003; Higano, 2004).

Treatment of Cancer Treatment-Induced Bone Loss

Lifestyle Changes

The primary treatment goal for CTIBL is to reduce fracture risk. Although an awareness of cancer treatment history and the potential for chemotherapy or hormonal therapy to increase bone loss is important, patients can adopt lifestyles that contribute to preserving bone health and maintaining or increasing bone mineral density. Patients should be counseled about smoking cessation, moderate alcohol consumption, and participation in a regular weight-bearing exercise program. Weight-bearing exercise should include resistance and endurance activities, such as walking or stair climbing, and patients should consult a healthcare professional before beginning an exercise program (Follin, 2003; Ramaswamy & Shapiro, 2003; Smith, 2003b; Twiss et al., 2001). In patients with prostate cancer receiving androgen-deprivation therapy, resistance-exercise activities have been shown to improve quality of life by reducing fatigue and contributing to increased muscular fitness, which indirectly reduces fracture risk (Follin; Segal et al., 2003). Resistance exercises also have been shown to be helpful in older adults. The results of a study evaluating 62 men and women aged 60–83 years showed increased bone mineral density of the femoral neck and increased bone turnover after high-intensity resistance training (Vincent & Braith, 2002).

Calcium and vitamin D intake is essential for patients with CTIBL unless a medical contraindication, such as hypercalcemia, exists (Pfeilschifter & Diel, 2000). The results of clinical trials consistently have shown that oral calcium supplementation reduces the incidence of fractures and decreases bone loss in postmenopausal women (Dawson-Hughes, Harris, Krall, & Dallal, 1997; Peacock et al., 2000; Recker et al., 1996; Reid, Ames, Evans, Gamble, & Sharpe, 1995). The adequate daily intake of calcium is 1,200–1,500 mg (Hillner et al., 2003; Ramaswamy & Shapiro, 2003; Smith, 2002). An adequate daily vitamin D intake for adults is 400 IU (Smith, 2002; Vieth, 2001); however, some clinicians recommend a daily vitamin D intake of 600–800 IU for postmenopausal women whose sun exposure is low (Messinger-Rapport & Thacker, 2002).

Safety is an additional consideration for patients with CTIBL. Preventing falls that could lead to injury or fracture is essential (Brown & Josse, 2002; Follin, 2003). If necessary, patients should use assistive devices, such as a cane or walker, to maintain balance and protect against falls (Viale & Sanchez Yamamoto, 2003).

Drug Therapies

Currently, no drugs have been approved by the U.S. Food and Drug Administration (FDA) specifically for the prevention or treatment of CTIBL; however, numerous drugs, including some bisphosphonates and selective estrogen receptor modifiers (SERMs), calcitonin (Miacalcin®, Novartis Pharmaceuticals), estrogen with or without progestin, and teriparatide (Forteo®, Eli Lilly, Indianapolis, IN), are FDA approved for preventing or treating osteoporosis in certain patients, such

as postmenopausal women or men with osteoporosis (Follin, 2003). Nonetheless, these drugs also are likely to be effective in patients with CTIBL, and several of these drugs, including etidronate, risedronate, pamidronate, tamoxifen, and zoledronic acid, have been evaluated in patients with breast or prostate cancer with CTIBL.

Although estrogen and teriparatide may be effective in preventing or treating CTIBL, these drugs are not recommended for use in patients with breast or prostate cancer (Hillner et al., 2003). Estrogen, with or without progestins, may increase the risk of breast cancer recurrence or a second primary breast cancer and has not been evaluated thoroughly in patients with prostate cancer (Hillner et al.; Taxel et al., 2002). Teriparatide may increase the risk of osteosarcoma in patients with bone metastases or hypercalcemia and therefore is not recommended for use in patients at risk of developing these complications, such as patients with breast or prostate cancer (Hillner et al.; NOF, 2003). Bisphosphonates, SERMs, and calcitonin, however, are not contraindicated in these patients. Table 3 lists the available drug therapies for the prevention and treatment of CTIBL in patients with breast or prostate cancer and their FDA-approved indications.

Bisphosphonates

Four oral bisphosphonates are available in the United States—alendronate (Fosamax®, Merck & Co., Inc., Whitehouse Station, NJ), etidronate (Didronel®, Procter & Gamble Pharmaceuticals, Cincinnati, OH), risedronate (Actonel®, Procter & Gamble Pharmaceuticals,), and tiludronate (Skelid®, Sanofi-Synthelabo, Inc., New York, NY). Alendronate and risedronate commonly are used to prevent or treat postmenopausal osteoporosis and osteoporosis in men (Berruti, Tucci, et al., 2002; USP DI® Editorial Group, 2004). Although etidronate has been evaluated as a bone-loss therapy, it is less potent than alendronate or risedronate and is not commonly used (Berruti, Tucci, et al.). Tiludronate has not been evaluated for the prevention or treatment of CTIBL. Clinical trials evaluating oral bisphosphonates in patients with breast or prostate cancer suggest that some of these drugs may be effective for the prevention or treatment of CTIBL, but the oral formulations require frequent administration without food, which may reduce compliance (Berruti, Tucci, et al.; Delmas et al., 1997; Diamond et al., 1998; Reid et al., 2002). Additionally, gastrointestinal adverse effects of oral bisphosphonates limit the administration of optimal doses and may be accentuated with the use of nonsteroidal anti-inflammatory drugs (Graham & Malaty, 2001; Reid et al., 2002). Therefore, the use of IV bisphosphonates for the prevention or treatment of CTIBL may be more appealing because these drugs can be administered less frequently without regard to timing of food intake and are more potent than oral bisphosphonates (Berruti, Tucci, et al.; Viale & Sanchez Yamamoto, 2003).

Currently, three IV bisphosphonates are available commercially in the United States—etidronate (Didronel), pamidronate (Aredia®, Novartis Pharmaceuticals) and zoledronic acid (Zometa®, Novartis Pharmaceuticals) (USP DI® Editorial Group, 2004). Only pamidronate and zoledronic acid have been shown to be effective in preventing bone loss in patients with prostate cancer at risk for developing CTIBL; IV etidronate has not been evaluated for prevention or treatment of CTIBL (Diamond et al., 2001; Smith et al., 2001, 2003). Clinical trials evaluating zoledronic acid in patients with breast or prostate cancer at risk for developing CTIBL are ongoing (ClinicalTrials.gov, 2004d, 2004e, 2004f; Gnant et al., 2002). Although IV bisphosphonate therapy is administered less frequently than oral bisphosphonate therapy, IV administration requires a visit to a healthcare practitioner. Additionally, monitoring of serum creatinine levels should be performed before each IV dose (Novartis Pharmaceuticals, 2003, 2004; Procter & Gamble Pharmaceuticals, 2003). Regular monitoring of serum calcium, magnesium, and phosphate levels following administration of pamidronate or zoledronic acid is recommended (Novartis Pharmaceuticals, 2003, 2004). Additionally, hemoglobin and hematocrit levels and complete blood count with differential should be monitored regularly in patients receiving zoledronic acid and pamidronate, respectively (Novartis Pharmaceuticals, 2003, 2004). The optimal bisphosphonate, dose, and regimen for patients with CTIBL are unknown. Therefore, clinicians should discuss available treatment options, including advantages and disadvantages, with each patient.

Selective Estrogen Receptor Modifiers

SERMs, such as tamoxifen and raloxifene (Evista®, Eli Lilly), are options for prevention or treatment of CTIBL in some patients with breast cancer. Tamoxifen is modestly effective in preventing bone loss in postmenopausal women but does not prevent bone loss in premenopausal women; therefore, it is not considered a stand-alone therapy for preventing bone loss in patients with breast cancer. Raloxifene has not been evaluated as a CTIBL therapy in patients with breast cancer, but it is effective in the treatment of postmenopausal osteoporosis (Hillner et al., 2003). Because preclinical study results have shown that raloxifene may stimulate tamoxifen-dependent cells, raloxifene should not be administered after tamoxifen therapy (Hillner et al.). Additionally, concurrent use of raloxifene and aromatase inhibitors is not recommended because the results of the ATAC trial suggest that the combination of a SERM and aromatase inhibitor in the treatment of postmenopausal women with breast cancer results in decreased antitumor efficacy compared with aromatase inhibitor therapy alone (Hillner et al.).

Calcitonin

Intranasal calcitonin is another potential option for the prevention or treatment of CTIBL, but it has not been evaluated in patients with breast or prostate cancer. Additionally, intranasal administration may reduce compliance.

Nursing Implications

Clinical Implications

With the increasing use of androgen deprivation therapy for treatment of early-stage prostate cancer and aromatase inhibitors for the treatment of postmenopausal breast cancer, CTIBL is likely to become a common problem for patients with cancer. Because bone mass is difficult to rebuild once lost, interventions should begin with early identification of high-risk patients (Twiss et al., 2001). Height should be measured regularly during follow-up visits to accurately determine any loss of height, which may suggest possible vertebral fractures or vertebral trabecular bone loss (Twiss et al.). Additionally, a clinical history assessing possible bone loss risk factors, such as past cancer therapies, current lifestyles, and menstrual history, should be obtained.

Table 3. Available Drug Therapies for Treatment of Cancer Treatment-Induced Bone Loss in Patients With Breast or Prostate Cancer[a]

Drug	Dosage	Comments
Oral bisphosphonates		
Alendronate[b-f]	Prevention: 5 mg per day or 35 mg per week Treatment: 10 mg per day or 70 mg per week	Not evaluated in patients with breast or prostate cancer; however, has been shown to be effective for prevention and treatment of bone loss in postmenopausal women and for treatment of bone loss in men. Gastrointestinal adverse events are common and are minimized by administering with 8 ounces of water 30 minutes before eating or drinking and maintaining an upright position for 30 minutes after administration; avoid antacid or mineral supplement use.
Etidronate[f]	Prevention or treatment: 400 mg every day for two weeks every three months	Only oral bisphosphonate evaluated in patients with prostate cancer; results of open-label, crossover study showed that six months of cyclic etidronate (400 mg every day for two weeks every three months) significantly increased spine bone mineral density and decreased amount of femoral neck bone mineral density loss in patients with prostate cancer receiving combined androgen blockade compared with placebo-treated patients. Not evaluated in patients with breast cancer. Well tolerated Not commonly used because more potent oral bisphosphonates, such as alendronate and risedronate, are available.
Risedronate[c-f]	Prevention or treatment: 5 mg per day or 35 mg per week	Only oral bisphosphonate evaluated in patients with breast cancer; not evaluated in patients with prostate cancer. Results of randomized, double-blind, placebo-controlled study showed that two years of cyclic risedronate (30 mg per day for 14 days every 12 weeks) increased spine and trochanter bone mineral density (0.3% and 0.6%, respectively) in patients with breast cancer with chemotherapy- or radiation therapy-induced menopause compared with placebo-treated patients; bone loss recurred following discontinuation of treatment. Effective for prevention and treatment of bone loss in postmenopausal women Gastrointestinal adverse events are common and are minimized by administering with 8 ounces of water 30 minutes before eating or drinking and maintaining an upright position for 30 minutes after administration; avoid antacid or mineral supplement use. Ongoing clinical trials are evaluating prevention of cancer treatment-induced bone loss (CTIBL) in premenopausal women with breast cancer receiving adjuvant or neoadjuvant chemotherapy and patients with prostate cancer undergoing androgen-deprivation therapy.
IV bisphosphonates		
Pamidronate[f]	Prevention or treatment: 60 mg IV every 12 weeks[g] or 90 mg IV x 1 dose[g]	Not evaluated in patients with breast cancer; however, bone mineral density increases have been observed in postmenopausal women with osteoporosis receiving pamidronate 30 mg via IV every three months or 15 mg via IV for three days every three months. Results of open-label, randomized study showed that pamidronate 60 mg via IV every 12 weeks effectively preserved bone mineral density at multiple skeletal sites in patients with prostate cancer receiving androgen-deprivation therapy. Results of randomized, double-blind, placebo-controlled study showed that one-time dose of pamidronate 90 mg via IV increased spine and femoral neck bone mineral density by 7.8% and 2%, respectively, in patients with prostate cancer receiving combined androgen blockade. Well tolerated; some patients may experience transient fevers and arthralgias after administration.
Zoledronic acid[f]	Prevention or treatment: 4 mg IV every three months[g]	Preliminary results of a study evaluating premenopausal women with breast cancer receiving anastrozole and tamoxifen with or without zoledronic acid (4 mg via IV every six months) showed that zoledronic acid improved lumbar spine bone mineral density.

(Continued on next page)

[a] These drugs are not approved by the U.S. Food and Drug Administration (FDA) for the prevention or treatment of CTIBL.

[b] FDA approved for treatment of male osteoporosis

[c] FDA approved for treatment of postmenopausal osteoporosis

[d] FDA approved for treatment of glucocorticoid-induced osteoporosis

[e] FDA approved for prevention of postmenopausal osteoporosis

[f] FDA approved for indications other than prevention or treatment of osteoporosis (e.g., bone metastases from solid tumor, heterotropic ossification, hypercalcemia, multiple myeloma, osteolytic metastases, Paget's disease)

[g] Optimal dose is unknown.

[h] FDA approved for prevention or treatment of breast cancer, including in situ ductal carcinoma

Note. Based on information from Berruti, Tucci, et al., 2002; ClinicalTrials.gov, 2004a, 2004b, 2004c, 2004d, 2004e, 2004f; Delmas et al., 1997; Diamond et al., 1998, 2001; Follin, 2003; Gnant et al., 2002; Hillner et al., 2003; Jordan et al., 2001; Love et al., 1992; Morabito et al., 2003; National Osteoporosis Foundation, 2003; Powles et al., 1996; Procter & Gamble Pharmaceuticals, 2003; Reid et al., 2002; Smith et al., 2001, 2003; Thiebaud et al., 1994; USP DI® Editorial Group, 2004; Ward et al., 1993.

Table 3. Available Drug Therapies for Treatment of Cancer Treatment-Induced Bone Loss in Patients With Breast or Prostate Cancer[a] (Continued)

Drug	Dosage	Comments
		Bone mineral density increases were observed in postmenopausal women with osteoporosis receiving various doses of zoledronic acid via IV.
		Results of a multicenter, randomized, double-blind, placebo-controlled study showed that zoledronic acid increased spine and femoral neck bone mineral density by 5.6% and 1.2%, respectively, in patients with nonmetastatic prostate cancer receiving androgen-deprivation therapy.
		Well tolerated; some patients may experience transient arthralgias after administration.
		Ongoing clinical trials are evaluating CTIBL prevention in patients with breast cancer undergoing adjuvant chemotherapy and further evaluating CTIBL prevention in patients with prostate cancer undergoing androgen-deprivation therapy.
Selective estrogen receptor modulators		
Raloxifene[c,e]	Prevention or treatment: 60 mg by mouth every day	Not evaluated in patients with breast or prostate cancer; however, was shown to be effective for prevention and treatment of postmenopausal women with osteoporosis.
		Raloxifene also may be effective in patients with breast cancer, but healthcare providers are concerned that its administration after tamoxifen use may promote the growth of new tumor cells and coadministration with aromatase inhibitors may decrease antitumor efficacy; therefore, risk and benefits should be considered when prescribing.
		Adverse events include hot flashes, leg cramps, and increased risk of venous thromboembolism.
Tamoxifen[h]	Prevention or treatment: 10 mg by mouth twice daily	Effective in postmenopausal patients with breast cancer; not evaluated in patients with prostate cancer.
		Results of clinical trials in postmenopausal patients with breast cancer showed increases in spine and femoral neck bone mineral density (0.09%–0.61% and 1.4%, respectively).
		Results of a clinical trial in postmenopausal women receiving tamoxifen for breast cancer prevention showed increases in bone mineral density.
		Adverse events included hot flashes, weight gain, increased risk of cataract formation, venous thromboembolism, and endometrial cancer.
		An ongoing clinical trial is evaluating CTIBL prevention in premenopausal patients with breast cancer undergoing adjuvant chemotherapy.
Calcitonin[c,f]	Treatment: 200 IU intranasally every day	Not evaluated in patients with breast or prostate cancer.
		Effective as treatment of postmenopausal women with osteoporosis
		Adverse events included rhinitis and, rarely, epistaxis.

[a] These drugs are not approved by the U.S. Food and Drug Administration (FDA) for the prevention or treatment of CTIBL.

[b] FDA approved for treatment of male osteoporosis

[c] FDA approved for treatment of postmenopausal osteoporosis

[d] FDA approved for treatment of glucocorticoid-induced osteoporosis

[e] FDA approved for prevention of postmenopausal osteoporosis

[f] FDA approved for indications other than prevention or treatment of osteoporosis (e.g., bone metastases from solid tumor, heterotropic ossification, hypercalcemia, multiple myeloma, osteolytic metastases, Paget's disease)

[g] Optimal dose is unknown.

[h] FDA approved for prevention or treatment of breast cancer, including in situ ductal carcinoma

Note. Based on information from Berruti, Tucci, et al, 2002; ClinicalTrials.gov, 2004a, 2004b, 2004c, 2004d, 2004e, 2004f; Delmas et al., 1997; Diamond et al., 1998, 2001; Follin, 2003; Gnant et al., 2002; Hillner et al., 2003; Jordan et al., 2001; Love et al., 1992; Morabito et al., 2003; National Osteoporosis Foundation, 2003; Powles et al., 1996; Procter & Gamble Pharmaceuticals, 2003; Reid et al., 2002; Smith et al., 2001, 2003; Thiebaud et al., 1994; USP DI® Editorial Group, 2004; Ward et al., 1993.

Although no drug therapies are FDA approved for treatment of CTIBL, clinical practice guidelines provide recommendations for managing bone health in patients with breast or prostate cancer. According to the American Society of Clinical Oncology (ASCO) bone health guidelines for women with breast cancer, patients should be stratified into low- and high-risk groups depending on the presence of risk factors (Hillner et al., 2003) (see Table 4). High-risk patients, such as women aged 65 years or older, postmenopausal women receiving aromatase inhibitors, premenopausal women with therapy-induced premature menopause, and women aged 60–64 years with general osteoporosis risk factors, should undergo a baseline hip and spine bone mineral density measurement and be counseled about lifestyle changes and appropriate oral calcium and vitamin D intake (Hillner et al.). The ASCO guidelines stated that patients with a T score of –2.5 or lower should receive CTIBL treatment with alendronate, risedronate, or zoledronic acid; raloxifene also may be an option, except in patients who have received previous tamoxifen therapy or are currently receiving aromatase inhibitors; thereafter, annual bone mineral density measurement should be performed (Hillner et al.). The guidelines do not recommend bone mineral density screening for low-risk patients; instead, their risk status should be monitored annually by obtaining a clinical history, and these patients should be counseled about lifestyle changes and appropriate calcium and vitamin D intake (Hillner et al.). Other clinicians have recommended that all postmenopausal patients with breast cancer undergo baseline bone mineral density measurements of the spine, hip, and forearm, with repeat measurements performed every three to five years (Twiss et al., 2001).

Table 4. Recommended Bone Loss Management Strategy for Patients With Breast or Prostate Cancer[a]

Cancer Type and Risk Factor Status	Management Strategy		
	Normal Bone Mineral Density (T Score > –1)	Osteopenia (T Score = –1 to –2.5)	Osteoporosis (T Score < –2.5)
Breast cancer			
Low risk[b]	Not applicable[c]	Not applicable[c]	Not applicable[c]
High risk[d]	Encourage lifestyle modifications. Begin daily calcium and vitamin D therapy. Perform annual bone mineral density testing.	Encourage lifestyle modifications. Begin daily calcium and vitamin D therapy. Individualize therapy.[f] Perform annual bone mineral density testing.	Encourage lifestyle modifications. Exclude secondary causes of bone loss.[e] Begin daily calcium and vitamin D therapy. Begin bisphosphonate or raloxifene therapy.[g] Perform annual bone mineral density testing.
Prostate cancer			
Low risk[h]	Encourage lifestyle modifications. Assess need for daily calcium and vitamin D therapy. Perform bone mineral density testing and assess risk factors every 24 months.	Encourage lifestyle modifications. Assess need for daily calcium and vitamin D therapy. Begin bisphosphonate therapy if fracture occurs.[i] Perform bone mineral density testing and assess risk factors annually.	Encourage lifestyle modifications. Exclude secondary causes of bone loss.[e] Assess need for daily calcium and vitamin D therapy. Begin bisphosphonate therapy.[i] Perform bone mineral density testing and assess risk factors annually.
High risk[h]	Encourage lifestyle modifications. Assess need for daily calcium and vitamin D therapy. Perform bone mineral density testing and assess risk factors annually.	Encourage lifestyle modifications. Assess need for daily calcium and vitamin D therapy. Begin bisphosphonate therapy if fracture occurs.[i] Perform bone mineral density testing and assess risk factors every six months.	Encourage lifestyle modifications. Exclude secondary causes of bone loss.[e] Assess need for daily calcium and vitamin D therapy. Begin bisphosphonate therapy.[i] Perform bone mineral density testing and assess risk factors annually.

[a] Patients with nonmetastatic breast cancer or prostate cancer undergoing androgen-deprivation therapy

[b] Patients with no risk factors

[c] Bone mineral density screening is not recommended; however, lifestyle advice, daily calcium and vitamin D administration, and annual assessment of risk factors are recommended.

[d] All women older than 65 years; all women aged 60–64 years with a family history of fracture, weight less than 70 kg, history of nontraumatic fracture, other bone loss or fracture risk factors; postmenopausal women receiving aromatase inhibitors; or premenopausal women with therapy-induced menopause

[e] By evaluating serum chemistries and parathyroid hormone, thyroid-stimulating hormone, and 25-dihydroxyvitamin D levels

[f] No clinical trials exist to support routine cancer treatment-induced bone loss therapy, but some patients may benefit.

[g] Bisphosphonate therapy includes alendronate, risedronate, or zoledronic acid; the optimal drug, dose, and regimen are unknown. Raloxifene is reserved for patients who have not received tamoxifen or are not receiving aromatase inhibitors.

[h] One or more of the following characteristics: duration of androgen-deprivation therapy of more than six months, previous fractures, family history of osteoporosis, low body weight, smoking, excessive alcohol consumption, corticosteroid use, medical comorbidities, or low vitamin D levels

[i] Alendronate, risedronate, pamidronate, or zoledronic acid; the optimal drug, dose, and regimen are unknown.

Note. Based on information from Diamond et al., 2004; Higano et al., 2003; Hillner et al., 2003; Pfeilschifter & Diel, 2000; Smith, 2003b.

ASCO guidelines for the prevention and treatment of CTIBL do not exist for patients with prostate cancer; however, a consensus group consisting of oncologists specializing in the treatment of prostate cancer (Diamond et al., 2004) recently published recommendations for the diagnosis and treatment of CTIBL in patients with prostate cancer receiving androgen-deprivation therapy. Because androgen-deprivation therapy is associated with significant loss of bone mineral density, the consensus group recommended that every patient receiving androgen-deprivation therapy undergo a baseline bone mineral density measurement and receive adequate calcium and vitamin D intake. Patients with osteoporosis (i.e., T score $\leq$ 2.5), fracture, or suspected vertebral fracture should receive alendronate, risedronate, pamidronate, or zoledronic acid. Measuring bone mineral density every 6–12 months during the first year of androgen-deprivation therapy and every 12–24 months thereafter also is recommended (Berruti, Tucci, et al., 2002; Diamond et al., 2004; Smith, 2003a).

Oncology nurses can play a valuable role in educating patients with breast or prostate cancer who are beginning treatment with therapies known to produce bone loss about CTIBL, its treatment options and effects, and specific lifestyle modifications that can reduce the likelihood of developing bone complications (Gholz et al., 2002). For example, patients at risk for developing CTIBL would benefit from learning about the value of regular follow-up visits with an endocrinologist or general practitioner after cancer therapy completion. Additionally, oncology nurses should reinforce the importance of calcium and vitamin D intake, lifestyle modifications, and compliance with CTIBL therapies (Follin, 2003).

Reimbursement

Because none of the available bone loss therapies are FDA approved for the treatment of CTIBL, insurance coverage and reimbursement for CTIBL therapies vary widely among insurers. Reimbursement generally is determined using a

case-by-case review and often requires preauthorization. Because many of the oral CTIBL therapies are FDA approved for similar indications (e.g., osteoporosis), many private insurers and Medicaid programs have created formularies or preferred-drug lists that have different coverage criteria and copayments. Currently, Medicare does not cover most oral or self-administered CTIBL therapies but may cover products that require physician administration (i.e., incident to a physician's service), such as pamidronate and zoledronic acid. For example, Wisconsin Physician Service Medicare Administrators, which is the Medicare Part B carrier for Illinois, Michigan, Minnesota, and Wisconsin, covers IV bisphosphonate drug therapy for treatment of CTIBL when appropriate documentation supporting the medical necessity of the treatment is contained in the medical record and appropriate diagnosis and service codes are used in the billing process (WPS Medicare Administrators, 2004). However, verification of the reimbursement requirements for off-label use before claim submission is recommended for all payers.

Summary

Current therapies for breast and prostate cancer have increased overall survival times; therefore, long-term toxicities, such as CTIBL, should be considered in the long-term care and follow-up of these patients. Patients with breast or prostate cancer receiving cancer therapies that cause hypogonadism are at highest risk for developing CTIBL and should receive regularly scheduled assessments of bone mass and bone loss risk factors. Additionally, patients should be instructed to optimize calcium and vitamin D intake; participate in an individualized resistance-exercise program; modify any lifestyles known to increase the risk of further bone loss, such as smoking or excessive alcohol intake; and take measures to prevent falls. Patients with breast cancer and CTIBL also should receive bone loss therapy, such as a bisphosphonate (oral or IV) or a SERM (unless on current aromatase inhibitor therapy or have been treated previously with tamoxifen); patients with prostate cancer should receive an oral or IV bisphosphonate. Although the most effective drug, dose, and regimen for the treatment of CTIBL have not been identified, IV bisphosphonates should be considered because of their potency, minimal adverse effects, infrequent administration, and likelihood of reimbursement. Ongoing clinical trials are determining the best CTIBL therapy for patients with breast or prostate cancer.

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References

Basaria, S., Lieb, J., II, Tang, A.M., DeWeese, T., Carducci, M., Eisenberger, M., et al. (2002). Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clinical Endocrinology, 56,* 779–786.

Baum, M., Buzdar, A.U., Cuzick, J., Forbes, J., Houghton, J.H., Klijn, J.G., et al. (2002). Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *Lancet, 359,* 2131–2139.

Begerow, B., Pfeifer, M., Pospeschill, M., Scholz, M., Schlotthauer, T., Lazarescu, A., et al. (1999). Time since vertebral fracture: An important variable concerning quality of life in patients with postmenopausal osteoporosis. *Osteoporosis International, 10,* 26–33.

Berruti, A., Dogliotti, L., Terrone, C., Cerutti, S., Isaia, G., Tarabuzzi, R., et al. (2002). Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *Journal of Urology, 167,* 2361–2367.

Berruti, A., Tucci, M., Terrone, C., Gorzegno, G., Scarpa, R.M., Angeli, A., et al. (2002). Background to and management of treatment-related bone loss in prostate cancer. *Drugs and Aging, 19,* 899–910.

Bines, J., Oleske, D.M., & Cobleigh, M.A. (1996). Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology, 14,* 1718–1729.

Brown, J.P., & Josse, R.G. (2002). 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Canadian Medical Association Journal, 167*(10, Suppl.)*,* S1–S34.

Bruning, P.F., Pit, M.J., de Jong-Bakker, M., van den Ende, A., Hart, A., & van Enk, A. (1990). Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *British Journal of Cancer, 61,* 308–310.

Center, J.R., Nguyen, T.V., Schneider, D., Sambrook, P.N., & Eisman, J.A. (1999). Mortality after all major types of osteoporotic fracture in men and women: An observational study. *Lancet, 353,* 878–882.

Chen, Z., Maricic, M., Nguyen, P., Ahmann, F.R., Bruhn, R., & Dalkin, B.L. (2002). Low bone density and high percentage of body fat among men who were treated with androgen deprivation therapy for prostate carcinoma. *Cancer, 95,* 2136–2144.

ClinicalTrials.gov. (2004a). Calcium with or without estrogen and/or risedronate in preventing osteoporosis in patients with prostate cancer. Retrieved February 23, 2004, from http://clinicaltrials.gov/ct/show/NCT00043069?order=1

ClinicalTrials.gov. (2004b). Risedronate in preventing bone loss in premenopausal women receiving chemotherapy for primary breast cancer. Retrieved February 23, 2004, from http://clinicaltrials.gov/ct/show/NCT00054418?order=2

ClinicalTrials.gov. (2004c). Tamoxifen to prevent bone loss and heart disease in premenopausal women receiving chemotherapy for stage I or stage II breast cancer. Retrieved February 23, 2004, from http://clinicaltrials.gov/ct/show/NCT00005605?order=1

ClinicalTrials.gov. (2004d). Zoledronate and estradiol in preventing bone loss in patients with prostate cancer. Retrieved February 23, 2004, from http://clinicaltrials.gov/ct/show/NCT00049491?order=1

ClinicalTrials.gov. (2004e). Zoledronate, calcium, and vitamin D in preventing bone loss in women receiving adjuvant chemotherapy for breast cancer. Retrieved February 23, 2004, from http://clinicaltrials.gov/ct/show/NCT00022087?order=8

ClinicalTrials.gov. (2004f). Zoledronate in preventing bone loss in premenopausal women receiving chemotherapy after surgery for early stage breast cancer. Retrieved February 23, 2004, from http://clinicaltrials.gov/ct/show/NCT00049452?order=9

Coombes, R.C., Hall, E., Gibson, L.J., Paridaens, R., Jassem, J., Delozier, T., et al. (2004). A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New England Journal of Medicine, 350,* 1081–1092.

Cooper, C. (1997). The crippling consequences of fractures and their impact on quality of life. *American Journal of Medicine, 103*(2A), 12S–17S.

Cummings, S.R., Bates, D., & Black, D.M. (2002). Clinical use of bone densitometry: Scientific review. *JAMA, 288,* 1889–1897.

Cummings, S.R., & Melton, L.J., III. (2002). Epidemiology and outcomes of osteoporotic fractures. *Lancet, 359,* 1761–1767.

Daniell, H.W. (1997). Osteoporosis after orchiectomy for prostate cancer. *Journal of Urology, 157,* 439–444.

Daniell, H.W., Dunn, S.R., Ferguson, D.W., Lomas, G., Niazi, Z., & Stratte, P.T. (2000). Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *Journal of Urology, 163,* 181–186.

Dawson-Hughes, B., Harris, S.S., Krall, E.A., & Dallal, G.E. (1997). Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *New England Journal of Medicine, 337,* 670–676.

Delmas, P.D. (2002). Treatment of postmenopausal osteoporosis. *Lancet, 359,* 2018–2026.

Delmas, P.D., Balena, R., Confravreux, E., Hardouin, C., Hardy, P., & Bremond, A. (1997). Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: A double-blind, placebo-controlled study. *Journal of Clinical Oncology, 15,* 955–962.

Delmas, P.D., Eastell, R., Garnero, P., Seibel, M.J., & Stepan, J. (2000). The use of biochemical markers for bone turnover in osteoporosis. *Osteoporosis International, 11*(Suppl. 6), S2–S17.

Diamond, T., Campbell, J., Bryant, C., & Lynch, W. (1998). The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma. Longitudinal evaluation and response to intermittent cyclic etidronate therapy. *Cancer, 83,* 1561–1566.

Diamond, T.H., Higano, C.S., Smith, M.R., Guise, T.A., & Singer, F.R. (2004). Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: Recommendations for diagnosis and therapies. *Cancer, 100,* 892–899.

Diamond, T.H., Winters, J., Smith, A., De Souza, P., Kersley, J.H., Lynch, W.J, et al. (2001). The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combine androgen blockade: A double blind, randomized, placebo-controlled crossover study. *Cancer, 92,* 1444–1450.

Eastell, R., Hannon, R.A., Cuzick, J., Clack, G., & Adams, J.E. (2002). *Effect of anastrozole on bone density and bone turnover: Results of 'Arimidex' (anastrozole), tamoxifen, alone or in combination (ATAC) study.* Abstract 1170 presented at the 24th annual meeting of the American Society of Bone and Mineral Research, San Antonio, TX.

Eriksson, S., Eriksson, A., Stege, R., & Carlstrom, K. (1995). Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. *Calcified Tissue International, 57,* 97–99.

Finkelstein, J.S. (2000). Osteoporosis. In L. Goldman & J.C. Bennett (Eds.), *Cecil textbook of medicine* (21st ed., pp. 1366–1373). Philadelphia: Saunders.

Follin, S.L. (2003). Update in osteoporosis. In B.A. Mueller, K.E. Bertch, T.S. Dunsworth, S.C. Fagan, M.S. Hayney, M.B. O'Connell, et al. (Eds.), *Pharmacotherapy self-assessment program: Book 11 women's health, men's health* (4th ed., pp. 329–366). Kansas City, MO: American College of Clinical Pharmacy.

Gholz, R.C., Conde, F., & Rutledge, D.N. (2002). Osteoporosis in men treated with androgen suppression therapy for prostate cancer. *Clinical Journal of Oncology Nursing, 6,* 88–93.

Gnant, M., Hausmaninger, H., Samonigg, H., Mlineritsch, B., Taucher, S., Luschin-Ebengreuth, G., et al. (2002). Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial. *Breast Cancer Research and Treatment, 76*(Suppl.), 531.

Goss, P.E. (2004). *NCIC CTG MA.17: Final analysis of updated data. A placebo-controlled trial of letrozole following tamoxifen as adjuvant therapy in postmenopausal women with early stage breast cancer.* Presentation at the 40th annual meeting of the American Society of Clinical Oncology, New Orleans, LA.

Goss, P.E., Ingle, J.N., Martino, S., Robert, N.J., Muss, H.B., Piccart, M.J., et al. (2003). A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *New England Journal of Medicine, 349,* 1793–1802.

Graham, D.Y., & Malaty, H.M. (2001). Alendronate and naproxen are synergistic for development of gastric ulcers. *Archives of Internal Medicine, 161,* 107–110.

Hatano, T., Oishi, Y., Furuta, A., Iwamuro, S., & Tashiro, K. (2000). Incidence of bone fracture in patients receiving luteinizing hormone-releasing agonists for prostate cancer. *British Journal of Urology International, 86,* 449–452.

Higano, C.S. (2003). Bone loss and the evolving role of bisphosphonate therapy in prostate cancer. *Urologic Oncology, 21,* 392–398.

Higano, C.S. (2004). Understanding treatments for bone loss and bone metastases in patients with prostate cancer: A practical review and guide for the clinician. *Urologic Clinics of North America, 31,* 331–352.

Higano, C.S., Jiang, P.Y.Z., Miller, M., Pitzel, M., & Jensen, M. (2003). Prospective evaluation of bone mineral density in prostate cancer patients without bone metastases treated with intermittent androgen therapy. *Oncology, 17*(4, Suppl.), 32–33.

Hillner, B.E., Ingle, J.N., Chlebowski, R.T., Gralow, J., Yee, G.C., Janjan, N.A., et al. (2003). American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *Journal of Clinical Oncology, 21,* 4042–4057.

Hofbauer, L.C., & Khosla, S. (1999). Androgen effects on bone metabolism: Recent progress and controversies. *European Journal of Endocrinology, 140,* 271–286.

Jonat, W., Kaufmann, M., Sauerbrei, W., Blamey, R., Cuzick, J., Namer, M., et al. (2002). Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association study. *Journal of Clinical Oncology, 20,* 4628–4635.

Jordan, V.C., Gapstur, S., & Morrow, M. (2001). Selective estrogen receptor modulation and reduction in risk of breast cancer, osteoporosis, and coronary heart disease. *Journal of the National Cancer Institute, 93,* 1449–1457.

Kanis, J.A. (2002). Diagnosis of osteoporosis and assessment of fracture risk. *Lancet, 359,* 1929–1936.

Kaufman, J.M., Johnell, O., Abadie, E., Adami, S., Audran, M., Avouac, B., et al. (2000). Background for studies on the treatment of male osteoporosis: State of the art. *Annals of the Rheumatic Diseases, 59,* 765–772.

Kiralti, B.J., Srinivas, S., Perkash, I., & Terris, M.K. (2001). Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. *Urology, 57,* 127–132.

Leder, B.Z., LeBlanc, K.M., Schoenfeld, D.A., Eastell, R., & Finkelstein, J.S. (2003). Differential effects of androgens and estrogens on bone turnover in normal men. *Journal of Clinical Endocrinology and Metabolism, 88,* 204–210.

Lips, P., Wilco, C., Graafmans, W.C., Ooms, M.E., Bezemer, D., & Bouter, L.M. (1996). Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Annals of Internal Medicine, 124,* 400–406.

Love, R.R., Mazess, R.B., Barden, H.S., Epstein, S., Newcomb, P.A., Jordan, V.C., et al. (1992). Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *New England Journal of Medicine, 326,* 852–856.

Maillefert, J.F., Sibilia, J., Michel, F., Saussine, C., Javier, R.M., & Tavernier, C. (1999). Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *Journal of Urology, 161,* 1219–1222.

Melton, L.J., III, Alothman, K.I., Khosla, S., Achenbach, S.J., Oberg, A.L., & Zincke, H. (2003). Fracture risk following bilateral orchiectomy. *Journal of Urology, 169,* 1747–1750.

Messinger-Rapport, B.J., & Thacker, H.L. (2002). Prevention for the older woman: A practical guide to prevention and treatment of osteoporosis. *Geriatrics, 57*(4), 16–18, 21–24, 27.

Miller, P., & Lane, N.E. (2001). Osteoporosis: Clinical and laboratory features. In J.H. Klippel, L.J. Crofford, J.H. Stone, & C.M. Weyand (Eds.), *Primer on the rheumatic diseases* (12th ed., pp. 518–523). Atlanta, GA: Arthritis Foundation.

Mincey, B.A., Moraghan, T.J., & Perez, E.A. (2000). Prevention and treatment of osteoporosis in women with breast cancer. *Mayo Clinic Proceedings, 75,* 821–829.

Mittan, D., Lee, S., Miller, E., Perez, R.C., Basler, J.W., & Bruder, J.M. (2002). Bone loss following hypogonadism in men with prostate cancer treated with gonadotropin-releasing hormone analogs. *Journal of Clinical Endocrinology and Metabolism, 87,* 3656–3661.

Morabito, N., Gaudio, A., Lasco, A., Vergara, C., Tallarida, F., Crisafulli, G., et al. (2003). Three-year effectiveness of intravenous pamidronate versus pamidronate plus slow-release sodium fluoride for postmenopausal osteoporosis. *Osteoporosis International, 14,* 500–506.

National Osteoporosis Foundation. (2003). *Physician's guide to prevention and treatment of osteoporosis.* Washington, DC: Author.

National Osteoporosis Foundation. (2004a). America's bone health: The state of osteoporosis and low bone mass. Retrieved January 22, 2004, from http://www.nof.org/advocacy/prevalence/index.htm

National Osteoporosis Foundation. (2004b). Osteoporosis: Men. Retrieved January 14, 2004, from http://www.nof.org/men/index.htm

Novartis Pharmaceuticals. (2003). Aredia® [Package insert]. East Hanover, NJ: Author.

Novartis Pharmaceuticals. (2004). Zometa® [Package insert]. East Hanover, NJ: Author.

O'Connell, M.B. (1999). Osteoporosis and osteomalacia. In J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, & L.M. Posey (Eds.), *Pharmacotherapy: A pathophysiological approach* (4th ed., pp.1406–1426). Stamford, CT: Appleton and Lange.

Oefelein, M.G., Ricchuiti, V., Conrad, W., Seftel, A., Bodner, D., Goldman, H., et al. (2001). Skeletal fracture associated with androgen suppression induced osteoporosis: The clinical incidence and risk factors for patients with prostate cancer. *Journal of Urology, 166,* 1724–1728.

Oursler, M.J., Landers, J.P., Riggs, B.L., & Spelsberg, T.C. (1993). Oestrogen effects on osteoblasts and osteoclasts. *Annals of Medicine, 25,* 361–371.

Peacock, M., Liu, G., Carey, M., McClintock, R., Ambrosius, W., Hui, S., et al. (2000). Effect of calcium or 25OH vitamin D_3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *Journal of Clinical Endocrinology and Metabolism, 85,* 3011–3019.

Pfeilschifter, J., & Diel, I.J. (2000). Osteoporosis due to cancer treatment: Pathogenesis and management. *Journal of Clinical Oncology, 18,* 1570–1593.

Powles, T.J., Hickish, T., Kanis, J.A., Tidy, A., & Ashley, S. (1996). Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. *Journal of Clinical Oncology, 14,* 78–84.

Procter & Gamble Pharmaceuticals. (2003). Didronel® [Package insert]. North Norwich, NY: Author.

Ramaswamy, B., & Shapiro, C.L. (2003). Osteopenia and osteoporosis in women with breast cancer. *Seminars in Oncology, 6,* 763–775.

Recker, R.R., Hinders, S., Davies, K.M., Heaney, R.P., Stegman, M.R., Lappe, J.M., et al. (1996). Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *Journal of Bone and Mineral Research, 11,* 1961–1966.

Reid, I.R., Ames, R.W., Evans, M.C., Gamble, G.D., & Sharpe, S.J. (1995). Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: A randomized controlled trial. *American Journal of Medicine, 98,* 331–335.

Reid, I.R., Brown, J.P., Burckhardt, P., Horowitz, Z., Richardson, P., Trechsel, U., et al. (2002). Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *New England Journal of Medicine, 346,* 653–661.

Saarto, R., Blomqvist, C., Valimake, M., Makela, P., Sarna, S., & Elomaa, I. (1997). Chemical castration induced by adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy causes rapid bone loss that is reduced by clodronate: A randomized study in premenopausal breast cancer patients. *Journal of Clinical Oncology, 15,* 1341–1347.

Segal, R.J., Reid, R.D., Courneya, K.S., Malone, S.C., Parliament, M.B., Scott, C.G., et al. (2003). Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology, 21,* 1653–1659.

Shapiro, C.L., Manola, J., & Leboff, M. (2001). Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. *Journal of Clinical Oncology, 19,* 3306–3311.

Smith, M.R. (2002). Osteoporosis during androgen deprivation therapy for prostate cancer. *Urology, 60*(Suppl. 3A), 79–86.

Smith, M.R. (2003a). Bisphosphonates to prevent osteoporosis in men receiving androgen deprivation therapy for prostate cancer. *Drugs and Aging, 20,* 175–183.

Smith, M.R. (2003b). Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. *Cancer, 97*(3, Suppl.), 789–795.

Smith, M.R., Eastham, J., Gleason, D.M., Shasha, D., Tchekmedyian, S., & Zinner, N. (2003). Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for non-metastatic prostate cancer. *Journal of Urology, 169,* 2008–2012.

Smith, M.R., McGovern, F.J., Zietman, A.L., Fallon, M.A., Hayden, D.L., Schoenfeld, D.A., et al. (2001). Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *New England Journal of Medicine, 345,* 948–955.

Taxel, P., Fall, P.M., Albertsen, P.C., Dowsett, R.D., Trahiotis, M., Zimmerman, J., et al. (2002). The effect of micronized estradiol on bone turnover and calciotropic hormones in older men receiving hormonal suppression therapy for prostate cancer. *Journal of Clinical Endocrinology and Metabolism, 87,* 4907–4913.

Thiebaud, D., Burckhardt, P., Melchior, J., Eckert, P., Jacquet, A.F., Schnyder, P., et al. (1994). Two years' effectiveness of intravenous pamidronate (APD) versus oral fluoride for osteoporosis occurring in the postmenopause. *Osteoporosis International, 4,* 76–83.

Townsend, M.F., Sanders, W.H., Northway, R.O., & Graham, S.D., Jr. (1997). Bone fractures associated with luteinizing hormone–releasing hormone agonists used in the treatment of prostate carcinoma. *Cancer, 79,* 545–550.

Twiss, J.J., Waltman, N., Ott, C.D., Gross, G.J., Lindsey, A.M., & Moore, T.E. (2001). Bone mineral density in postmenopausal breast cancer survivors. *Journal of the American Academy of Nurse Practitioners, 13,* 276–284.

USP DI® Editorial Group. (Ed) (2004). *USP DI® drug information for the health care professional* [Electronic version] (24th ed.). Taunton, MA: Micromedex, Inc. Retrieved July 20, 2004, from http://online.statref.com/document.aspx?DocID=1&StartDoc=1&EndDoc=4569&FxID=6&offset=7&level=0&State=False&Local=True&SessionID=25E5E6ESFYXRXNKH&

Vehmanen, L., Saarto, T., Elomaa, P., Makela, P., Valimaki, M., & Blomquist, C. (2001). Long-term impact of chemotherapy-induced ovarian failure on bone mineral density (BMD) in premenopausal breast cancer patients. The effect of adjuvant clodronate treatment. *European Journal of Cancer, 37,* 2373–2378.

Viale, P.H., & Sanchez Yamamoto, D. (2003). Bisphosphonates: Expanded roles in the treatment of patients with cancer. *Clinical Journal of Oncology Nursing, 7,* 393–401.

Vieth, R. (2001). Vitamin D nutrition and its potential health benefits for bone, cancer and other conditions. *Journal of Nutritional and Environmental Medicine, 11,* 275–291.

Vincent, K.R., & Braith, R.W. (2002). Resistance exercise and bone turnover in elderly men and women. *Medicine and Science in Sports and Exercise, 34,* 17–23.

Ward, R.L., Morgan, G., Dalley, D., & Kelly, P.J. (1993). Tamoxifen reduces bone turnover and prevents lumbar spine and proximal femoral bone loss in early postmenopausal women. *Bone and Mineral, 22,* 87–94.

WPS Medicare Administrators. (2004). Wisconsin medical policy index: Bisphosphonate drug therapy. Retrieved July 20, 2004, from http://www.wpsic.com/medicare/policies/wisconsin/inj25.shtml

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