Screening, Prevention, Detection, and Treatment of Cancer Therapy–Induced Bone Loss in Patients With Breast Cancer

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Purpose/Objectives: To identify protocols to screen, detect, prevent, and treat cancer therapy–induced bone loss resulting in osteoporosis in patients with breast cancer.

Data Sources: Published books and articles.

Data Synthesis: Normal bone remodeling is affected by hormonal stimulation. Breast cancer therapies target hormones that promote cancer cell growth. Chemotherapy regimens and hormone ablation may cause ovarian failure, resulting in decreased hormone levels. A decrease in hormones, in estrogen- and progesterone-positive and -negative patients, introduces an environment for decreased bone remodeling, which may result in thinning bone and osteoporosis. The acceleration of bone loss leading to osteoporosis can result in higher fracture rates among breast cancer survivors.

Conclusions: With proper use of screening tools, patient education, and advice about lifestyle changes, all prior to cancer treatment, healthcare professionals may decrease or prevent bone loss in patients with breast cancer. Doing so minimizes healthcare costs and decreases morbidity and mortality rates in breast cancer survivors.

Implications for Nursing: As more individuals diagnosed with breast cancer are surviving for extended periods of time, oncology nurses are providing long-term follow-up care. Part of the care should include proper screening and patient education for healthier recovery and prevention of further healthcare complications as a result of cancer treatment.

Goal for CNE Enrollees

To enhance nurses' knowledge regarding cancer therapy–induced bone loss in patients with breast cancer.

Objectives for CNE Enrollees

1. Describe the physiologic consequences associated with osteoporosis.
2. Discuss lifestyle habits that are risk factors associated with osteoporosis.
3. Describe nursing management issues related to treatment available for osteoporosis.

Key Points . . .

- Because of a decrease in circulating exogenous hormones, patients with breast cancer are at higher risk for bone loss.
- The clinical consequences of decreased bone mass are skeletal fractures, abdominal protrusion, height loss, and kyphosis secondary to multiple vertebral fractures; acute and chronic pain resulting from fractures; decreased respiratory capacity; and increased morbidity and mortality rates.
- Primary management of chemotherapy treatment–induced bone loss begins with screening, which allows nurses to identify risk and allow patients at risk to make appropriate lifestyle changes for prevention.

Patients with breast cancer who are undergoing therapy experience myriad side effects. Decreased bone mass, often overlooked, potentiates another disease process, osteoporosis. Several factors contribute to bone loss in patients undergoing treatment for breast cancer, including chemotherapy and hormonal therapy (Daniell, 1997; Maxwell

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& Viale, 2005). The treatments, aimed at curing or controlling breast cancer by different mechanisms, can result in bone loss from decreased estrogen levels.

Two-thirds of patients with breast cancer are found to express positive estrogen and progesterone nuclear hormone receptors (Merck & Co., Inc., 2006). The receptors promote DNA replication and cell division of breast cancer cells when they are bound to the appropriate hormones (Merck & Co., Inc.). Patients receive therapies aimed at blocking estrogen and progesterone receptors to reduce the amount of circulating endogenous estrogens that may enable breast cancer cell growth (Ramaswamy & Shapiro, 2003).

As the amount of estrogen decreases in patients with breast cancer, the ability to rebuild bone also is decreased (Ramaswamy & Shapiro, 2003) because decreased estrogen levels decrease osteoblast and osteoclast activity (Kowalak et al., 2001). With decreased bone formation, patients develop a higher risk of cancer treatment–induced bone loss (CTIBL) (Hawkins, Campos, & Fessele, 2005). Bone loss leads to osteoporosis, which is the most common bone disease in humans (National Osteoporosis Foundation, 2006).

With proper screening, detection, and prevention programs, nurses can identify patients at risk for developing osteoporosis and aid them in decreasing their risk. Decreased risk of osteoporosis enables patients, their caregivers, and healthcare providers to escape the high costs of morbidity and mortality related to the disease.

Pathophysiology of Bone Loss

Normal bone formation is an ongoing activity that is determined by estrogen and progesterone stimulation, dietary factors, and the amount of stress put on the bone (Kowalak et al., 2001). The process requires ongoing osteoblast and osteoclast activity. Osteoblasts are cells that continually form bony matrixes to replace areas of bone that have been digested by phagocytic cells called osteoclasts (Kowalak et al.). The continual process of bone remodeling through osteoblast and osteoclast activity amounts to a preventive maintenance program allowing for a healthy skeleton (National Osteoporosis Foundation, 2006). When the remodeling is altered because of an imbalance between bone removal and replacement, the result is bone thinning or osteoporosis, which is "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (Kanis, 2002, p. 1929) (see Figure 1). Without the proper level of estrogens and progesterones available in the body, the process of bone remodeling is compromised (Hawkins et al., 2005).

Bone Mineral Density Measurement

Low bone density is the characterizing feature of osteoporosis (Pfeilschifter & Diel, 2000). Bone mineral density (BMD) measurements are used to diagnose and classify osteoporosis (Pfeilschifter & Diel). The measurement is expressed in standard deviations (SDs) from the mean in relationship to two norms: a T score, the bone mass of "normal, young" adults of the same gender, and a Z score, an age- and gender-matched population (National Osteoporosis Foundation, 2006). The World Health Organization classifies women with a T score between –1 and –2.5 SD as osteopenic, women with a T score –2.5 SD below the young adult mean as osteoporotic, and women with a T score ≥ –2.5 SD in the presence of fracture as severely osteoporotic (Kanis, 2002).

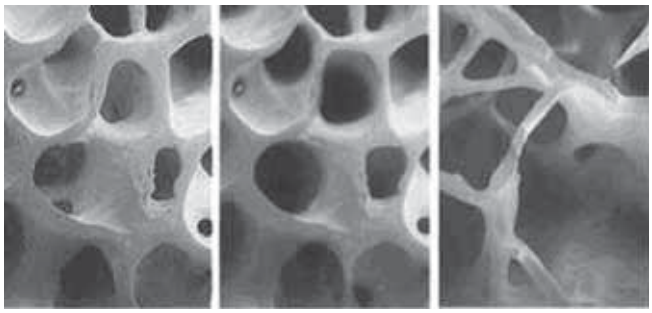


Figure 1. Progression of Osteoporosis

Note. From "Osteoporosis," by Orthopaedic Specialists, 2005. Retrieved June 15, 2005, from http://www.louisvillebones.com/osteoporosis.html. Reprinted with permission.

BMD measurement not only assists nurses in identifying osteoporosis but also enables them to estimate fracture risk associated with bone loss. Maillefert et al. (1999) established that a 10% decrease in BMD doubles the risk of fracture.

Cancer Therapy–Induced Bone Loss

Oncology therapies used to treat breast cancer induce ovarian failure (Pfeilschifter & Diel, 2000). Therefore, women treated for breast cancer can develop osteoporosis at an accelerated rate (Daniell, 1997) because of reductions in estrogen and progesterone. Of the approximately 213,000 women diagnosed with breast cancer in 2006, 22% will be younger than 50 (American Cancer Society, 2006). When women are treated with chemotherapy, the onset of menopause may be induced 5–10 years earlier than might have been the case naturally (Coleman, 2004). Women who are close to natural menopause age (i.e., older than 40) experience ovarian failure during the first few months of chemotherapy (Mincey, Moraghan, & Perez, 2000) and have a higher incidence of chemotherapy-induced amenorrhea, ranging from 49%–100% (Bines, Oleske, & Cobleigh, 1996). Women younger than 40 experience amenorrhea at an incidence rate of 21%–71% (Bines et al.). Pfeilschifter and Diel indicated that 64% of premenopausal women with breast cancer who were treated with combinations of cyclophosphamide, methotrexate, fluorouracil, and doxorubicin developed ovarian insufficiency within one year of therapy.

Patients with breast cancer are treated with a variety of chemotherapeutic agents for varying periods of time; some receive dose-dense therapy. No matter the length or dose of therapy, when ovarian failure occurs, patients develop an estrogen-deficient state and bone resorption increases (Ramaswamy & Shapiro, 2003). The increase in bone resorption causes a decrease in bone density in the first few years after cessation of menses (Saarto, Blomqvist, Valimaki, Sarna, & Elomaa, 1997), thereby decreasing vertebral bone density by 21% below that of age-matched eumenorrheic women (Cann, Martin, Genant, & Jaffe, 1984). Shapiro, Manola, and Leboff (2001) found that

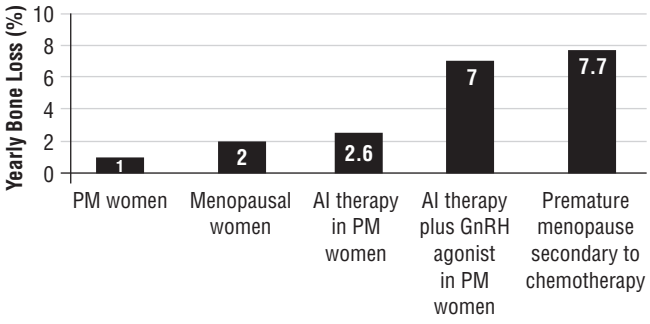
women who experienced ovarian failure as a result of cancer therapy had significant decreases in BMD within six months of beginning chemotherapy, and the decreases continued through 12 months (Ramaswamy & Shapiro).

Estrogen receptor–positive patients also receive hormonal therapy to prevent recurrence of breast cancer. Such therapies, known as selective estrogen receptor modulators (SERMs), are antiestrogen drugs that bind to estrogen receptor sites on breast cancer cells. This blocks the uptake of estrogen and interferes with cell proliferation (Otto, 2001). The oldest SERM is tamoxifen. It may be prescribed for women with hormone receptor–positive breast cancer before and after menopause (Breastcancer.org, 2006).

Premenopausal patients receiving tamoxifen may be at increased risk for bone loss. Powles, Hickish, Kanis, Tidy, and Ashley (1996) found that premenopausal women who received tamoxifen had a decrease in spine BMD by approximately 1.4% for each year of therapy.

Postmenopausal women who are found to be estrogen receptor–positive also may be treated with aromatase inhibitors (AIs). The drugs help prevent the growth of breast cancer cells by lowering the amount of estrogen in the body (National Cancer Institute, 2004). AIs do not block estrogen production by the ovaries; however, they can block other tissues from making the hormone. That is why AIs are indicated in women who have reached menopause, when the ovaries no longer produce estrogen (National Cancer Institute). The decrease in circulating estrogen has shown a trend toward increased bone loss, as indicated in the letrozole study, which found that patients who received AIs developed osteoporosis 8% of the time whereas patients who did not receive the drugs developed osteoporosis only 6% of the time (Coombes et al., 2004).

Data indicate that even though treatment regimens are not the same for all patients with breast cancer, their risk for developing bone loss accelerates. The acceleration places patients with breast cancer at a higher risk for osteoporosis, as indicated in Figure 2. With significant decreases in BMD, 67% of breast cancer survivors become osteopenic and 11% become osteoporotic (Gross, Ott, Lindsey, Twiss, & Waltman, 2002). Chen et al. (2005) indicated that breast cancer survivors exhibit a 15% increased risk for total fractures when compared to other women in the same age group.



AI—aromatase inhibitor; GnRH—gonadotropin-releasing hormone agonist, PM—postmenopausal

Figure 2. Bone Loss Is Accelerated With Cancer Therapies

Note. Based on information from Hawkins et al., 2005.

Oral Bisphosphonates

Alendronate (Fosamax®, Merck & Co., Inc., Whitehouse Station, NJ)
Etidronate (Didronel®, Proctor and Gamble Pharmaceuticals, Cincinnati, OH)
Risedronate (Actonel®, Procter and Gamble Pharmaceuticals and sanofi-aventis, Bridgewater, NJ)
Ibandronate (Boniva®, Roche Pharmaceuticals, Nutley, NJ, and GlaxoSmithKline, Research Triangle Park, NC)

IV Bisphosphonates

Pamidronate (Aredia®, Novartis Pharmaceuticals, East Hanover, NJ)
Zoledronic acid (Zometa®, Novartis Pharmaceuticals)

Intranasal Spray

Calcitonin (Miacalcin®, Novartis Pharmaceuticals, and Fortical®, Upsher-Smith Laboratories, Maple Grove, MN)

Figure 3. Pharmacologic Therapy for Osteoporosis

Note. Based on information from Pfeilschifter & Diel, 2000.

Consequences of Decreased Bone Mass

The clinical consequences of decreased bone mass are expressed not only as skeletal fractures, but also as sequelae related to bone loss. The sequelae may present as abdominal protrusion, height loss, and kyphosis secondary to multiple vertebral fractures; acute and chronic pain resulting from fractures; decreased respiratory capacity; and increased morbidity and mortality rates (Maxwell & Viale, 2005).

The consequences affect patients through poorer quality of life as a result of fear, anxiety, depression, and decreased functional ability (National Institutes of Health, 2000). Decreased functional ability is secondary to more than 1.5 million fractures of the hip, spine, and wrist in the United States each year (National Institutes of Health, 2006), and healthcare expenditures approach $18 billion when healthcare provider visits, emergency room visits, hospitalizations, and nursing home placements increase (U.S. Department of Health and Human Services, 2004).

In addition to healthcare expenditures, costs also include potential job and other economic losses (International Osteoporosis Foundation, 2002). Fractures as a result of osteoporosis also may result in debilitating injury, which may cause individuals to suffer severe loss of self-esteem, which is associated with large emotional costs (International Osteoporosis Foundation). Employers of affected individuals may face loss of efficiency, productivity, and possibly experienced employees (International Osteoporosis Foundation). The indirect costs of osteoporosis are estimated to be $8.1 million annually in the United States. With proper tools, healthcare providers may be able to aid in preventing such losses through screening, detection, and prevention of bone loss associated with cancer therapies.

Screening for Bone Loss

Primary management begins with screening. Screening tools allow nurses to identify the risk of CTIBL (Hillner et al., 2003) and allow at-risk patients to make appropriate lifestyle changes for further prevention. The following screening guidelines for patients with breast cancer, as outlined by the American Society of Clinical Oncology (Hillner et al.), indicate that BMD screening is beneficial for

- All women older than 65
- All women aged 60–64 with a family history of osteoporosis
- All women with body weight less than 70 kg
- All women with prior nontraumatic fracture
- All women with other risk factors
- All postmenopausal women of any age receiving AIs
- All premenopausal women with therapy-associated premature menopause.

Prevention

Reduction in BMD indicates that appropriate steps should to be taken to prevent additional bone loss. Appropriate lifestyle changes are the first step in prevention. Proper intake of calcium and vitamin D is necessary to decrease bone reduction. Ninety-nine percent of the body's calcium stores are contained in the skeleton. When an exogenous calcium supply is inadequate, the body draws from the stores to maintain serum calcium levels (National Osteoporosis Foundation, 2006). Calcium supplements decrease the amount of calcium drawn from the bone to replace the exogenous supply. A daily dose of 1,200 mg per day is recommended. Vitamin D (400–800 IU per day recommended) facilitates the process by helping the body to absorb the calcium from the intestine and use it in the bloodstream (National Osteoporosis Foundation). It also assists the kidneys to resorb calcium that otherwise would be excreted (National Osteoporosis Foundation).

Exercise helps bones to become stronger and denser as demands are placed on them (National Osteoporosis Foundation, 2006). Weight-bearing exercises, during which muscles and bones work against gravity, and resistance exercises to improve muscle mass and strengthen bone are important for building and maintaining bone mass and density (National Osteoporosis Foundation).

Cigarette smoking was identified as a risk for osteoporosis more than 20 years ago and most recently has been found to have a direct correlation with decreased bone mass (International Osteoporosis Foundation, 2002). Smoking has been shown to decrease calcium absorption (National Osteoporosis Foundation, 2006).

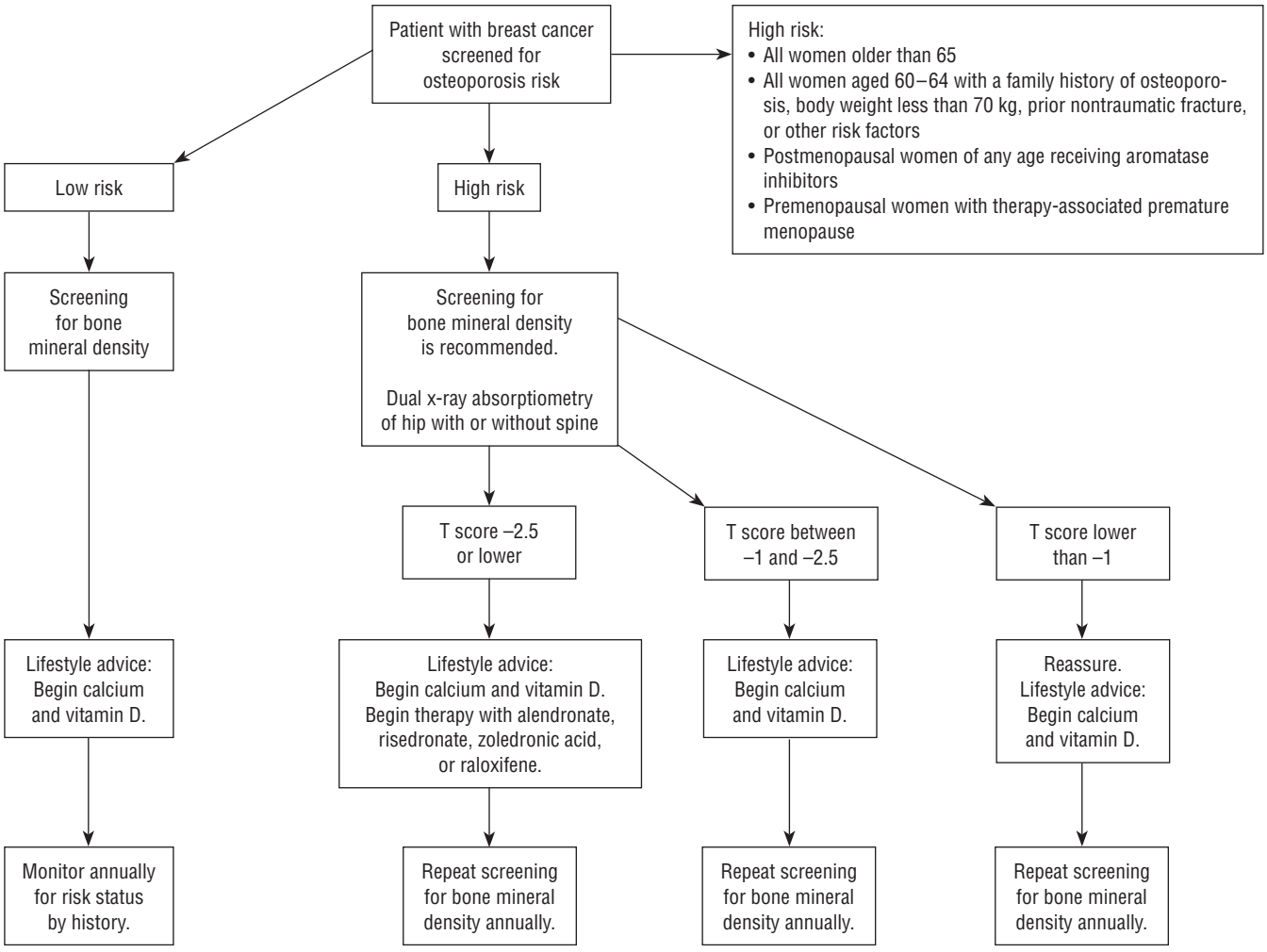


Figure 4. Screening, Detection, and Treatment of Bone Loss in Patients with Nonmetastatic Breast Cancer

Note. From "American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer," by B. Hillner, J. Ingle, R. Chlebowski, J. Gralow, G. Yee, N. Janjan, et al., 2003, *Journal of Clinical Oncology, 21,* p. 4054. Copyright 2003 by the American Society of Clinical Oncology. Reprinted with permission.

Increased fractures of the hip, spine, and wrist have been linked to chronic alcohol use (International Osteoporosis Foundation, 2002). Alcohol in excess of two drinks per day also may interfere with the balance of calcium in the body. Alcohol affects the production of hormones and vitamins (International Osteoporosis Foundation). Additionally, falls and fractures may be related to excessive alcohol consumption (International Osteoporosis Foundation).

Finally, caffeine intake should be limited in patients at risk for osteoporosis. Studies have shown that some substances, such as high dietary protein, caffeine, phosphorus, and sodium, can adversely affect calcium balance (National Institute of Arthritis, 2005).

Detection

Detection of low bone mass involves proper radiologic evaluation by single and dual x-ray absorptiometry to assess mineral content of the entire skeleton (Kanis, 2002). The amount of bone mineral scanned at a specific site is divided by the area measured. Once a score is obtained, it is compared with young, healthy adults (T score) and adults of the same age and gender (Z score). Patients at risk for osteoporosis or CTIBL should be screened yearly (Hillner et al., 2003).

Treatment

Management with bisphosphonates may be indicated when patients present as osteoporotic or after appropriate lifestyle and behavioral changes have failed to control bone loss. Bisphosphonates significantly reduce skeletal morbidity and fractures in patients with bone loss (Rosen, 2004). They do so by preferentially binding to the bone surfaces that are actively undergoing remodeling and aid in inhibiting osteoclast maturation, suppressing osteoclast activity, and inducing osteoclast death (Rosen). Additionally, by inhibiting osteoclast

Goal	Before Program	Six Months Into Program
Screening		
95% of patients with breast cancer will have a documented height and weight at initial evaluation.		
95% of patients will have a documented history and physical[a] at initial visit.		
95% of patients with breast cancer will be screened for osteoporosis risk.		
95% of women older than 65 will be considered at high risk for osteoporosis.		
95% of women aged 60–64 with family history of osteoporosis, body weight less than 70 kg, or prior nontraumatic fracture will be considered at high risk for osteoporosis.		
95% of postmenopausal women of any age receiving aromatase inhibitors will be considered at high risk for osteoporosis.		
95% of premenopausal women with therapy-associated premature menopause[b] will be considered at high risk for osteoporosis.		
Management		
95% of patients with breast cancer will have documentation of lifestyle advice[c] for the prevention of osteoporosis.		
90% of patients with breast cancer will begin calcium and vitamin D supplement therapy with initiation of chemotherapy.		
85% of patients with breast cancer screened and found to be at high risk will receive bone mineral density screening via dual x-ray absorptiometry of hip and spine.		
95% of patients with breast cancer with a T score between –1 and –2.5 will have documentation of lifestyle advice for the prevention of osteoporosis.		
90% of patients with breast cancer with a T score –2.5 or lower will receive bisphosphonate therapy recommended first line.		
90% of patients with breast cancer will receive education about osteoporosis.		
90% of patients with breast cancer will have a documented height and weight, blood pressure, and pulse on every visit.		
90% of patients with breast cancer at low risk for bone loss will have risk status reviewed annually.		
85% of patients with breast cancer at high risk for bone loss will have repeat bone mineral density screening annually.		
90% of patients with breast cancer will be monitored for side effects of bisphosphonates at every visit.		
80% of patients with breast cancer with bone mineral density less than –2.5 will be referred to an endocrinologist.		
Patient Outcomes		
Less than 30% of patients with breast cancer will experience a skeletal-related event[d] secondary to osteoporosis.		

[a] Complete history and physical will include review of lifestyle indicators (i.e., smoking, alcohol intake, caffeine intake, exercise, diet, and vitamin supplements).

[b] Premature menopause: no menses for more than six months in women who were having monthly menstrual cycles prior to beginning cancer treatment

[c] Lifestyle advice to include daily calcium and vitamin D supplements, regular weight-bearing exercise, smoking cessation, limits on alcohol ingestion, and avoidance of excessive caffeine use

[d] Skeletal-related event defined as bone fracture or compressive spinal fracture

Figure 5. Quality Care Provider Score Sheet for Cancer Therapy–Associated Bone Loss

recruitment to the sites of bone resorption, bisphosphonates reduce bone-resorbing cytokine and growth factor production (Pfeilschifter & Diel, 2000; Rosen). Bisphosphonates are almost equivalent to estrogen and progesterone with regard to their effects on the skeleton (Pfeilschifter & Diel).

Another class of drug used to treat bone loss is polypeptide hormones called calcitonins, which are involved in calcium regulation and bone metabolism (National Institutes of Health, n.d.). The drugs cause osteoclasts to shrink and decrease their bone-resorbing activity (Pfeilschifter & Diel, 2000).

Various forms of oral and IV bisphosphonate therapies are available (see Figure 3), and treatment can be individualized for each patient depending on the extent of disease and patient preferences (National Institutes of Health, n.d.). As with any medication, the drugs have potential side effects. Oral bisphosphonates have been shown to cause gastrointestinal problems such as difficulty swallowing, inflammation of the esophagus, and gastric ulcers (National Institutes of Health, n.d.). The side effects may be prevented by taking the medication on an empty stomach with a full glass of water first thing in the morning and then remaining in an upright position and refraining from eating or drinking for at least 30 minutes after ingestion (National Institutes of Health, n.d.).

IV bisphosphonates may be indicated or better tolerated in some patients. The most common side effects experienced by patients receiving the drugs by that route are upset stomach, diarrhea, and bone pain (National Institutes of Health, n.d.). Patients' renal function must be monitored because deterioration of renal function sometimes occurs (Perry & Figgitt, 2004).

Nursing Implications

Because patients with breast cancer experience numerous side effects as a result of therapy, practitioners' role in proper screening, prevention, detection, and treatment of CTIBL focuses on prevention of further morbidities. Practitioners should provide counseling about appropriate lifestyle habits and preventive measures to all patients, while also identifying high-risk patients in need of further screening. Proper identification of patients at high risk for bone loss may decrease morbidity and mortality rates associated with skeletal-related events secondary to decreases in BMD. Evaluation and treatment of osteoporosis are of particular importance to nurses who treat patients with breast cancer because the cancer therapies themselves increase women's lifetime risk of developing osteoporosis and fractures (Ravdin, 2004; Ross & Small, 2002). Current reports indicate that most women undergoing breast cancer therapy are not screened for bone loss even though nurses are aware of CTIBL, because osteoporosis is less feared than cancer (Daniel et al., 2000; Ravdin). Appropriate standards of care remind nurses to consistently screen, prevent, detect, and treat bone loss.

Identification of patients at risk begins with a history and physical examination (Ravdin, 2004). Once a medical and lifestyle history has been reviewed properly, adherence to the American Society of Clinical Oncology guidelines for screening patients with nonmetastatic breast cancer for osteoporosis risk is beneficial. The guidelines are a tool for nurses to classify patients at low and high risk (see Figure 4). A BMD T score of –2.5 indicates the need for pharmacologic treatment (Ravdin).

Nurses can monitor patient adherence to recommendations and standards by using a provider score sheet for the screening, prevention, detection, and treatment of CTIBL (see Figure 5).

Conclusion

Osteoporosis and its complications are preventable with proper screening, prevention, detection, and treatment. Patients undergoing therapy for breast cancer and other hormone-modulated cancers are at increased risk for developing low BMD as a result of therapies that suppress estrogen, which is a necessary part of the process of bone formation and prevention of bone breakdown. Although this article focused on patients with breast cancer, all patients undergoing cancer treatment that affects hormonal balance are at risk for increased bone loss leading to osteoporosis.

Without the proper mechanisms to form bone and prevent its breakdown, the skeletal structure becomes thinner and less dense, creating architecture at risk for fracture. As survival rates for breast cancer increase, nurses must prevent serious consequences, such as osteoporosis, from cancer therapy. Monitoring and treatment empower patients to decrease their risk for CTIBL and decrease morbidity and mortality associated with osteoporosis.

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The continuing nursing education examination and test form for the preceding article appear on the following pages.