ABSTRACT

Low bone mass can be associated with an increased risk of fragility fractures, which affects a person’s independence, quality of life, and survival. Women with a history of breast cancer may be particularly at risk for osteoporosis secondary to advancing age and the negative effects that some breast cancer therapies can have on bone. Dietary and lifestyle counseling are the foundation for ensuring that adequate calcium and vitamin D are consumed, that the individual is participating in weight-bearing exercises, and that the person is not abusing tobacco or alcohol. Screening by using bone mineral density is critical for identifying and managing individuals at risk for low bone mass. When indicated, pharmacologic agents may be used; bisphosphonates are generally the preferred intervention in women with a history of breast cancer. Maintaining bone integrity is an important component of general health maintenance and may have particular relevance in the long-term care of women with a history of breast cancer.


OSTEOPOROSIS IS CHARACTERIZED BY LOW BONE MASS AND ARCHITECTURAL DETERIORATION OF BONE TISSUE THAT LEADS TO AN INCREASED RISK OF FRACTURE. Bone is a dynamic organ in which remodeling is constantly occurring. In osteoporosis, there is an imbalance in bone remodeling, in which the bone resorption rate exceeds the bone formation rate. These changes lead to bone fragility.

Osteoporosis affects approximately 10 million Americans, 8 million of whom are women; 55% of people 50 years of age and older have low bone mass. The probability that a 50-year-old woman will have a hip fracture in her lifetime is 14% for a white woman and 6% for an African American woman.

Osteoporosis frequently affects postmenopausal women, as does breast cancer, a disease that will be diagnosed in more than 200,000 US women this year. The incidence of osteoporosis and breast cancer increases with age, and these 2 diagnoses are often made in the same individual. Recently, the survival rates of women with early breast cancer have been improving. The success in treating early stage breast cancer is associated with a need to ensure that the long-term toxicities of cancer therapy are minimized. Similarly, the overall long-term health maintenance of the individual needs to be addressed; this task includes addressing maintenance of bone integrity.

RAISING BONE-HEALTH AWARENESS

The importance of promoting bone health and preventing fractures was recognized in the US Surgeon General’s report on bone health and osteoporosis of 2004. This report addressed the public health concerns of osteoporosis, in addition to emphasizing the need to consume adequate amounts of calcium and...
vitamin D, to maintain a healthy weight, to keep physically active, and to reduce the risk of falls. Other major health-promoting organizations, such as the US Preventive Services Task Force (USPSTF), the National Osteoporosis Foundation (NOF), and the National Institutes of Health, have also identified postmenopausal bone health as a major public health concern. The American Association of Clinical Endocrinologists, NOF, and USPSTF have recommended screening bone mineral density (BMD) in postmenopausal women age 65 years and older in addition to younger postmenopausal women at increased risk for osteoporotic fracture. The American Society of Clinical Oncology (ASCO) has published guidelines to assist the oncologist in addressing bone health in women with a history of breast cancer. Only a limited number of clinical trials have specifically addressed bone health in women with cancer, and the ASCO guidelines drew heavily from the literature on osteoporosis in postmenopausal women in general. Cancer-specific, bone-related data are being generated, and publication of an updated, evidence-based version of the ASCO guidelines that addresses the unique subpopulation of cancer survivors is anticipated.

**Bone Mass, Breast Cancer, and Quality of Life**

Breast cancer and osteoporosis predominantly affect postmenopausal women, and these 2 conditions are frequently diagnosed in the same individual. Both conditions can have an adverse impact on an individual’s quality of life (QOL). Osteoporosis-related fractures can result in physical and psychological morbidity. Vertebral fractures may result in chronic pain, disfigurement, loss of height, impaired body image, and decreased self-esteem. After a fracture, QOL can be impaired because of decreased mobility, fear of falling and having another fracture, and the social isolation, sense of helplessness, and depression that result. One in 5 individuals who experience a hip fracture will die within 1 year of that fracture, and approximately 1 in 3 will require nursing home placement. In patients with a history of breast cancer, a fracture may herald breast cancer recurrence with bone metastases and, for optimal treatment planning, the nature of the fracture must be defined. This article focuses on bone health in women without metastatic breast cancer. For management of bone integrity in patients with metastatic breast cancer, refer to the ASCO guidelines.

Fragility fractures may have devastating effects for patients, their families, and their social networks. Like their physical and psychological impact, the economic impact of fractures is also high: Estimates of the direct medical costs of fracture care range from $12 to $18 billion annually in 2002 dollars. Given that there are established methods for screening for BMD in addition to preventing and treating low bone mass, there is room to improve these statistics.

Similar to osteoporosis, breast cancer causes psychological and physiological morbidity. Shortly after primary treatment, patients with breast cancer commonly report compromised physical functioning and emotional well-being. Whereas pain and fatigue affect physical well-being, distress from surgery, impaired self-concept, and fear of recurrence affect psychological well-being. Such psychological distress can depress mood and ability to cope; adversely impact marital, familial, and social relationships; impair functioning at home and work; and reduce overall QOL. Although QOL is generally good in postmenopausal women with a history of breast cancer after as many as 3 years of follow-up, bone loss related to anticancer therapy requires monitoring and management to avoid the long-term impact on QOL with osteoporotic fractures.

**Risk Factors for Osteoporosis**

Risk factors associated with osteoporosis include advancing age (>65 years), female gender, glucocorticoid use, malabsorption syndromes, primary hyperparathyroidism, hypogonadism, and menopause before age 45. The Study of Osteoporotic Fractures found that older women with the highest BMD had at least twice the risk of breast cancer as those with the lowest BMD; having had breast cancer does not protect older women against developing osteoporosis, and certain breast cancer therapies may increase an individual’s risk for loss of bone mass. In patients with a history of breast cancer, endocrine treatment strategies and other systemic therapies, such as chemotherapy or the supportive medications used with chemotherapy (eg, steroids and growth factors), may have a negative effect on BMD.

A retrospective study of 53 patients with early stage breast cancer (mean age = 60 years) found that dual-energy x-ray absorptiometry results within 1 year of
Breast cancer diagnosis indicated that approximately 60% of patients had osteopenia or osteoporosis. This finding suggests that the bone mass of patients with a history of breast cancer is lower than what would be expected on the basis of the national average. Using the database from the Women’s Health Initiative Observational Study, Chen et al found a 15% increase in overall fracture risk and a 36% increase in forearm or wrist fractures in postmenopausal breast cancer survivors (n = 5298) compared with postmenopausal women who had no cancer history (n = 80 848). These data suggest that breast cancer diagnosis and/or its treatment may affect fracture risk.

**Bone Is an Endocrine-Responsive Organ**

Bone is an organ that is in constant flux. Adult bone is continually remodeling itself, and this process has 4 phases: resorption, reversal, formation, and resting (Figure 1). Systemic hormones that affect bone metabolism include growth hormone, insulin-like growth factor, thyroid hormone, and cortisol. Local factors such as cytokines also help to regulate bone remodeling. Bone remodeling involves a delicate balance between bone formation and bone resorption. This balance is influenced by systemic and local factors in addition to mechanical stressors.

**Medications and Bone Health**

A wide range of medications can adversely influence bone health (Table 1). In reviewing risk factors for osteoporosis, the patient’s medication list should be examined for drugs or supplements that may have a negative impact on bone and, if clinically appropriate, an alternative agent should be considered.

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Representative Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants</td>
<td>Heparin, warfarin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin, sodium, valproate</td>
</tr>
<tr>
<td>Conventional antipsychotics and other agents that increase prolactin levels</td>
<td>Chlorpromazine, fluphenazine, haloperidol, perphenazine, thiothixene, thioridazine, trifluoperazine, metoclopramide</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>Azathioprine, cyclophosphamide, methotrexate</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Aldosterone, beclomethasone, betamethasone, cortisol, dexamethasone, fluoroicosine, hydrocortisone, methylprednisolone, prednisone, prednisolone, triamcinolone</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone agonists</td>
<td>Buserelin, goserelin, leuprolide</td>
</tr>
<tr>
<td>Highly active antiretroviral therapy</td>
<td>Nucleoside/tide reverse transcriptase inhibitors, protease inhibitors, non-nucleoside reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>Hormones</td>
<td>Adrenocorticotropic hormone, thyroid hormone (eg, thyroxine)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Cyclosporine, glucocorticoids, tacrolimus</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Bumetanide, ethacrynic acid, furosemide, torsemide</td>
</tr>
<tr>
<td>Vitamin supplements</td>
<td>Vitamins A and D</td>
</tr>
</tbody>
</table>

Glucocorticoid-induced osteoporosis is a clinically relevant problem, and those using more than 5 mg of prednisone daily for 3 months or longer are at increased risk for loss of bone mass. Approximately 30% to 50% of patients who take glucocorticoids experience fracture. Other medications used in adjuvant breast cancer therapy may also affect bone health.

**BREAST CANCER THERAPIES THAT MAY ADVERSELY AFFECT BONE HEALTH**

**PREMATURE OVARIAN FAILURE**

Premenopausal women with breast cancer may be at risk for premature menopause secondary to anticancer treatment. Age and systemic adjuvant therapy affect the likelihood of amenorrhea. Age at time of adjuvant therapy and the type of systemic therapy used are important factors that govern whether or not a woman experiences chemotherapy-induced premature ovarian failure. In women older than age 40, the risk of menopause ranges from 49% to 100%. However, the definition of amenorrhea and menopause may vary between different clinical trials, as does the duration of follow-up to confirm complete cessation of menses. The onset of menopause, whether natural or chemotherapy-induced, is associated with a rapid loss of bone in response to the declining level of estrogen. Clinical trials investigating bone mass in young women treated with adjuvant tamoxifen and/or chemotherapy for breast cancer have shown an associated loss of bone mass, which can be tempered with the use of bisphosphonates.

Young women who retain ovarian function during chemotherapy or resume menstruation after completing chemotherapy may be at risk of eventually experiencing premature menopause (reaching menopause before the expected natural age of menopause for that individual). Moreover, in premenopausal women with hormone-receptor–positive breast cancer, ovarian suppression may sometimes be deliberately induced as part of adjuvant breast cancer therapy. For example, the use of luteinizing-hormone–releasing hormone agents to cause the cessation of menstrual function is associated with loss of bone mass.

**ADJUVANT CHEMOTHERAPY**

Adjuvant chemotherapy carries a risk of inducing premature ovarian failure in young women. Aside from the endocrine effects of changing menstrual status, chemotherapy may have a direct effect on bone, as has been seen in preclinical studies. The supportive medications used with adjuvant chemotherapy may include corticosteroids and growth factors such as filgrastim, and these agents may have a negative impact on BMD. In a retrospective study of 130 postmenopausal women with early stage breast cancer, the BMD scores of the hip and spine were lower in patients who had received adjuvant chemotherapy than in those who did not. A prospective clinical trial examining the impact of chemotherapy on BMD in postmenopausal women is ongoing.

**ADJUVANT HORMONAL THERAPY**

Approximately 80% of breast cancers express the estrogen or progesterone receptor, and patients whose tumor is considered endocrine sensitive are offered adjuvant hormonal therapy. Presently, 2 classes of endocrine therapies have been approved by the US Food and Drug Administration (FDA) for use in the adjuvant treatment of breast cancer: the selective estrogen receptor modulator (SERM), tamoxifen; and the aromatase inhibitors (AIs), which include anastrozole, exemestane, and letrozole. In addition, ovarian ablation, performed biochemically or surgically, may also be incorporated into the adjuvant breast cancer care of some premenopausal women with breast cancer.

Tamoxifen has a positive effect on bone in a postmenopausal woman; however, in a premenopausal woman, tamoxifen can promote bone loss. In a recent publication by Vehmanen et al, young women who retained ovarian function after chemotherapy and were treated with tamoxifen experienced significant (P < .0001) loss of bone mass, whereas, in those who became amenorrheic, bone mass was positively affected by tamoxifen.

AIs have become part of routine clinical practice when treating postmenopausal women with estrogen- and/or progesterone-receptor–positive breast cancer in the adjuvant setting, and this practice is supported by ASCO. AIs may be used in sequence with tamoxifen or may be used as the initial hormonal therapy. With the increased use of adjuvant AIs comes concern about the long-term toxicities of this drug class and its effect on bone health.

The third-generation AIs—anastrozole, exemestane, and letrozole—are able to inhibit approximately 80% to 90% of total body aromatization of estrogen in postmenopausal women, and this profound sup-
pression of estrogen production raises concerns about bone health. The negative impact of the AIs on bone has been observed in prospective clinical trials and through review of databases. In a large, retrospective study of patients with breast cancer who had neither metastases nor osteoporosis before being treated for breast cancer, the prevalence of osteoporosis and of clinical fracture in the 1354 patients who received an AI was compared with that in those in a control group of 11,014 patients. This study found that the relative risk of osteoporosis in the AI group compared with the control group was 1.3 and that the relative risk of fracture in the AI group compared with the control group was 1.4. After adjustment for age and comorbidities, risk of osteoporosis remained 27% higher in the AI group than in the control group, and risk of fracture remained 21% higher (P = .02 for osteoporosis and fracture risk). These findings suggest that the use of adjuvant AIs is a risk factor for osteoporosis and fracture.

Bone-specific endpoints have been captured in studies examining the use of adjuvant AIs. Randomized, clinical trials of the third-generation AIs include the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. The main study showed an increased risk of fractures (11.0% vs 7.7%; hazard ratio, 1.49 [confidence interval (CI), 1.25–1.77]; P = .0001) in the anastrozole treatment arm compared with the tamoxifen treatment arm. The ATAC bone subprotocol 5-year data were presented at the 2006 ASCO meeting (anastrozole, n = 81; tamoxifen, n = 86). The anastrozole-treated group experienced bone loss throughout the follow-up period; however, in years 2 through 5, the rate of BMD loss in the lumbar spine decreased, although the rate of BMD loss in the hip did not. No patient who had a normal BMD at study baseline became osteoporotic after 5 years of therapy. Similarly, use of an AI as initial therapy was related to increased risk of fracture in the Breast International Group 1-98 trial. In that trial, after approximately 2 years of follow-up, letrozole was associated with more fractures than tamoxifen alone (letrozole, 5.7% vs tamoxifen, 4%; P < .001). Prior tamoxifen exposure and duration of AI use may be important factors that influence the risk of bone mass loss and fracture. However, regardless of prior tamoxifen exposure or duration of AI exposure, AI use alone still appears to have a negative impact on bone. The National Cancer Institute of Canada Clinical Trials Group study MA.17 is a placebo-controlled trial of the use of the AI letrozole after standard adjuvant tamoxifen in postmenopausal women with early stage breast cancer. In an updated analysis of the trial, the fracture incidence after 30 months of follow-up was higher in the letrozole group (5.3%) than in the placebo group (4.6%); however, this difference was not statistically significant. In the bone subprotocol of MA.17, postmenopausal women with a T score of at least -2.0 in the hip or the lumbar spine were evaluated for markers of bone turnover and BMD. At 24 months, patients who had received letrozole had a significant decrease in total hip BMD (3.6% vs 0.71%; P = .044) and in lumbar spine BMD (5.35% vs 0.70%; P = .008).

In a combined analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 8 and Arimidex-Nolvadex trial, which also examined sequential use of an AI after tamoxifen, fractures were more than twice as common in the anastrozole group as in the tamoxifen group. However, in the Italian Tamoxifen Anastrozole Trial, in which tamoxifen was compared with sequential use of tamoxifen then anastrozole, the 2 arms showed no difference in the rate of fractures after a median follow-up of 36 months. In the Intergroup Exemestane Study, after 58 months of follow-up, more fractures were found to have occurred in the exemestane group than in the tamoxifen group (P = .003). Whether exemestane results in less bone loss or fewer fractures than anastrozole when given as adjuvant hormonal therapy for breast cancer is currently being investigated in the MA-27 trial.

The findings of these studies suggest that the third-generation AIs available today in the United States are associated with loss of bone mass and/or increased risk of fracture, and that the magnitude of the change in bone may be tempered by prior exposure to tamoxifen and duration of aromatase inhibition. ASCO technology assessment and ASCO guidelines for use of bisphosphonates in women with breast cancer address the importance of monitoring patients for bone loss in this subpopulation.

Management of Bone Health in Women with a History of Early Stage Breast Cancer

Guidelines for screening and treating those at high risk for osteoporosis have been developed by the NOF and other health organizations. In general, consensus exists regarding osteoporosis screening in postmenopausal women older than age 65. Uniform
consensus is lacking regarding screening recommendations in other populations. ASCO has written specific bone health guidelines for women with a history of breast cancer. However, little prospective data exist regarding optimal screening intervals or treatment options for women with a history of breast cancer, although recommendations formulated for the general population may be reasonably applied to patients with a history of breast cancer until more breast-cancer–specific data become available.

The thresholds for screening and intervention for patients with a history of breast cancer may be lower than those for the general population. According to ASCO guidelines, a high risk of osteoporosis is conferred by age greater than 65; age 60 to 64 in women with a history of previous nontraumatic fracture, low body weight (less than 70 kg), a family history of osteoporosis, or other risk factors; postmenopausal status at any age in women receiving AI therapy; or cancer-therapy–associated premature menopause. Screening BMD is recommended for women who are deemed to be at high risk for osteoporosis, and ASCO guidelines recommend annual BMD measurement thereafter.

Assessment of risk of fragility fracture involves obtaining a history that includes assessment of modifiable and unmodifiable risk factors for osteoporosis. The physical examination is also an important component of risk assessment and may uncover signs that suggest an increased risk of osteoporosis, including tooth count less than 20, rib-to-pelvis distance less than 2 finger breadths, and wall-occiput distance greater than 0 cm. Measurement of the BMD, reported as grams per cubic centimeter and standard deviation (SD) from the mean in a reference population, can be assessed by using a variety of technologies; however, dual-energy x-ray absorptiometry is considered the gold standard. The World Health Organization defines osteoporosis as a BMD T-score 2.5 SDs less than the mean for a reference population, can be assessed by using a variety of technologies; however, dual-energy x-ray absorptiometry is considered the gold standard. The World Health Organization defines osteoporosis as a BMD T-score 2.5 SDs less than the mean for a reference population, and osteopenia as a BMD T-score from 1.0 to 2.5 SDs less than the young-adult mean. Measurement of biochemical markers of bone resorption, such as collagen cross-links in serum or urine, are associated with increased fracture risk. However, insufficient data exist to recommend use of these assays in routine care, although they may be useful in certain circumstances.

Counseling a patient on adequate calcium and vitamin D intake, weight-bearing exercise, fall risks, and healthy lifestyle choices can be done during assessment of risk factors for osteoporosis. If an individual is identified as being at risk for an osteoporotic fracture, the value of pharmacologic therapy should be considered, and the present guidelines uniformly recommend that those with a BMD T-score of less than -2.5 be considered for pharmacologic treatment of osteoporosis. The initiation of pharmacologic therapy for women with osteopenia lacks complete consensus and requires prior assessment of other risks for fragility fractures (Table 2).

Postmenopausal women with osteoporosis are a population at increased risk for fractures. However, postmenopausal women with osteopenia comprise a larger population, and, although women with osteopenia are less likely to experience a fracture than those with osteoporosis, the absolute number of fractures in this population may exceed that in postmenopausal women with osteoporosis. The National Osteoporosis Risk Assessment of nearly 15,000 postmenopausal women, 82% of women who experienced a fracture were found to have a T-score greater than -2.5. These results highlight the need for future research to develop strategies to stratify the fracture risk of women with osteopenia and to address fracture-reducing interventions. It is likely that certain breast cancer therapies may be included in future algorithms for fracture risk stratification.

Nutritional Interventions
Optimizing nutrition with a well-balanced diet is sound advice for all individuals. Adequate calcium and vitamin D intake is critical to the accumulation and maintenance of bone mass. In older adults, calcium intake should be 1000 to 1500 mg daily; however, only approximately 50% of this population meet this requirement. Consumption of 400 to 800 IU of vitamin D daily is an established recommendation. Postmenopausal US women typically consume only 600 mg of dietary calcium daily. Therefore, dietary modification and/or calcium supplementation would be appropriate in these individuals. Similarly, vitamin D intake may be insufficient in these individuals.

In a retrospective chart-review study of patients with early stage breast cancer who were receiving adjuvant follow-up care, only 10% of women were reportedly consuming a minimum of 1000 mg of calcium and 400 IU of vitamin D daily.
with ASCO guidelines in premenopausal women with breast cancer and chemotherapy-induced ovarian failure, researchers found that approximately 57% were consuming the recommended dosage of calcium and vitamin D and that only 72% exercised regularly.58 These study findings highlight the need to increase awareness and practice of appropriate diet and exercise.

**Pharmacologic Interventions for Osteopenia/Osteoporosis**

All of the agents presently approved by the US FDA for the prevention and treatment of osteopenia and osteoporosis may not be appropriate for patients with low bone mass and a history of breast cancer. Hormone replacement therapy (HRT) is generally not recommended for women with a history of breast cancer regardless of the estrogen- and progesterone-receptor status of the tumor. The Women's Health Initiative trial of combination HRT for healthy postmenopausal women with an intact uterus was stopped early because the test statistic for invasive breast cancer exceeded the predetermined stopping boundary and the risk of HRT was found to exceed its benefit.59 Moreover, the open, randomized HABITS trial (Hormone Replacement Therapy after Breast Cancer—Is It Safe?) found that, after 2 years, 26 of 174 women in the HRT group with at least 1 follow-up visit (15%) had a new breast cancer event compared with 7 of 171 in the placebo group (4%). As a result, the study investigators decided that HRT posed an unacceptable risk of breast cancer recurrence (relative hazard, 3.5; 95% CI, 1.5–8.1), and the trial was terminated early.60

The use of other hormone therapies may be considered cautiously in patients with a history of breast cancer. The SERM raloxifene is US FDA approved for the prevention and treatment of osteoporosis in postmenopausal women. However, manipulating the hormonal milieu of patients with a history of cancer with raloxifene may be particularly problematic because it may alter the efficacy of AI therapy and pose the risks documented for serial use of SERMs.61 Use of the parathyroid hormone teriparatide is contraindicated in patients who have had radiation therapy because it may increase the risk of osteosarcoma.62 Moreover, because it is an anabolic agent, teriparatide may stimulate the growth of micrometastatic disease.62 Although calcitonin increases BMD modestly, it is less effective than alendronate.63 Thus, bisphosphonates are generally considered the drugs of choice for treating low bone mass in patients with a history of breast cancer.64 In studies of postmenopausal osteoporosis, the oral bisphosphonates have been shown to decrease the risk of fracture by approximately 50%.65

**Ongoing Studies Investigating Bone Health in**

<table>
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<tr>
<th>NOF</th>
<th>Canadian</th>
<th>AACE</th>
<th>ASCO</th>
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<tbody>
<tr>
<td>T-score ≤2.0 by hip DXA with no risk factors</td>
<td>T-score ≤2.5</td>
<td>All postmenopausal women with low-trauma fracture</td>
<td>Women with a fragility fracture</td>
</tr>
<tr>
<td>T-score ≤1.5 by hip DXA with &gt;1 risk factor</td>
<td>T-score ≤1.5 and nontraumatic vertebral compression deformities, personal history of fragility fracture after age 40, or other clinical risk factors</td>
<td>All women in whom preventive interventions have been ineffective (bone loss continues or low trauma fracture occurs)</td>
<td>Women without fracture but with borderline low T-score (≤1.0) and other risk factors (to be decided on an individual basis)</td>
</tr>
<tr>
<td>Previous vertebral or hip fracture</td>
<td>Those receiving long-term glucocorticoid therapy</td>
<td>Women with borderline low T-scores (≤1.5) if risk factors are present</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All women with T-scores ≤2.5</td>
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**WOMEN WITH A HISTORY OF BREAST CANCER**

Patients with a history of breast cancer may comprise a unique subpopulation at risk for fragility fracture, and clinical trials are ongoing to define risks and interventions for this group of patients. Although the absolute increased risk of fracture associated with the first few years of AI therapy may be small (1% for hip fracture in those 60–70 years old after 2 years of AI therapy), early bone-preserving pharmacologic intervention may be warranted because treatment cannot completely restore bone strength or the structural integrity of the skeleton once severe damage to bone has occurred.17

Studies investigating the use of bisphosphonates in postmenopausal women receiving adjuvant AI therapy include the Zometa Femara Adjuvant Synergy Trial (Z-FAST) and its European counterpart, Zo-FAST:65 These 2 trials are investigating zoledronic acid, 4 mg, given every 6 months. In these 2 trials, women with hormone-receptor–positive breast cancer and T-scores less than -2.0, who were starting to receive 5 years of adjuvant letrozole, 2.5 mg daily, were randomized to receive zoledronic acid either at the initiation of the AI or when a T-score of less than -2.0 or fracture was found.66 The primary endpoint of the trials was the percentage change in lumbar spinal BMD between treatment groups. Results of Z-FAST showed that after 12 months, lumbar spinal BMD in those who immediately received zoledronic acid therapy increased by a mean of 2.0% compared with a mean decrease of 2.6% in those who received delayed zoledronic acid therapy, which resulted in a difference of 4.6% between groups ($P < .001$). Also after 12 months, total hip BMD in the immediate-therapy group increased by a mean of 1.4% compared with a mean decrease in the delayed-therapy group of 2.1%, which resulted in a difference of 3.5% between groups ($P < .001$).67 In the delayed-therapy group, patients required zoledronic acid therapy as early as a median of 6.3 months after the trial began because they had reached the protocol-defined T-score barrier of -2.0. This development argues for early use of supportive bisphosphonate therapy for prevention of bone loss instead of waiting for bone loss to occur before initiating treatment.68

However, zoledronic acid is not a US FDA-approved agent for this indication, and the optimal dose and dose interval for this high-potency bisphosphonate has not been defined. Results of a large, randomized, placebo-controlled study of zoledronic acid, 5 mg, given annually in patients with postmenopausal osteoporosis, were recently presented at the American Society of Bone and Mineral Research Annual Meeting. These results suggest that this regimen may have a role in the future care of patients with low bone mass.69 Additional studies may guide selection of drug, dose, and schedule.

The SABRE study is an ongoing, multicenter, phase III/IV, 3-arm study designed to evaluate the effects of risedronate, at the US FDA-approved dose and dosage interval, on BMD and bone turnover profiles in postmenopausal women with hormone-receptor–positive, early stage breast cancer treated with anastrozole. SABRE stratified patients by risk of fragility fracture (high, moderate, or low).70 The first results of this study will include 6-month data on markers of bone turnover and will be presented at the San Antonio Breast Cancer Symposium in December 2006.

The effect of chemotherapy on the bone mass of postmenopausal women being treated in the adjuvant setting is being investigated in a clinical trial sponsored by the Susan G. Komen Breast Cancer Foundation and the Memorial Sloan-Kettering Cancer Center Survivorship Program. This prospective, observational study seeks to identify changes in BMD and serum markers of bone metabolism to aid in defining chemotherapy’s impact on bone in postmenopausal women; accrual is ongoing.

The maintenance of BMD in premenopausal women diagnosed and treated for breast cancer is being explored in a series of clinical trials. These studies include the Cancer and Leukemia Group B protocol 79809, which is evaluating the use of zoledronic acid to prevent bone loss in patients who have localized breast cancer and chemotherapy-induced ovarian failure. This study is closed to accrual, and the results are being awaited eagerly.71 The investigators for the Austrian Breast Cancer Study Group Trial 12 of ovarian ablation with goserelin and either tamoxifen or anastrozole with or without zoledronic acid have reported that combination endocrine treatment without zoledronic acid frequently led to significant bone loss after 1 and 2 years of treatment (overall: -12% after 24 months; relative T-score: -1.2). Bone loss was considerably more severe in patients who had received anastrozole plus goserelin (mean -16%, relative T-score: -1.6) than in patients who had received tamoxifen plus goserelin (mean -8%, relative T-score: -1.0).
In both groups treated with zoledronic acid, BMD remained stable \((P < .0001)\).\textsuperscript{35} Although studies to date have shown the positive effect of bisphosphonate therapy in maintaining bone mass in this population, the impact of bisphosphonate therapy on fracture risk has not yet been determined.\textsuperscript{26,29,35}

**Novel Investigational Agents**

In addition to ongoing clinical trials exploring the means of optimizing the use of bisphosphonate therapy, novel agents that target bone loss are being investigated. The monoclonal antibody denosumab, which targets the receptor activator of the nuclear factor-κB ligand, has been reported to have a positive effect on bone mass. In a study of 412 postmenopausal women with low BMD, 12 months of denosumab therapy increased lumbar spinal BMD by 3% to 6.7% compared with an increase of 4.6% for alendronate and a decrease of 0.8% for placebo.\textsuperscript{72} Additional trials to determine the effect of denosumab on postmenopausal BMD are ongoing, as are studies of the ability of denosumab to maintain bone mass in cancer patients who are receiving hormonal manipulation, and studies investigating the efficacy of denosumab in treating metastatic bone disease.\textsuperscript{73} Other novel bone-targeting agents in development include drugs affecting cathepsin K, metalloproteinases, bone sialoprotein, bone morphogenetic proteins, the Src receptor tyrosine kinase pathway, and the integrins, including \(αvβ3\).

**Investigation of the Potential for Bone-Altering Therapies to Prevent Bone Metastases**

Bisphosphonates are potent inhibitors of osteoclast-driven bone resorption, and it has been hypothesized that, by limiting the release of bone-derived growth factors, reduction in bone resorption may reduce the risk of breast cancer relapse in bone. Mixed results of 3 clinical trials that explored the ability of the oral bisphosphonate clodronate to affect risk of relapse have been reported, and additional studies are ongoing.\textsuperscript{74,75} The National Surgical Adjuvant Bowel and Breast Program B-34 trial of adjuvant clodronate has completed accrual of more than 3000 women and is awaiting results. In addition, the South West Oncology Group (SWOG) is studying the use of bisphosphonates to reduce the risk of breast cancer relapse. The SWOG 0307 trial will enroll 6000 patients with stage I, II, or IIIA breast cancer who are receiving adjuvant breast cancer therapy to compare survival and BMD after 3 years of treatment with oral clodronate or ibandronate or with intravenous zoledronic acid. In addition to these 2 large US trials, the European Adjuvant Zoledronic Acid to Reduce Recurrence trial will compare the disease-free survival time and time to metastasis of patients with breast cancer who receive standard therapy alone with that of those who receive standard therapy plus zoledronic acid. These trials are expected to clarify the effect of adjuvant bisphosphonate therapy on survival, development of metastases, and BMD in patients with breast cancer.

The use of bisphosphonates in patients with cancer has been associated with a phenomenon termed “bisphosphonate-associated osteonecrosis of the jaw” (ONJ). The incidence of ONJ in patients with metastatic bone disease is estimated to range between 1% and 10%.\textsuperscript{77} ONJ has been noted in patients who were receiving oral bisphosphonates for benign conditions for which the incidence of ONJ was estimated to be 0.7 cases per 100 000 person-years of exposure.\textsuperscript{78} The SWOG 0307 trial will prospectively gather data that may clarify risk factors for ONJ, although the incidence of ONJ in this clinical trial is expected to be low. As data on ONJ accumulate, clinicians will need to assess the risk-benefit ratio of bisphosphonate therapy in patients being treated with curative intent.

**Conclusions**

Osteoporosis is a public health problem that affects millions of women. Low bone mass can be prevented and treated, and interventions can reduce the risk of fracture in patients with low bone mass. Ensuring adequate calcium and vitamin D intake is fundamental to bone health, in addition to engaging in regular weight-bearing exercise and consistently making appropriate lifestyle choices. Patients with a history of breast cancer may be at increased risk for osteoporosis because of the toxicities of anticancer therapy, including chemotherapy-induced premature ovarian failure and profound estrogen deprivation secondary to aromatase inhibition. Women with a history of breast cancer may comprise a unique subpopulation that may require more care when screening for and treating low bone mass than the general population. ASCO guidelines for the use of bisphosphonates and the management of bone health in women with breast cancer provide a clinically relevant tool for the treating medical oncologist and an algorithm for identifying risk factors for
low bone mass. They also provide guidance on screening for and treating osteoporosis in this patient population. Clinical trials are ongoing to investigate strategies likely to optimize bone health in women with a history of breast cancer.

REFERENCES

34. de Hoes H, Olschewski M, Kaufmann M, et al. Quality of life in goserelin-treated versus cyclophosphamide + methotrexate + fluorouracil-treated premenopausal and perimenopausal patients with node-positive, early breast can-


