

Managing Bone Loss in Cancer Patients

Deborah Pate, DC, DACBR

Cancer patients are at a higher risk for developing osteoporosis due to accelerated loss in bone density associated with many anticancer treatments. There are a variety of hormonal and non-hormonal treatments that may promote bone loss by inducing hypogonadism, which increases bone resorption and bone turnover. Examples include endocrine therapies for breast cancer (e.g., selective estrogen-receptor modulators [SERMs] and aromatase inhibitors [AIs]), androgen deprivation therapy (ADT) for prostate cancer, various chemotherapeutics and glucocorticoids (Table 1).¹ Surgical gonadal ablation, such as bilateral orchiectomy in prostate cancer and oophorectomy in breast cancer, also results in hypogonadism and bone loss in patients with hormone-sensitive tumors.

Table 1: Cancer Therapies Associated With Bone Loss

Therapy	Neoplasm
Bilateral orchiectomy	Prostate
Oophorectomy	Breast
Androgen deprivation	Prostate
Chemotherapy	Various
Cylophosphamide	Breast
Methotrexate/ifosfamide	Osteosarcoma
Alkylating agents	Hodgkin's/non-Hodgkin's lymphoma
Estrogen-receptor modulators	Breast
Aromatase inhibitors	Breast
Glucocorticoids/cyclosporine	Stem cell transplantation, Various malignancies
Radiation therapy	Various

The more pressing issue is that the bone loss which occurs with cancer therapy is generally more rapid and severe than postmenopausal bone loss in women or normal age-related osteoporosis in men. Rates of bone loss occurring with cancer therapy can be up to 10 times higher than normal.¹⁻⁴ In normal men, bone mineral density (BMD) decreases at a rate of 0.5 percent to 1 percent per year starting in midlife.⁴ Women have higher rates of bone loss around menopause - an average of 2 percent loss in bone mass per year for five to 10 years - which then declines over time.

Patients receiving cancer therapy experience significantly greater degrees of bone loss; for example, bone loss in men with prostate cancer on ADT can occur at a rate of 4 percent to 5 percent per year. Marked changes are detectable six months after initiation of hormonal therapy in men with prostate cancer.⁵ Significant bone loss can occur in women with breast cancer who are treated with AIs or other endocrine therapies. Results of recent trials found bone loss of 4 percent and 6.1 percent in the lumbar spine after two years and five years, respectively.⁶⁻⁸ This is on top of the "normal" bone loss associated with the aging process and menopause. Such bone loss leads to osteoporosis and, ultimately, fractures which diminish the quality of life and increase mortality.

I am not prepared to review all the countless studies done on the various therapies for cancer that are associated with bone loss. It is very clear that many of the drugs used in cancer treatment cause bone loss, some more than others. For the purpose of this article, we do not need to know

the specific rates of bone loss associated with each specific treatment. It is my opinion that if a patient had or is having treatment for cancer, the matter of avoiding bone loss should, at the very least, be considered and a plan for intervention and management should be implemented.

We already know that nearly one-third of postmenopausal, Caucasian women suffer from osteoporosis, and 25 percent have at least one vertebral deformity. It isn't difficult to determine that most women who undergo therapy for breast, ovarian and uterine cancer should be treated and/or monitored for osteoporosis.⁹ Similar precautions should be performed for men with prostate and testicular cancer.

It is unfortunate that even with all the information available, osteoporosis often remains undetected in patients with cancer until a bone fracture occurs. Studies suggest that bone density testing is performed in only 3 percent to 32 percent of high-risk patients.¹⁰ These patients are literally falling through the cracks. Several organizations have developed clinical guidelines for screening cancer patients for bone loss. The U.S. Surgeon General's office, the American Society of Clinical Oncology and the U.S. Preventive Services Task Force all have guidelines for women with risk factors, but none for men. The National Comprehensive Cancer Network does have clinical practice guidelines for men with prostate cancer. To summarize these guidelines, it is recommended that patients undergo BMD screening at baseline and at annual intervals to monitor for further bone loss.^{23,33} Just based on my minimal experience within my film-reading practice, these guidelines are not being used with any regularity. It is my opinion that as health care professionals, chiropractors can and should monitor their own patient pool for possible accelerated bone loss.

Just as a review, the standard approach for measuring bone loss is with DXA (dual-energy absorptiometry). The T-score reflects the number of standard deviations a patient's bone mass varies from the mean value for sex-matched young adults. Professional guidelines recommend only high-risk breast cancer patients with T-scores between -1 and -2.5 undergo monitoring on an annual basis for changes in BMD. However, many professionals (including myself) are of the opinion that all patients receiving therapy which depletes estrogen and male patients with prostate cancer should be monitored on an annual basis. The same guideline also should be used for patients being treated for osteoporosis. All patients should receive guidance regarding lifestyle changes such as proper exercise, calcium and vitamin D supplementation and dietary modification. Also patients with existing osteopenia and osteoporosis should be evaluated for conditions that further insult skeletal health, such as vitamin D deficiency, hyperthyroidism, hyperparathyroidism and hypercalciuria. Table 2 summarizes the presently accepted recommendations for monitoring patients with below-normal T-scores.

Table 2: T-Score

Risk Level	>-1 (Normal BMD)	-1 to -2.5 (Osteopenia)	<-2.5 (Osteoporosis)
Low Risk	Lifestyle changes Daily supplements Calcium & vitamin D Annual assessment of risk factors	Lifestyle changes Daily supplements Calcium & vitamin D Annual assessment of risk factors Annual BMD test	Lifestyle changes Daily supplements Calcium & vitamin D Annual assessment of risk factors

High Risk	Annual BMD test Lifestyle changes Daily supplements Calcium & vitamin D Annual assessment of risk factors	Annual BMD test Lifestyle changes Daily supplements Calcium & vitamin D Annual assessment of risk factors Consider therapy with bisphosphonates or raloxifene	Annual BMD test Lifestyle changes Daily supplements Calcium & vitamin D Therapy with bisphosphonates or raloxifene Annual assessment of risk factors
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The true incidence of bone fracture in older cancer patients (e.g., postmenopausal women) is likely underestimated as a result of the occurrence of undetected or "silent" fractures. It is estimated that up to two-thirds of all vertebral fractures may not be clinically diagnosed, since they are often caused by inconsequential trauma and often go unrecognized by patients and physicians.¹³ Routine BMD screening of at-risk patients can help identify bone loss and allows initiation of therapy as indicated, in order to avoid future fractures.

Existing treatment guidelines recommend that men and women who are osteoporotic should be strongly considered for bisphosphonate therapy.¹⁴⁻¹⁶ Bisphosphonates may even be used in conjunction with chemotherapy and endocrine therapy. Currently, bisphosphonate alendronate is approved in the U.S. for the treatment and prevention of osteoporosis in men and postmenopausal women. Other drugs including risedronate and ibandronate (oral and IV) also are approved for use in postmenopausal women, and alendronate and isedronate are approved for glucocorticoid-related osteoporosis in both men and women. Of course, these drugs do come with side effects, and the goal should be to preserve the patient's bone density so they might avoid developing osteoporosis without the need for interventional drugs. Unfortunately, for many patients with a low BMD at baseline, these drugs are often the only option for the prevention of further bone loss, along with lifestyle changes, exercise and nutritional support.

Chiropractors have been managing patients with osteoporosis for decades. They are in a unique position to monitor patients with osteoporosis, as they often treat these patients for musculoskeletal disorders. The health care community often is not aware of the service that most chiropractors provide their patients, such as nutrition counseling, exercise programs and lifestyle changes. In particular, cancer patients should be counseled on lifestyle changes that include proper nutrition, daily exercise and avoiding smoking and caffeine. Chiropractors can play a crucial role in helping to manage cancer patients at risk for osteoporosis.

It should be stressed that avoiding osteoporosis and future fractures is not just a matter of taking bisphosphonates regularly, but more importantly includes exercise, proper nutrition and lifestyle changes. Exercise is crucial; both weight-bearing aerobic exercise and muscle-strengthening exercise should be performed four to five times per week for at least 30 minutes a day.⁴ One of the better exercise programs that I've found is the "BEST Exercise Program," developed by an interdisciplinary research team from the University of Arizona and recommended by the National Osteoporosis Foundation (<http://nof.confex.com/nof/2005/techprogram/P256.HTM>).

Calcium and vitamin D are key for bone formation and maintenance. Patients should be counseled to eat foods rich in these nutrients and to get adequate sunlight exposure for vitamin D production.¹⁷ For patients unable to reach the daily target levels of calcium and vitamin D, bioavailable supplements are necessary. Total recommended calcium intake is 1,200 mg/day; any calcium should be taken in divided doses to improve absorption. Vitamin D recommended intake is 800 IU daily. New information regarding vitamin D emphasizes the great importance of this

vitamin. So keep updated on the most recent information, as recommended dosages may be increased, especially for older patients.

Routine monitoring of serum levels of 25-hydroxyvitamin D will help identify vitamin D deficiencies.¹⁸ A 25OHD concentration of 30 ng/ml or higher is desirable. All patients on bisphosphonate therapy should have routine assessment of their vitamin D status, along with BMD assessment. These patients are not being followed up. Chiropractors are seeing more and more cancer survivors, as these patients come in with musculoskeletal complaints. We need to make certain they are properly managed not only for the initial complaints, but also evaluated for possible bone loss, and that we continue to give them supportive care and counseling.

In summary, patients with cancer are at significant risk for bone loss and fracture, not only from their disease and age-related osteoporosis, but also from therapy for their malignancy. This loss of bone density has serious clinical consequences, increasing the risk for fracture and other morbidities that can decrease survival. Unfortunately, low awareness of this problem and infrequent screening result in many cancer patients with undiagnosed bone loss. Recognition of the magnitude of this problem and early identification of patients at risk for bone loss are key to effective management.

References

1. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. *J Clin Oncol*, 2000;18:1570-93.
2. Higano CS. Management of bone loss in men with prostate cancer. *J Urol*, 2003;170:S59-S63;discussion S64.
3. Hoff AO, Gagel RF. Osteoporosis in breast and prostate cancer survivors. *Oncology* (Williston Park), 2005;19:651-8.
4. Higano CS. Understanding treatments for bone loss and bone metastases in patients with prostate cancer: a practical review and guide for the clinician. *Urol Clin North Am*, 2004;31:331-52.
5. Maillefert JF, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J Urol*, 1999;161:1219-22.
6. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*, 2005;365:60-2.
7. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*, 2005;97:1262-71.
8. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*, 2004;350:1081-92.
9. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med*, 1997;103:12S-17S; discussion 17S-19S.
10. Smith MD, Ross W, Ahern MJ. Missing a therapeutic window of opportunity: an audit of patients attending a tertiary teaching hospital with potentially osteoporotic hip and wrist fractures. *J Rheumatol*, 2001;28:2504-8.
11. Diamond TH, Higano CS, Smith MR, et al. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. *Cancer*, 2004;100:892-9.
12. Ross RW, Small EJ. Osteoporosis in men treated with androgen deprivation therapy for prostate cancer. *J Urol*, 2002;167:1952-6.
13. Haczyński J, Jakimiuk AJ. Vertebral fractures: a hidden problem of osteoporosis. *Med Sci Monit*, 2001;7:1108-17.

14. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol*, 2003;21:4042-57.
15. Nelson HD, Helfand M, Woolf SH, et al. Screening for postmenopausal osteoporosis: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*, 2002;137:529-41.
16. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Prostate Cancer v.2, 2005. Available at www.nccn.org/professionals/physician_gls/PDF/prostate.pdf.
17. U.S. Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, Md.: U.S. Department of Health and Human Services, Office of the Surgeon General, 2004. Available at www.surgeongeneral.gov/library/bonehealth/html.
18. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*, 2004;80(suppl):1678S-88S.

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