Quantitation of Individual Risk for Osteoporotic Fracture

July 15, 2010
By William A. Wood, MD, MPH [1] and Hyman B. Muss, MD [2]

Dr. Balducci has presented a timely and useful overview of bone health in elderly patients undergoing cancer treatment. This topic has important implications, not only within geriatric oncology but also throughout the entire age spectrum. Dr. Balducci’s focus on the elderly population is especially relevant, as this group is at particularly high risk for bone complications over the course of cancer therapy. In his review, Dr. Balducci provides an introduction to the physiology of bone reabsorption and formation, and discusses risk factors for the interruptions in usual physiologic homestasis that lead to osteoporosis.

Dr. Balducci has presented a timely and useful overview of bone health in elderly patients undergoing cancer treatment. This topic has important implications, not only within geriatric oncology but also throughout the entire age spectrum. Dr. Balducci's focus on the elderly population is especially relevant, as this group is at particularly high risk for bone complications over the course of cancer therapy.

In his review, Dr. Balducci provides an introduction to the physiology of bone reabsorption and formation, and discusses risk factors for the interruptions in usual physiologic homestasis that lead to osteoporosis. He further links osteoporosis to a geriatric syndrome, frailty, highlighting the importance of this problem within the elderly population. Moving to the more specific effects of cancer therapy on bone health and available treatment options, Dr. Balducci describes selected specific circumstances (androgen deprivation in patients with prostate cancer, aromatase inhibitors in patients with breast cancer) and notes specific agents (bisphosphonates, denosumab [Prolia]) which may be of help and that deserve further study.

We wholeheartedly agree that this is a topic worthy of exploration and further investigation. This review is quite useful in contextualizing the discussion and orienting the reader to the relevant issues. Several professional groups, including the World Health Organization (WHO), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) have recently recognized the importance of this area as well, and a wealth of data regarding the role of bisphosphonates and newer agents such as denosumab is currently proliferating, inside and outside of the cancer treatment setting.

To make use of these data, and to guide decision-making in the clinic, we believe that the next step in moving the field forward is to more accurately quantitate individual patient risk of bone loss or osteoporotic fracture in a variety of clinical circumstances. This would subsequently allow for a prediction of expected risk reduction using particular pharmacologic agents, which could then be counterbalanced against the potential risk of the drug in question. Unfortunately, the issue here is the current relative lack of prospective randomized data to generate these kinds of risk models. In the absence of this, expert consensus recommendations and carefully designed observational cohort studies to further strengthen these recommendations will have to suffice. This is the approach that pediatric oncologists have used over the last several decades to construct risk-based care for children with cancer or survivors of childhood cancer, in order to mitigate potential late effects of therapy.

TABLE 1

Risk for Major Osteoporotic Fracture or Hip Fracture for Elderly Females of Different Ages in the Absence of Anticancer Therapy, by the Online FRAX Calculator
Fortunately, in the case of osteoporosis in older individuals, we do have available a model that allows for a background quantitation of individual risk for osteoporotic fracture in the absence of cancer therapy. This algorithm, FRAX, has been developed by the WHO using population-based cohorts in several different parts of the world, and is easily publicly accessible online at [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX).

In addition to the results of a bone mineral density test, a clinician can input several clinical risk factors (age, weight, height, previous fracture, family history, smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, alcohol use, and femoral neck BMD T-score) to receive a 10-year probability of any major osteoporotic fracture or a hip fracture. Intervention is typically recommended for patients with a 10-year FRAX risk of 3% for hip fractures and more than 20% for all major fractures. Age remains an especially important risk factor for osteoporosis, as illustrated in Table 1, which further points out the relevance of this issue in older patients treated for cancer.

Upon this background, a clinician can overlay the risk from anticancer therapy, depending on the type of disease and the type of risk assessed (eg, bone loss and fracture in the presence or absence of known skeletal metastases). Perhaps the three best studied malignancies for this type of assessment are breast cancer, prostate cancer, and multiple myeloma, and ASCO guidelines are available for risk assessment in two of these. If a patient is deemed to have sufficient risk for fracture to warrant an intervention, there are several possible treatment options available. In the cancer setting, the best data in terms of patient numbers and efficacy appear to be associated with the use of more potent, often intravenously administered, bisphosphonates; data are also emerging for the use of the RANK-L (receptor activator for nuclear factor-κ-B ligand) inhibitor denosumab.

It is challenging to properly assess the risks and benefits of each particular agent in order to decide which agent is best used in which setting. Some published data come from non-cancer-patient populations at risk for osteoporotic fracture, and it is difficult to know how to extrapolate these data for patients who are exposed to treatments that further accelerate bone loss, and who may be at higher risk for treatment-related side effects such as osteonecrosis of the jaw. Additionally, the data suggesting that bisphosphonates may have a benefit in preventing cancer relapse (as in early stage breast cancer) are alluring, but this hypothesis is still largely unproven and in any case not relevant to the issue of osteoporotic fracture.

Thankfully, disease-specific data are emerging for the role of bisphosphonates and RANK-L inhibition in preventing bone loss in specific cancers. As noted previously, randomized trials have demonstrated the benefit of zoledronic acid (Zometa) and denosumab in maintaining bone density in early stage breast cancer. Zoledronic acid has also been shown to increase BMD in hypogonadal patients with prostate cancer. The results of an ongoing trial of denosumab in patients receiving androgen-deprivation therapy for prostate cancer are awaited, as are other trials investigating different agents in disease-specific settings.

**FIGURE 1**

Risk-Adapted Approach for Management of Bone Health in Elderly Cancer Patients

How can a risk-adapted approach be used in the clinic at this time? The NCCN recently convened a task force on bone health in cancer care, and the recommendations of this group seem a reasonable place to start. In their schema, cancer patients at risk for bone loss should undergo baseline bone mineral density (BMD) testing, history and physical examination, and FRAX analysis via the WHO algorithm. Lifestyle modification, and dietary supplementation with calcium and vitamin D should be discussed with all patients. Further pharmacologic therapy and follow-up DEXA scanning depend on the specific T-score on initial BMD scan, or on an elevated risk as determined by the FRAX score. An example of a risk-adapted approach is shown in Figure 1.

This kind of approach, in which a risk assessment is based on general population data combined with therapy-specific considerations, appears to be the right way to think about risk-adapted care moving forward. Construction of large observational cohort studies to complement the phase III trial data will be helpful to further refine patient assessment and treatment algorithms for bone health in elderly patients.
cancer patients.

**Financial Disclosure:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**

**Suggested Reading**


**Source URL:**

**Links:**