NCCN Bone Health Task Force: Key Recommendations

Presented by Azeez Farooki, MD

Abstract

For patients with advanced cancers involving bone, the standard of care for maintaining bone health is the use of antiresorptive therapies such as bisphosphonates, selective estrogen-receptor modulators, and denosumab. However, although long-term adverse events are rare and the risk-benefit ratio of these agents is usually markedly in favor of treatment, clinicians should be aware that they can occur. At the NCCN 19th Annual Conference, Dr. Azeez Farooki presented the key findings of the NCCN Bone Health Task Force, focusing on such topics as screening for osteoporosis; the controversial use of drug holidays from chronic bisphosphonate therapy; the provocative yet unclear story surrounding the potential anticancer benefits of antiresorptive agents; imaging for metastatic bone disease; and safety considerations linked to calcium supplements, vitamin D, and bone-strengthening agents. (*J Natl Compr Canc Netw* 2014;12:813–816)

"The antiresorptives certainly are the king of the hill in cancer therapy, both for benign bone disease and advanced cancer involvement of the bone," announced Azeez Farooki, MD, an endocrinologist at Memorial Sloan-Kettering Cancer Center, New York City, who served on the NCCN Bone Health in Cancer Care Task Forces in 2008 and 2012. Bisphosphonates and denosumab have been extensively studied both for prevention of bone loss due to cancer therapies and for prevention of skeletal-related events (SREs). Although the risk/benefit ratio is usually markedly in favor of treatment, clinicians should be aware of potential adverse effects from these potent antiresorptive agents. Duration of treatment with bisphosphonates and denosumab appears to modulate the risk of osteonecrosis of the jaw and atypical femur fracture (AFF).

Presented by Azeez Farooki, MD, from Memorial Sloan-Kettering Cancer Center, New York, New York.

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Correspondence: Azeez Farooki, MD, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 284, New York, NY 10065. E-mail: farookia@mskcc.org

Screening for Osteoporosis to Reduce the Risk of Fracture

Characterized by low bone mass and structural deterioration of the microarchitecture of bone tissue, osteoporosis leads to an increased risk of fracture. "This is a silent disease until fracture occurs and is akin to hypertension," noted Dr. Farooki. Among the many risk factors for osteoporosis, including glucocorticoid therapy, parental history of hip fracture, low body weight, current cigarette smoking, and excessive alcohol consumption, Dr. Farooki discussed 2 in detail: advancing age and previous fracture.

Studies have shown that the 10-year probability of any fracture (except of forearm fractures in men) increases with age and T score.[1] At any given T score, older age equaled higher fracture risk. "Age is an independent risk factor," said Dr. Farooki. In addition, prior fracture is a signal of future fracture. "The same can be said of skeletal-related events: one event can increase the risk of a future event," he added. As expected, the risk of fracture is higher in those with osteoporotic bone mineral density (BMD) T scores.

Furthermore, Dr. Farooki briefly mentioned the role of the online FRAX analysis, which uses epidemiologic data from many different countries as well as factors such as age, height, and weight to estimate the 10-year patient-specific absolute fracture risk. FRAX analysis indicates the need for treatment if the risk for any major osteoporotic fracture is more than 20% or the risk for hip fracture is more than 3%. "Hip fracture is a devastating fracture, with a mortality rate of 20% the year after in many analyses," he noted.

Bone loss has been associated with various cancer therapies, including aromatase inhibitor (AI) therapy in postmenopausal women and AI therapy and gonadotropin-releasing hormone (GnRH) agonists in premenopausal women with breast cancer, bone marrow transplantation in patients with hematologic cancers, and androgen deprivation therapy (ADT)/ and GnRH agonists in men with prostate cancer. For AI-induced bone loss, the slope seems to be highest in the first 2 years of therapy, revealed Dr. Farooki, and all 3 of the AIs (anastrozole, exemestane, and letrozole) have been shown to increase the risk of fracture compared with tamoxifen. Osteoporotic fracture is a concern in men, because up to 25% of men older than 50 suffer one, he added. ADT appears to increase the risk of fracture in men (relative to the number of doses), according to Dr. Farooki. "This is something we should pay attention to in our male cancer patients and survivors."

The NCCN Bone Health Task Force created an algorithm for management of bone health in cancer patients in the United States. For those at increased risk for bone loss or fracture, first steps include history, physical examination, BMD screening, and FRAX analysis (if the patient is osteopenic). Another important consideration is height loss; silent compression of vertebrae may indicate the need for treatment. In addition, necessary lifestyle modifications and calcium and vitamin D intake require attention.

T scores, based on bone density, predict fracture risk and can guide subsequent steps. For instance, if a patient has a T score greater than negative 1, a repeat dual-energy X-ray absorptiometry scan should be performed every 2 years.

For patients on bisphosphonates, a drug holiday should be considered after 3 years of treatment on a case by case basis per recent FDA guidance.[2] If a patient has a T score between negative 1 and negative 2, 25 [OH] vitamin D levels and other laboratory values should be checked. For cancer patients at risk for bone loss who have a T score less than 2 or a FRAX risk analysis above the thresholds for treatment, the 25 [OH] vitamin D level and other laboratory values should be checked and drug therapy strongly considered.

The Debate Over Drug Holidays and the Anticancer Effects of Bisphosphonates

Dr. Farooki raised the question of drug holidays from chronic bisphosphonate therapy (after 3 to 5 years), suggesting that it represents an evolving question, with few data.[2]

The use of antiresorptive agents to reduce tumor recurrence or improve long-term outcomes has been explored,[3,4] with provocative data still unfolding. A meta-analysis of more than 8,000 postmenopausal women with early-stage breast cancer who received zoledronic acid indicated a highly significant disease-free survival benefit.[3] Furthermore, according to a more recent update, no effect was seen on disease outcomes in premenopausal women, but women who had low levels of reproductive hormones did appear to have a relative clinical benefit.[4] This update was revealed after the NCCN Bone Health Task Force met and is itself debated now. During the meeting, the task force felt the large amount of data available in breast cancer was provocative but not conclusive enough to make recommendations.

The task force does not recommend the use of osteoclast targeted therapy for the prevention of bone metastases in prostate cancer.

Metastatic Bone Disease: Focus on Imaging

The most common site of metastases is the skeleton, with bone lesions causing SREs in many patients with breast, prostate, and lung cancers as well as multiple myeloma, said Dr. Farooki. The composite endpoints of SREs include spinal cord compression, need for radiation or surgery to bone, and pathologic fracture. "Hypercalcemia is not considered anymore and definitely has become rare in the era of potent antiresportives," he revealed. Furthermore, SREs are extremely common in patients with thyroid cancer.[5]

The algorithm for imaging for patients with cancer in the United States centers on the clinical suspicion of bone metastases. In such cases, a bone scan should be performed to guide the next steps. If the bone scan is negative and there are no symptoms, the lesions are typical of nonmetastatic disease. However, if the bone scan is positive or there are symptoms, plain film should be ordered to determine the presence of metastases. If the plain film is indeterminate, other imaging options include CT and MRI.

The imaging modalities used in metastatic bone disease—^{99m}Tc-MDP scan, ^{18}F Na PET/CT scan, and ^{18}F-fluorodeoxyglucose (FDG)-PET/CT scan—were briefly reviewed by Dr. Farooki. "A relatively new bone

Table 1 The Dose and Frequency of Administration of Zoledronic Acid and Denosumab for Treating Osteoporosis, Preventing Bone Loss From Endocrine Therapies, and Preventing Skeletal-Related Events in Patients With Cancer

		Zoledronic Acid		Denosumab	
Indication		Zometa (4 mg)	Reclast (5 mg)	Prolia (60 mg)	Xgeva (120 mg)
Reduction in skeletal-related events due to advanced cancer involving the bone	Bone metastases (monthly)*	√	–	–	√
	Hypercalcemia	√	–	–	–
	Multiple myeloma (monthly)	√	–	–	–
Reduction in bone loss	AI-induced bone loss	√	–	√	–
	ADT-induced bone loss	√ (every 3 mo or yearly)	–	√ (every 6 mo	–
	Postmenopausal osteoporosis	–	√ (yearly)	√ (every 6 mo)	–
	Prevention of postmenopausal osteoporosis (osteopenia) (once every 2 y)	–	√	–	–
	Men	–	√	√	–
	Glucocorticoid therapy (yearly)	–	√	–	–

Abbreviatons: ADT, androgen deprivation therapy; AI, aromatase inhibitor.
*Bismark study in breast cancer; Coleman RE, Wright J, Houston S, et al. Randomized trial of marker-directed versus standard schedule zoledronic acid for bone metastases from breast cancer. J Clin Oncol 2012:30(Suppl): Abstract 511.

scan is the ^{18}F Na PET/CT bone scan, which appears to have some advantages over the technetium bone scan," he said The standard uptake values can be obtained with the newer scans but not with the technetium scan, and the newer scans may prove to be more useful in osteoblastic metastases. Benefits of ^{18}F-FDG-PET/CT scanning to assess response are higher spatial resolution and quantitative capability. In addition, changes in FDG uptake seem to correlate with clinical response and changes in breast cancer tumor markers, added Dr. Farooki. Finally, combination FDG and ^{18}F Na PET scanning can measure both sclerotic and lytic lesion response, although it is expensive, he noted.

Treatment of Bone Disease: Focus on Calcium, Vitamin D, and Antiresorptive Agents

The goal calcium intake is 1,200 mg/day, stated Dr. Farooki. "Too much calcium through supplements will increase the risk of kidney stones." He also noted the importance of careful scrutiny of exactly how much calcium a patient is taking in from all sources, including both diet (food) and supplements. An unanswered question regarding the use of calcium is the potential increase in cardiovascular disease (myocardial infarction from one meta-analysis[6]), although Dr. Farooki admitted that more data are needed to conclusively settle this issue.

For vitamin D, more than 10,000 IU/day could lead to toxicity. The target vitamin D level is debatable, although 3 national organizations that Dr Farooki cited favor a level of at least 30 in patients with bone loss. The IOM review from 2010 suggested that a level of 20 ng/mL is sufficient for all populations. Patients with osteoporosis, chronic kidney disease, and hepatic failure are among those who should be screened for vitamin D insufficiency, although Dr. Farooki urged caution when treating patients at risk for hypercalciuria and hypercalcemia with vitamin D.

Antiresorptive agents have multiple roles in patients with cancer: to prevent bone loss due to cancer therapies and osteoporotic fractures in those with benign bone disease and to prevent SREs and relieve pain in those with advanced cancer involving the bone. The bisphosphonates and denosumb are well known and shown to have the above benefits. The anabolic agent teriparatide is an FDA-approved option

to reduce the risk of osteoporotic fractures as well, although it is contraindicated in patients with a history of radiation to the skeleton, with active malignant bone disease. Also, current task force opinion is that it is not recommended for patients with recent cancer. In addition, a monoclonal antibody against sclerostin is a promising but still investigational anabolic.

Denosumab has been shown to be superior to zoledronic acid for skeletal morbidity in both metastatic breast and prostate cancer, although the risk of hypocalcemia and hypophosphatemia is higher. Cumulative treatment durations beyond that of the pivotal studies with these agents are largely untested in terms of potential adverse effects. Dosing schedules for malignant bone disease are more intensive than those to treat osteoporosis or prevent bone loss and may carry a higher risk of "long-term" adverse effects (osteonecrosis of the jaw and AFF; Table 1). The BISMARK study, though underpowered, did not support less-intensive dosing. The NCCN Task Force agreed with the guidelines from ASCO regarding the use of antiresorptive therapy in breast cancer: therapy should be continued until evidence of substantial decline in general performance status is seen. A new radiopharmaceutical, radium-223, has been approved by the FDA for men with advanced prostate cancer based on a mortality benefit; the drug also reduced SREs in patients already receiving intravenous bisphosphonates.

Safety Considerations with Antiresorptive Agents

In closing, Dr. Farooki briefly addressed adverse events associated with bisphosphonates and denosumab. Among these are acute-phase reactions, AFF, hypocalcemia, renal complications, and osteonecrosis of the jaw (a rare complication of antiresorptive therapy that is affected by the duration of treatment). Dr. Farooki clarified that that raloxifene and estrogen have never been associated with AFF or osteonecrosis of the jaw; however, raloxifene and estrogen are not advised for patients with estrogen-dependent malignancies.

The risk of AFF appears to be related to the length of exposure to bisphosphonates and higher cumulative doses.[7] Although a rare phenomenon, a subtrochanteric stress reaction of the lateral femur has led to transverse fracture from long-term intravenous use of bisphosphonates.[7] "You can see these types of stress reactions prior to the fracture on various imaging modalities, but they may be underappreciated," stated Dr. Farooki. Other risk factors for iatrogenic AFF include younger age, Asian race, low vitamin D levels, use of multiple antiresorptive agents, and use of glucocorticoids or proton pump inhibitors, he added.

A clinical indicator of such fractures appears to be prodromal symptoms of thigh pain, noted Dr. Farooki. About 75% of these patients have a nagging, consistent pain in the anterior thigh or groin while walking, so imaging should be considered for these patients. These features are fundamentally different from those of common osteoporotic femur fractures and strongly suggest a distinct pathogenesis.[8]

Current expert consensus is to avoid concomitantly treating with 2 different antiresorptive therapies. The FDA suggested reassessment of risk status and the need to continue drug therapy after 3 to 5 years of bisphosphonate therapy. They also suggested considering a drug holiday where appropriate. To prevent hypocalcemia from potent antiresorptive agents (intravenous bisphosphonates and denosumab), the serum 25 [OH] D and calcium levels should be measured to ensure adequacy; hypovitaminosis D and hypocalcemia should be corrected before these drugs are administered, concluded Dr. Farooki.

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