Bone Related Events in High Risk Prostate Cancer

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Purpose: We provide recommendations for defining and treating bone related events in high risk prostate cancer.
Materials and Methods: A focused literature review was done.
Results: Men with prostate cancer often have osteoporosis and osteopenia even before initiating androgen deprivation therapy. After starting androgen deprivation therapy they experience accelerated bone loss. Bone mineral density is the most common tool to assess the degree of bone loss, although the use of bone turnover markers for this purpose is being actively explored. Bisphosphonates are effective for increasing bone mineral density and treating osteoporosis. The benefits derived from bisphosphonates should be weighed against the adverse effects, including the risk of osteonecrosis of the jaw. Treatment is indicated in patients with prostate cancer with osteoporosis and it may be considered in patients with osteopenia and/or additional risk factors. The time of initiation of therapy and duration of treatment have not been conclusively established.
Conclusions: Prolonged androgen deprivation therapy results in bone loss and it has a potential to impact quality of life. Additional research is needed to characterize patients who would benefit from therapy and optimize strategies to prevent osteoporosis.

Key Words: prostate, bone and bones, prostatic neoplasms, androgen antagonists, osteoporosis

Androgen deprivation therapy is commonly used in patients at high risk who have localized disease.[1,2] The adverse effects of ADT have been well described, including anemia, cholesterol and lipid changes, erectile dysfunction, fatigue, hot flashes, weight gain and osteoporosis.[3] We focused on bone related events in patients with localized nonmetastatic prostate cancer undergoing ADT. We address some of the more common clinical questions, including how frequently BMD measurements should be made, which patients should be started on drug therapy, when therapy should be initiated, how long therapy should last and which agents have been used to date for treating ADT induced bone loss.

RISK FACTORS FOR BONE LOSS IN THE PATIENT POPULATION

Risk factors for osteoporosis have been well described, such as hypogonadism (including that occurring with ADT), a family history of osteoporosis, low body weight, a sedentary life-style, tobacco use, excessive alcohol consumption, corticosteroid use, low vitamin D and previous fractures.[4]

Prostate Cancer

Osteopenia and osteoporosis are present in 29% to 38% and 5% to 25%, respectively, of men with prostate cancer before ADT initiation.[5,6] Men with prostate cancer appear to have low vitamin D, measured as 25-hydroxy vitamin D, perhaps accounting for the prevalence of osteopenia before starting ADT.[5] Low vitamin D results from aging, low sun exposure with associated decreased vitamin D synthesis and poor dietary habits. Low or inadequate calcium intake may exacerbate the negative effects that vitamin D insufficiency has on bone.

ADT and Bone Loss

After attaining peak bone mass in the mid third decade of life men normally experience a 0.5% to 1% loss of cortical bone mineral density yearly.[7] Iatrogenic decrease in testosterone by bilateral orchiectomy or an LHRH analogue can accelerate bone loss and may result in osteoporosis or osteopenia.[8] Androgen deprivation interferes with bone metabolism and the normal balance between bone formation and resorption. The result is increased bone resorption due to osteoclast stimulation. With ADT testosterone and estrogen decrease significantly, while biochemical markers of bone turnover increase.[9] BMD has been found to decrease by 1.9% to 4.6% in the lumbar spine and 1.1% to 3.9% in the femoral neck in patients who received LHRH analogues for 12 months.[10,11] Male sex offenders undergoing surgical castration have a spinal bone loss of about 4% yearly.[12]

ADT and Fractures

The most serious skeletal consequences of ADT are osteoporosis and an increased risk of fractures. According to small retrospective studies the incidence of fractures in men undergoing ADT is 5% to 14%.[13-16] Shahinian et al reported on 50,613 patients with prostate cancer listed in the Surveillance, Epidemiology and End Results, and Medicare databases who were undergoing ADT.[17] There was a 19% incidence of fractures in men undergoing ADT compared to 12% in those not treated with ADT. The relative risk of fracture increased with increasing doses of LHRH analogues and an increased duration of ADT. ADT also decreases lean body mass and increases frailty and the risk of falls.[18,19]

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MEASUREMENT OF BONE LOSS

DXA and QCT

BMD is a strong predictor of fracture risk.[20,21] BMD can be measured by 2 techniques, including DXA and QCT. DXA has several advantages. It can be used to measure BMD at multiple sites, is associated with low radiation exposure, costs little and can be done in rapid examination time. Its limitation is that it measures the density of cortical and trabecular bone, and for this reason BMD may be falsely increased in the presence of osteoarthritis.[9] QCT can measure cortical or trabecular bone separately and it has greater sensitivity than DXA. However, it is less readily available and more costly, and it requires strict adherence to protocol for reproducibility. The BMD criteria for diagnosing bone loss in men are adapted from WHO T score definitions. Osteopenia is defined as a BMD of between 1.0 and 2.5 SD below the mean in young adults and osteoporosis is defined as a BMD of more than 2.5 SD below the mean in young adults (see table). Baseline measurement of BMD is recommended in all patients with risk factors, such as increased age and prolonged anticipated ADT duration, before starting ADT. The frequency with which patients should be monitored depends on the baseline T score (range 6 to 24 months) (fig. 1).

Markers of Bone Metabolism

A biochemical approach to assessing bone loss in the presence of metastasis to the bone is via measurements of bone metabolism markers.[22] Bone turnover markers that have been found to reflect bone formation are serum bone specific alkaline phosphatase, osteocalcin, procollagen type 1 carboxyterminal propeptide and procollagen type 1 aminoterminal propeptide. Bone markers reflecting bone resorption are NTx, peptide-bound C-telopeptide of type 1 collagen, pyridinium cross-links and receptor activator of nuclear factor-κB ligand.[23] To date a few groups have addressed the clinical usefulness of measuring some of these bone markers for establishing the diagnosis of metastasis to the bone as well as prognosis in patients with prostate cancer.[24,25]

The question of whether bone turnover markers can be used to determine response to antiresorptive therapy with bisphosphonates has been addressed in various studies. For example, the measurement of urinary NTx and serum osteocalcin to assess the response to bisphosphonate therapy was found to be useful in a study in approximately 1,200 healthy postmenopausal women receiving alendronate to prevent osteoporosis.[26] In this study changes from baseline of at least 40% in urinary NTx and of at least 20% in osteocalcin 6 months after the initiation of bisphosphonate therapy correlated with the long-term response to treatment with alendronate. A minimum change of 30% to 60% in serum peptide-bound C-telopeptide of type 1 collagen was found to correlate with the response to therapy with bisphosphonates in other studies.[27,28]

WHO osteoporosis classification

Classification	BMD (SD*)
Normal	Greater than −1.0
Osteopenia	−1.0 to −2.5
Osteoporosis	Less than −2.5

* Derived from the mean peak value in young adults.

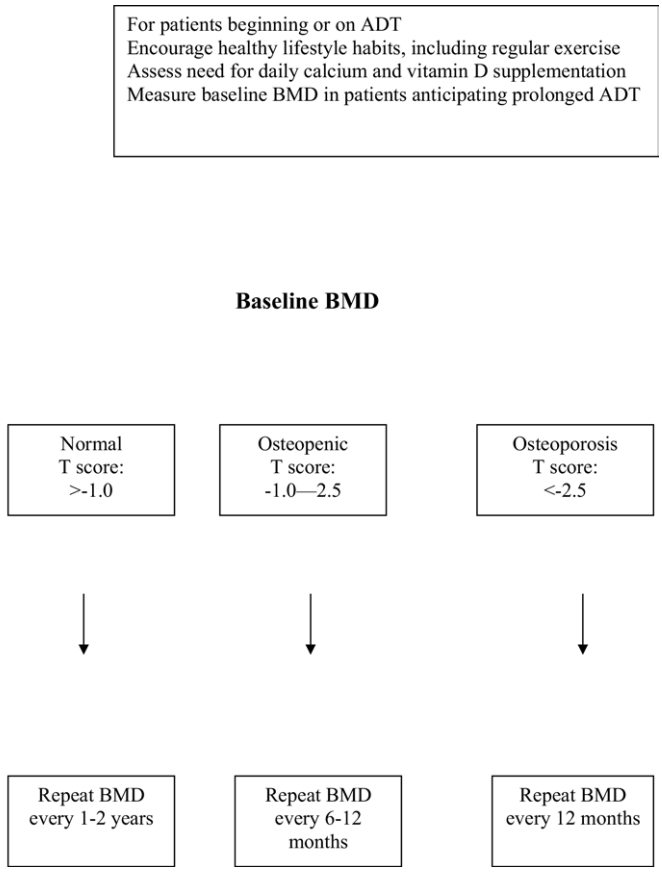

FIG. 1. Recommended schedule for monitoring bone loss in patients with prostate cancer undergoing ADT. Adapted from Higano.[45]

Briefly, bone turnover markers have been shown to aid in the diagnosis and prognosis of metastatic bone disease in patients with prostate cancer as well as in the assessment of the response to therapy and compliance with bisphosphonates. However, to date they have not been incorporated routinely into clinical practice in the care of patients with prostate cancer.

THERAPY

Not all men have osteoporosis while on ADT. Differences in peak bone mass and the rate of bone loss vary individually. Careful assessment of risk factors should be made in all patients on ADT. Before starting ADT patients should have calcium and vitamin D measured and adequately replaced. Dietary supplementation with 1,200 to 1,500 mg calcium daily and 400 IU vitamin D daily decreases bone loss in the hip and spine, and decreases the fracture incidence.[29]

No oral or intravenous medication has been approved to prevent bone loss from ADT. However, there exists a body of literature on various compounds for treating bone loss from ADT in men with prostate cancer. These agents include bisphosphonates, estrogens and pure antiandrogens.

Bisphosphonates

Bisphosphonates inhibit osteoclast mediated bone resorption, osteoclast precursor activity and osteoblast induced