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Rationale for zoledronic acid therapy in men with hormone-sensitive prostate cancer with or without bone metastasis

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Abstract

Men with prostate cancer are at risk for bone loss and skeletal complications throughout the course of their disease. Bone loss is prevalent in many men with prostate cancer at initial diagnosis, and initiating androgen deprivation therapy results in accelerated bone resorption, leading to bone loss and an increased risk of fracture. These men are also at high risk for disease progression and bone metastases that can result in significant skeletal morbidity, including pathologic fracture, spinal cord compression, and debilitating bone pain requiring additional therapy. Excessive osteoclast activity plays a central role in the pathophysiology of bone disease at each stage of prostate cancer disease progression. Zoledronic acid, a highly potent inhibitor of osteoclast-mediated bone resorption, has increased bone mineral density in men receiving androgen deprivation therapy and is the only bisphosphonate that has shown statistically significant reductions in skeletal morbidity in patients with bone metastases from prostate cancer. Furthermore, preclinical evidence suggests that zoledronic acid has antitumor activity in prostate cancer models. Recently, a treatment algorithm was developed by the 3rd International Consultation on Prostate Cancer recommending the use of zoledronic acid for the prevention of skeletal complications in patients with bone metastases from prostate cancer, regardless of their hormone status, and for the prevention of treatment-induced bone loss in patients without evidence of bone metastases. According to this algorithm, zoledronic acid should be considered for the prevention of skeletal morbidity in patients with prostate cancer throughout their treatment continuum.

Keywords: Bisphosphonates; Prostate cancer; Hormone sensitive; Bone metastases; Bone loss

1. Introduction

Worldwide, more than half a million men are diagnosed with prostate cancer, and at least 200,000 will die of their disease each year [1]. In the United States alone, prostate cancer is the most common nondermatologic cancer, with more than 230,000 new cases diagnosed annually, and it is the second leading cause of cancer death among men [2]. Approximately 50% of patients with prostate cancer will have disease recurrence after local radiation therapy or prostatectomy and most will receive androgen deprivation therapy (ADT) via pharmacologic or surgical castration [3,4]. Furthermore, bone metastases will develop in 65% to 75% of men with advanced prostate cancer, which is associated with significant skeletal morbidity, including severe bone pain and pathologic fractures. Consequently, the management of bone health represents a significant clinical challenge in the treatment of these patients [5].

The bone health of men with prostate cancer is at risk throughout the natural history of disease (Fig. 1) [6]. A variety of factors can contribute to the bone loss observed in these patients, including age-related bone loss. Nearly 1.5 million American men 65 years or older have osteoporosis [7], and bone mineral density (BMD) is often already low in men with prostate cancer at initial diagnosis [8–11]. In a study of 41 hormone-naive men with locally advanced prostate cancer, trabecular BMD of the lumbar spine assessed using quantitative computerized tomography revealed that 31% of patients were osteopenic (T score between −1.0 and −2.5), and 63% were osteoporotic (T score <−2.5) [11]. Treatment of these patients with ADT, the treatment of choice for patients with increasing prostate-specific antigen

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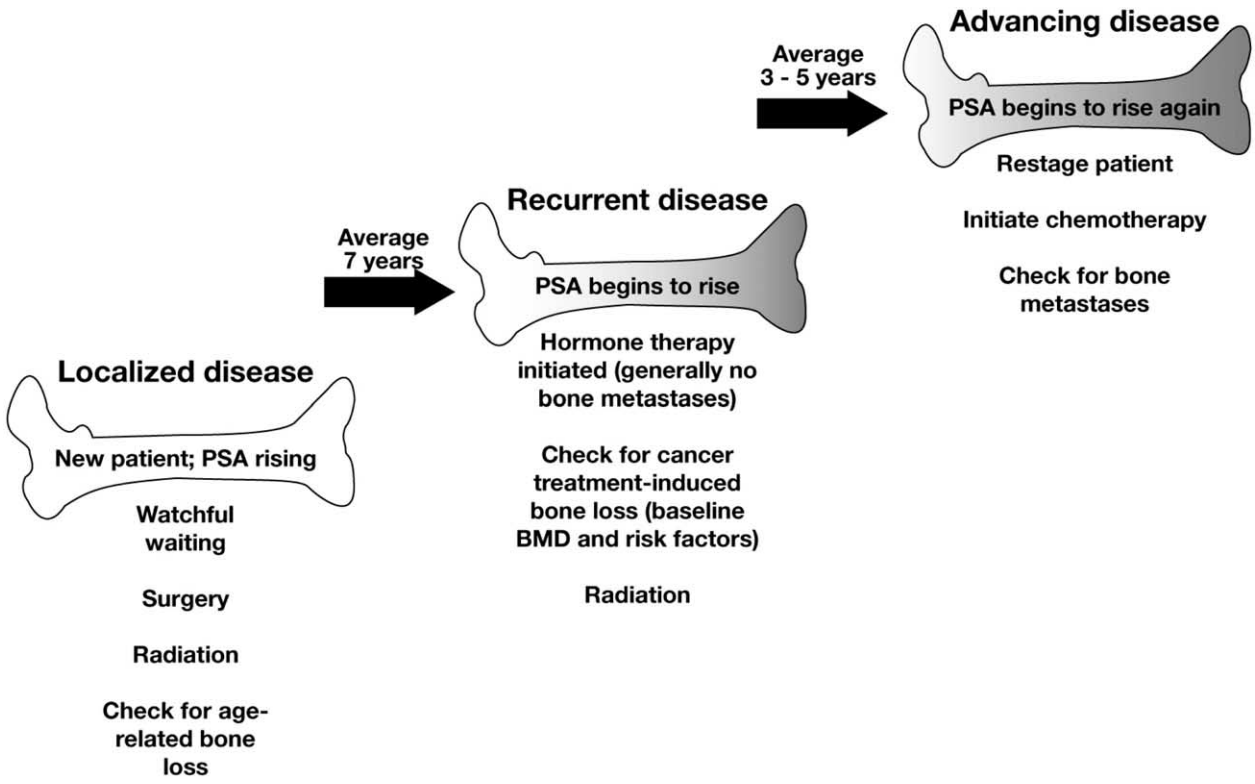

Fig. 1. Disease stages of prostate cancer. After diagnosis of prostate cancer, patients can survive for many years before disease progression and are at risk for skeletal complications throughout the course of their disease. BMD, bone mineral density; PSA, prostate-specific antigen. (Adapted from Crawford [6].)

(PSA) levels after failed local therapy, increases osteoclast activity and bone resorption, resulting in further compromise of bone integrity and an increased risk of fractures [8,12–14]. Furthermore, because early hormonal treatment of men with prostate cancer can improve survival and significantly delay the onset of disease progression, these patients may receive ADT for an extended period, resulting in accumulating and clinically significant cancer treatment-induced bone loss (CTIBL) [12,15–17].

The development of advanced disease and bone metastases in patients with prostate cancer, with the concomitant up-regulation of osteoclast activity, leads to local osteopenia and clinically significant skeletal complications. Bone metastases are classified according to their radiographic appearance as osteolytic, osteoblastic, or mixed lesions [5]. Patients with prostate cancer develop primarily osteoblastic lesions, but these lesions are also associated with markedly increased osteoclastic activity and increased bone resorption [18]. Evidence from biochemical studies confirms increased osteolytic and osteoblastic activity in patients with bone lesions from prostate cancer. In a recent study, urinary levels of N-telopeptide, a marker of bone resorption, and serum levels of bone-specific alkaline phosphatase, a marker of bone formation, were higher in patients with prostate cancer than in patients with osteolytic or mixed lesions other than prostate cancer (Fig. 2) [19]. The placebo group in a recent study of zoledronic acid in men with hormone-refractory prostate cancer (HRPC) and bone metastases provided evidence of the high incidence of skeletal morbidity in these patients [20,21]. Over 2 years of follow-up, nearly 50% of patients in the placebo group had a skeletal complication, including severe bone pain requiring radiotherapy (33%), pathologic fracture (25%), and spinal cord compression (8%), with a median time to onset of approximately 10.5 months.

Fractures in men, particularly hip fractures, result in significant morbidity and mortality. In a retrospective study of osteoporotic men, the 30-day fatality rate after hip fracture was 16%, and only 41% of surviving men recovered their pre-fracture level of functioning [22]. Studies have also shown that osteoporotic fractures generally result in higher morbidity and mortality in men than in women [23]. A recent prospective study determined that the mortality rate of patients older than 64 years who had had a hip fracture was approximately 4-fold higher for men than for women [24]. Furthermore, fractures appear to correlate negatively with overall survival in men with prostate cancer. A study of 195 men with prostate cancer receiving long-term ADT showed that patients who never had a fracture survived for a median of 3 years longer than patients who had at least 1 fracture [25].

Bisphosphonates are potent inhibitors of bone resorption and have significantly reduced skeletal complications in patients with bone metastases from a variety of solid tumors [26]. Zoledronic acid is the only bisphosphonate that has been shown to increase BMD in men with prostate cancer