New Clinical Tools for Urologists: Treatment of Bone Loss

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Abstract

Objectives: Androgen-deprivation therapy (ADT) is associated with significant bone loss. Methods for management of patients with ADT-associated bone loss are explored.

Methods: Existing and novel therapies were identified and researched through PubMed and published guidelines.

Results: Management of ADT-associated bone loss includes calcium and vitamin D supplementation and the implementation of behaviour modification techniques, such as initiation of weight-bearing exercise and smoking cessation. If bone mineral density (BMD) studies reveal significant bone loss, pharmaceutical intervention should be considered. However, because of the relatively low potency of oral bisphosphonates and their associated gastrointestinal adverse events and poor compliance, the more potent intravenous bisphosphonates should be considered. Nitrogen-containing bisphosphonates can effectively prevent bone loss during ADT, and zoledronic acid can actually increase BMD in this setting. These clinical management techniques are supported by international guidelines, including those of the European Association of Urology and the consensus recommendations from international panels of experts.

Conclusions: Patients who undergo ADT should be monitored for BMD loss, and pharmaceutical interventions should be considered for patients with osteopenia or osteoporosis. In this setting, BMD is considered an acceptable surrogate end point because of its significant association with the risk of fracture. Pharmacologic intervention should be considered in high-risk individuals. Dietary calcium, vitamin D supplementation, and intravenous bisphosphonates may be needed to prevent bone loss during ADT. Zoledronic acid is the most effective bisphosphonate in this clinical setting.

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1. Introduction

The use of androgen deprivation therapy (ADT) in men with prostate cancer has been associated with significant bone loss. Interruption of the hormonal signals that maintain the normal homeostasis of bone remodeling results in an increase in osteoclast activity and subsequent bone resorption. Thus
ADT-associated bone loss can be more rapid than that associated with the normal aging process. Because men receiving long-term ADT are at significant risk of osteopenia and osteoporosis, calcium and vitamin D supplementation and behaviour modification such as the initiation of weight-bearing exercise and smoking cessation should be considered. In addition, for men who demonstrate significant bone loss on screening bone mineral density (BMD) studies, bisphosphonate therapy should be considered.

Bisphosphonates inhibit osteoclast activity and thus reduce bone resorption. Oral bisphosphonates have demonstrated some efficacy for the prevention of bone loss during ADT. However, their utility in the oncologic setting may be limited by their relatively low potency, their associated gastrointestinal adverse events, and poor patient compliance [1–3]. Consequently, intravenous bisphosphonates are generally more effective (Fig. 1).

2. Results of clinical studies

Intravenous amino-bisphosphonates have been shown to decrease bone resorption and bone loss in men undergoing ADT [4]. In a further study of intravenous bisphosphonates for ADT-associated bone loss, Smith et al. [5] compared the effects of pamidronate (60 mg every 12 wk) versus no treatment in patients receiving ADT with leuprolide. After 48 wk, the mean trabecular BMD of the lumbar spine decreased by 8.5% in men treated with leuprolide alone, whereas the mean trabecular BMD of the lumbar spine did not significantly change in men treated with leuprolide and pamidronate ($p = 0.02$; Fig. 2) [5].

In a subsequent study in patients undergoing ADT with either a gonadotropin-releasing hormone agonist alone or in combination with an antiandrogen, the new-generation bisphosphonate, zoledronic acid, not only prevented bone loss but also increased BMD beyond baseline levels. Zoledronic acid is a nitrogen-containing bisphosphonate that exerts its effects on osteoclasts by inhibiting protein prenylation. This leads to a decrease in the numbers of mature osteoclasts and inhibition of their bone-resorbing activity. In this placebo-controlled trial, zoledronic acid, 4 mg given intravenously every 3 mo for 1 yr, increased mean lumbar spine BMD by 5.6%,

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**Fig. 1 – Rationale for intravenous (IV) bisphosphonate therapy during androgen deprivation therapy (ADT).**

**Fig. 2 – Pamidronate in patients with prostate cancer receiving androgen deprivation therapy (ADT). Reprinted with permission from Smith et al. [5].**

**Fig. 3 – Effects of zoledronic acid on lumbar spine BMD at 1 year. BMD = bone mineral density; LS = least squares; GnRH = gonadotropin-releasing hormone. Data from Smith et al. [6].**
compared with decreases of 2.2% among placebo-treated patients (\( p < 0.001; \) Fig. 3) [6]. Bone loss was most severe in patients receiving combined androgen blockade (gonadotropin-releasing hormone agonist and an antiandrogen), and zoledronic acid provided significant benefit regardless of therapy type.

3. Conclusions

Bone loss during ADT can result in clinically relevant skeletal morbidity. If fractures do occur, they are associated with decreased survival. Moreover, one study measuring quality of life (QOL) in patients undergoing long-term ADT has shown a significant decrease in QOL compared with patients not undergoing ADT (\( p = 0.001 \)) [7]. In addition, fractures are clearly associated with loss of mobility and decreased QOL [8]. However, bone loss is no longer an inevitable consequence of ADT. Guidelines from the European Association of Urology and independent panels of experts suggest routinely measuring baseline BMD before initiation of ADT and including calcium and vitamin D supplementation and behaviour modification to preserve BMD in patients undergoing ADT [9,10]. Interventions for preservation of bone health (e.g., use of bone-specific therapies such as bisphosphonates) should be considered for men with low baseline BMD or a high rate of bone loss. Pamidronate and zoledronic acid have demonstrated efficacy in decreasing the ADT-related bone loss and, in addition, zoledronic acid has been shown to actually increase BMD in patients undergoing single-agent ADT or complete androgen blockade.

References