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Collaborative Review – Prostate Cancer

Metastatic Prostate Cancer and the Bone: Significance and Therapeutic Options

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Abstract

Context: Skeletal involvement is common in metastatic prostate cancer (PCa) and is associated with skeletal-related events (SREs). The interaction of PCa with the bone microenvironment contributes to self-perpetuating progression of cancer in bone. Bone-targeted agents (BTAs) are available for use in metastatic castration-resistant prostate cancer (mCRPC).
Objective: To review the biology of bone metastases in PCa and to review the clinical trial data for BTAs in PCa.
Evidence acquisition: A literature search was conducted in October 2014. Keywords included *clinical trial, prostate cancer, denosumab, bisphosphonates, zoledronic acid, radium-223, bone turnover markers, skeletal-related events, and symptomatic skeletal events*.
Evidence synthesis: The biology of bone metastases in PCa is summarized. Data supporting the use of BTAs in PCa are reviewed, and issues related to the combination and sequencing of available agents are discussed.
Conclusions: The osteoclast-targeted agents zoledronic acid and denosumab decrease SREs in mCRPC, and the α-emitting radiopharmaceutical agent radium-223 improves survival and decreases symptomatic skeletal events. Limited data are available to guide the sequence and combination of BTAs with disease-modifying agents, although data support the use of osteoclast-targeted drugs with chemotherapy, androgen-targeted agents, and radium-223. Zoledronic acid does not reduce SREs when started prior to castration resistance, although osteoclast-targeted agents do improve outcomes when used in patients with asymptomatic to minimally symptomatic chemotherapy-naive mCRPC. The optimal sequence of radium-223 with chemotherapy is uncertain, although data suggest the efficacy and tolerability of radium-223 is similar with either sequence. Clinical trials evaluating the combination of BTAs with other agents are under way. The optimization of sequence and combination strategies will guide the best use of available agents.
Patient summary: The literature pertaining to bone metastases in prostate cancer (PCa) was reviewed, and the current understanding of the biology of PCa having spread to bone and the agents available to reduce skeletal complications was discussed.

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1. Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy in men with an estimated 233 000 new cases and 30 000 deaths in the United States in 2014 [1]. Although only 6% of men with PCa have metastatic disease at diagnosis, 90% of men who die of PCa have metastatic disease to bone [2,3]. Advanced PCa is driven by androgen signaling, and suppression of serum testosterone with androgen-deprivation therapy (ADT) allows for initial disease control in most patients. Unfortunately, ADT is noncurative, and progression of disease ultimately occurs in nearly all patients [4]. Progression in the setting of suppressed serum testosterone is termed *castration resistance*. Although a number of recently approved agents are available that have improved outcomes, metastatic castration-resistant prostate cancer (mCRPC) remains lethal. Owing to the frequent coexistence of bone metastases, patients with mCRPC are at risk for skeletal complications including skeletal-related events (SREs) that occur in nearly half of patients with mCRPC with bone involvement not treated with an osteoclast-targeted agent [5]. This review describes the current knowledge regarding the biology of bone metastases, describes the consequences of bone metastases, and reviews the clinical trial data that support the use of available bone-targeted agents (BTAs) in mCRPC.

2. Evidence acquisition

PubMed was searched in October 2014 to identify preclinical studies, clinical trials, and other relevant publications including review articles, editorials, and letters to the editor addressing the biology and treatment of bone metastases in mCRPC. In addition, abstracts from the European Society of Medical Oncology and American Society of Medical Oncology meetings were also searched for relevant abstracts in October 2014. Search terms included *clinical trial, prostate cancer, denosumab, bisphosphonates, zoledronic acid, radium-223, bone turnover markers, skeletal-related events*, and *symptomatic skeletal events*. Only articles published in English were evaluated for inclusion. Both published literature and abstracts from meetings for which publications were not yet available were included. A list of articles determined to be relevant was circulated among the authors, and final consensus was reached on both structure and the literature to include. The authors' knowledge of the literature was also used to ensure all pertinent articles were included.

3. Evidence synthesis

3.1. Skeletal events in prostate cancer

Advanced PCa is complicated by SREs. SRE is a composite end point used in clinical trials that includes the requirement for radiation or surgery to bone, pathologic fractures (both symptomatic and found incidentally), or spinal cord compression (SCC). More recently, an end point termed the *symptomatic skeletal event* (SSE) was introduced. This end point is similar but differs in that only symptomatic pathologic fractures are included in addition to radiation or surgery to bone and SCC.

Data from completed trials can be used to illustrate the burden of skeletal events in mCRPC. In the placebo arm of the clinical trial evaluating zoledronic acid for prevention of SREs in mCRPC (protocol 039), nearly half of the patients experienced an SRE over a 2-yr period [5]. Beyond being common events, SREs have a negative impact on patient well-being both in terms of quality and quantity of life [6,7].

Several prognostic factors have been identified that correlate with increased risk for SREs in mCRPC. These include progression of PCa, greater burden of skeletal metastases, and increased bone turnover markers (BTMs) [8–10]. In a trial evaluating BTAs in mCRPC, a number of baseline bone-related factors correlated with longer survival including low levels of BTMs, no or mild pain, no previous SRE, longer time from diagnosis to first bone metastasis, and longer time from first bone metastasis to randomization [11].

BTMs measured in either the serum or urine provide biochemical information on the rate of bone resorption (ie, N-telopeptide of type I collagen) and bone formation (ie, alkaline phosphatase [ALP]). Elevation of BTMs predicts the presence of bone metastases [12,13]. In patients with mCRPC, elevated BTMs predict increased SRE risk [10] and decreased survival [14,15]; normalization following treatment with an osteoclast-targeted agent correlates with improved outcomes [16]. The use of BTMs is not yet incorporated into routine clinical care in PCa.

3.2. Biology of bone metastases from prostate cancer

The maintenance of bone integrity requires a balance between production of bone matrix by osteoblasts and its resorption by osteoclasts. The most significant signaling molecules involved in regulating this process include receptor activator of nuclear factor-κβ ligand (RANKL) and its receptor RANK. RANKL is generated by a number of cell types including osteoblasts; RANK is expressed by osteoclasts [17]. RANKL-RANK signaling is the key driver of osteoclast formation and function with mouse models deficient in either gene displaying impaired osteoclastogenesis and a condition termed *osteopetrosis* characterized by dense and brittle bones [18,19]. Osteoprotegerin (OPG) acts as a decoy receptor to RANKL thereby inhibiting RANKL-RANK signaling. Mice lacking OPG develop severe early-onset osteoporosis [20].

The bone microenvironment provides a favorable environment for PCa metastasis. The seed and soil theory, initially proposed by Paget in 1889, ascribes the organ-specific pattern of metastatic disease to the interaction of cancer cells (seed) with the environment (soil) at metastatic sites [21]. The molecular mechanisms responsible for tropism of PCa to bone include an interaction between chemokines (ie, CXCL12) expressed in bone with receptors (ie, CXRCR4) on PCa cells along with the interaction of integrins on PCa cells with elements in the bone