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Review

Therapeutic management of bone metastasis in prostate cancer: an update

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Abstract

Introduction: Bone metastases affect the majority of patients with castration-resistant prostate cancer (CRPC), resulting in significant morbidity and mortality. This review describes the current therapies available for the management of CRPC patients with bone metastases.

Areas covered: Studies on the use of currently available therapeutic approaches for palliating pain, delaying skeletal-related events (SREs) and prolonging survival in CRPC patients with bone metastases have been examined. PubMed database was searched in May 2016 starting with the following keywords: ("castration-resistant prostate cancer" OR "CRPC") AND "bone metastases", and approximately 270 results were retrieved. More specific searches were then performed on the epidemiology and molecular pathogenesis (in particular, "vicious cycle" was used as a keyword), the management of pain, SREs and survival. The following keywords were also used individually: abiraterone, cabazitaxel, denosumab, docetaxel, enzalutamide, radium-223, sipuleucel-T, samarium-153, strontium-89, zoledronate. Randomized-controlled trials, observational studies, reviews, systematic reviews and meta-analyses were selected and articles were excluded if not in English.

Expert Commentary: Currently, clear recommendations on the optimal use of the agents available to treat mCRPC are lacking. Therefore, to ensure patients the best treatment, both their clinical characteristics and the features of each product have to be considered.

Keywords: Abiraterone; bone metastases; cabazitaxel; castration-resistant prostate cancer; denosumab; docetaxel; enzalutamide; radium-223; zoledronate.

1. Introduction

Prostate cancer (PCa) is the second most common type of cancer in men and accounts for nearly 20% of all newly diagnosed male tumors. In the US, 180,890 new cases have been estimated to be diagnosed in 2016 and 26,120 men to die of this disease [1].

At diagnosis, approximately 80% of patients present with localized PCa and 4% with distant metastases, the 5-year relative survival rate being 100% and 28% respectively [1].

Due to PCa cell growth dependance on androgens, recurrent or metastatic disease is managed with surgical or pharmaceutical castration. Indeed, androgen deprivation therapy (ADT) is the mainstay therapy in metastatic PCa, with response observed in 80-90% of cases. However, nearly all men eventually progress within one to three years leading to castration-resistant PCa (CRPC) [2]. The majority of patients with metastatic CRPC (mCRPC) develop bone metastases [3] resulting in a significant increase in morbidity and mortality [4,5]. Morbidity and impact on quality of life (QoL) are due to the increased risk of bone fractures, bone pain, nervous tissue compressions and hypercalcemia [5,6]. These complications, collectively referred to as skeletal-related events (SREs), are associated with impaired mobility, general suffering, reduced self-sufficiency, poor QoL, increased mortality, and increased health care costs [7–9].

Greater insight into the pathophysiology of bone metastases has led to the development of new bone-targeted agents aimed at reducing the rate of SREs and prolonging survival. While the number of available treatments that yield significant benefit in these patients has increased in recent years [10], initial survival benefit was observed only with docetaxel-based chemotherapy [11,12]. Therefore, it was approved by FDA in 2004. Since 2010, five new agents have emerged following phase III studies that have also gained FDA approval. These therapies include the CYP17 lyase inhibitor abiraterone acetate, the antiandrogen enzalutamide, the microtubule stabilizer cabazitaxel,

and the radiopharmaceutical radium−223 [13,14]. Although these drugs act through different mechanisms on different targets, they have been shown to be able to further prolong survival in chemo-naïve patients treated previously with docetaxel [15].

The aim of this review is to describe the current therapies available for patients with CRPC and bone metastases.

2. CRPC and mCRPC: epidemiology, natural history and prognosis

Two phase III randomized trials investigated the natural history of nonmetastatic CRPC patients included in the respective placebo arms [16,17]. Results showed that 33% [16] and 46% of [17] men had developed bone metastasis and 21% [16] and 20% [17] had died within 2 years from study entry. Also, a systematic review analyzing data from 71,179 patients observed for up to 12 years reported that 10-20% of PCa patients had experienced progression to CRPC within approximately 5 years and, at the time of CRPC diagnosis, ≥84% already presented with bone metastases and 33% of those without developed them within 2 years [18]. mCRCP patients had a shorter survival than CRPC cases (9-13 months vs. 9-30 months, respectively) and suffered from a rapid deterioration of QoL, with frequently reported pain and SREs such as bone fractures and spinal cord compression [18].

Pain can occur in each stage of PCa, although its incidence increases up to 90% during the terminal phase of disease [19]. SREs occur in 44% to 80% of PCa men with bone metastases [20–22], but their incidence and severity have been also linked to endocrine therapy [23] and ADT [24]. SREs and bone metastases negatively affect overall survival (OS). Indeed, it has been reported that the 1- and 5-year survival rate in PCa patients without bone metastasis is 87% and 56%, respectively, vs. 47% and 3% in those with bone metastasis and 40% and <1% in those with bone metastasis and SREs [20]. The presence of bone metastases increased the risk of death (hazard ratio [HR]=6.6, 95% confidence

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