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Therapeutic opportunities for castration-resistant prostate cancer patients with bone metastases

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Abstract

Patients with castration-resistant prostate cancer are burdened not only with an unavoidable risk of mortality but also by severe mobility issues. This disease has a high tendency to induce bone metastases with concomitant general suffering, impaired mobility, and reduced self-sufficiency. The treatment of bone pain consists of opioids, nonsteroidal anti-inflammatory drugs, radiopharmaceuticals, and radiotherapy. To date, abiraterone, enzalutamide, zoledronate and denosumab are the only drugs able to delay skeletal events, and docetaxel is the only chemotherapeutic agent able to prolong survival after castration progression. Recently, 5 new drugs have proven to be efficacious in prolonging survival. Sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and radium-223 have broadened the therapeutic choices, thus changing the

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clinical paradigm. This review analyzes the data supporting the use of all presently available therapeutic approaches for the management of pain, skeletal events, and survival in castration-resistant prostate cancer patients with bone metastases. Data based on phase 3 trials could identify new approaches depending on patient, disease, and therapy characteristics.

1. Introduction

The incidence of prostate cancer in Western countries accounts for an estimated 900 000 new cases per year, and this figure is expected to increase due to improvements in health education, the widening scope of screening campaigns, and longer life spans [1,2]. Even though the localized forms of this disease for the most part appear curable or fairly manageable and associated mortality is relatively low compared with other tumors, prostate cancer represents the second cause of mortality in men. Epidemiological investigations reported that in 2007 more than 28 000 related deaths were recorded in the United States [2].

For more than 70 years, surgery, radiotherapy, or pharmacologic therapies aimed at reducing levels of testosterone and its metabolites (androgen deprivation) have been the cornerstone for the treatment of this disease. In a relatively large number of cases, androgen deprivation, most often accomplished with luteinizing hormone-releasing hormone agonists with or without antiandrogen therapies, maintains tumor-control growth generally lasting a consistent length of time. After that, patients develop signs of progression independent of the maintenance of hormone blockade [3,4]. Such a condition, described as castration-resistant prostate cancer (CRPC) [4], results in a highly debilitating disease due to the high tendency of the tumor to induce bone metastases that dramatically increase the risk of pathologic fractures and skeletal complications including nervous tissue compressions and hypercalcemia [5].

These complications, together called *skeletal-related events* (SREs), are associated with impaired mobility, general suffering, reduced self-sufficiency, reduced quality of life, increased mortality, and increased health care costs [6–8]. Although only 3% of patients at initial diagnosis display bone involvement, this percentage rises to 90% in patients with metastatic CRPC (mCRPC) [8–10]. In contrast, visceral metastases (lung, liver, adrenal gland, and kidney) are estimated at approximately 25% and generally indicate an aggressive disease [11–13]. According to a recent paper, the incidence of visceral metastases have been increasing in the recent years, due to a more common detection and to the introduction of treatments increasing survival [12]. With the goal of extending survival as much as possible in these patients, positive results were initially obtained with chemotherapy. Docetaxel combined with prednisone was shown to delay tumor progression in patients with mCRPC achieving a survival of about 19 months [11]. Subsequently, phase 3 investigations with newer agents identified 5 agents: abiraterone, cabazitaxel, sipuleucel-T, enzalutamide, and radium-223. Although acting on different targets, all these drugs were able to further extend survival in both chemo-naive patients and those previously treated with docetaxel [14].

This review describes the therapies presently available for patients with CRPC and bone metastases. After reviewing international recommendations and phase 3 results, we focused on the agents currently helpful to improve overall survival (OS), reduce pain, and delay time to SREs.

2. Bone metastases in patients with metastatic castration-resistant prostate cancer

Among all human tumors, prostate cancer, because of its peculiarly strong cell avidity for bone tissue, displays a high risk of bony metastases. Such avidity is higher compared with breast and lung tumors that represent the second and third cancers characterized by bone dissemination [15,16], evidence substantiated by statistical and postmortem analyses, and by clinical studies [11,13,17,18].

Like breast cancer, the first site of the spread of prostate cancer is the spine followed by the pelvis, hip, femur, and skull [8]. In contrast to other human tumors, bone metastases along with their related complications represent the leading cause of death for mCRPC patients [19]. Some authors report that about 50% of patients with bone metastases die within 30–35 months from diagnosis [20–22]. Overall, it is believed that the dimension of bone metastases, the intensity of pain, and the presence of SREs indicate a shorter survival. Data report that for patients with bone metastases, the risk of death is 6.6 times greater than that of nonmetastatic patients, and this risk increases 10.2 times in patients whose bone metastases are associated with SREs [23]. Some authors consider the time to the onset of SREs as a prognostic factor for survival in patients with mCRPC [23,24]. Further important survival predictors are the volume of bone metastases and the intensity of the pain [25].

Although lytic bone lesions have been documented, the skeletal metastases from prostate cancer are predominantly "bone forming," defined as osteoblastic lesions. Studies demonstrated that the metastatic cells stimulate osteoblast proliferation to release specific growth factors causing an increased deposition in bone matrix and in the bone microenvironment (Fig. 1) [7,8].

Radiologic imaging of bone lesions shows an irregular shape and an imbalanced number of bone trabeculae without histologic evidence of an increase of the number of osteoclasts [13,26]. The level of markers of bone resorption in patients with bone metastases is greater than nonmetastatic

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