Bone Metastases in Prostate Cancer

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Clinically relevant bone metastases are a major cause of morbidity and mortality for prostate cancer patients. Distinct phenotypes are described: osteoblastic, the more common osteolytic and mixed. A molecular classification has been also proposed. Bone metastases start with the tropism of cancer cells to the bone through different multi-step tumor–host interactions, as described by the "metastatic cascade" model.

1. Introduction

Prostate cancer (PC) is the second most common cancer in men worldwide and more than half of PC occurs in men over the age of 70 years [1]. The propensity of PC cells to seed in the skeleton and then to progress into clinically relevant metastatic tumors is widely studied, and is a major cause of morbidity and mortality in PC patients [2]. Bone metastases most frequently affect the axial skeleton and often cause skeletal complications known as skeletal-related events (SREs), such as: pathological fracture, radiotherapy (RT), surgery, spinal cord compression (SCC) and hypercalcemia [3]. Despite the osteosclerotic nature of bone metastases, SREs in PC are still very common, reducing quality of life and worsening survival [3].

Bone metastases start with the tropism of cancer cells to the bone through specific migratory and invasive processes [4]. The complex molecular pathogenetic mechanism of bone metastases offers several potential targets for prevention and therapy [4].

Although the mechanisms underlying bone metastases are far from being fully elucidated, several translational models of PC bone metastases have been studied, including the application of molecular profiling techniques, animal model systems and engineered cell lines: all of these models could help to improve our treatment capacity.

Nowadays, several therapeutic options are available for PC patients. The milestone was androgen-deprivation therapy. Other possibilities now include chemotherapeutic agents, new-generation hormone therapies, radium 223 and, more recently, radioligand therapies. However, for these patients, special attention should be also placed on the management of bone health and the prevention of treatment-induced bone loss [3]. Bone-targeted agents, bisphosphonates and denosumab are active in bone metastases [1]; however, these drugs should still be evaluated even in the absence of bone metastases and under multidisciplinary evaluation, according to dedicated guidelines.

2. Bone Metastases in Prostate Cancer

PC cells show a preference for tropism to the bone. An autopsy study revealed that approximately 90.1% of men who had died with metastases of PC were diagnosed with bone metastases [5]. In PC patients with bone metastases, the 5-year survival rate was 33% [6]. In cases of spinal metastases of PC, the median overall survival (OS) appears to be 24 months with an estimated 1-year OS of 73% [7]. The extent of skeletal metastatic involvement correlates with survival in patients with advanced PC. The "bone scan index" allows us to quantify the extent of tumor skeletal involvement. Patients with low, intermediate and extensive skeletal involvement had a median overall survival of 18.3, 15.8, and 8.1 months, respectively, in a study of 191 patients with androgen-independent PC [8].

Distinct phenotypes of bone metastases have been described in patients with PC: osteolytic, osteoblastic and mixed. The existence of mixed lesions suggests that the processes that regulate tumor-associated osteolysis and bone formation may occur together in bone metastases and are not mutually exclusive. Furthermore, the relative activity of these two coexisting processes defines the bone metastases' phenotype. Osteolytic metastases, defined as a "punched-out" area of severe bone loss, are a consequence of tumor-induced activation of bone-matrix resorption. Resorption of mineralized

bone matrix is the natural function of the osteoclast, a multinucleated cell of hematopoietic origin residing in the bone, in cooperation with multiple other actors and with several stimuli (as reported below). Osteoblastic metastases, characterized by bone forming, are prevalent in advanced PC patients and induced by cancer cell interactions with osteoblasts and their progenitors through several interactions [9]. PC cells also demonstrate osteomimicry by responding to growth factor stimulation [10]. This would suggest that bone-forming tumors may also occur through differentiation of the cancer cells towards an osteoblastic bone-forming phenotype, which is a phenomenon that has been observed in the bone metastatic PC cell line, C42b [11]. A category of cancer and bone interactions likely to contribute to the metastatic tumor phenotype are those driven by sex steroid hormones. Prostate and breast cancers, both sex steroid-sensitive diseases, show a predilection to form bone metastases. In addition, it has been shown that hormone-sensitive PC cells can respond to sex steroid deprivation by activating de novo synthesis [12], which implies that bone cells interacting with metastatic cancer may be stimulated by androgen produced locally by tumor cells.

Osteoblatic metastases are more common in PC, representing 68% of all bone metastases [13]. Despite this, the osteolytic factor parathyroid hormone-related protein (PTHrP) is also highly expressed in PC. A proposed explanation is that PTHrP can also stimulate bone formation by activating the *ETAR* with NH2-terminal fragments of PTHrP, which share strong sequence homology with *ET-1* [14].

The prognosis of patients is markedly influenced by SREs, such as pathological fractures, hypercalcemia and pain, which occur in 49% of osteoblastic metastases [13]. To predict the risk of SREs, bone resorption markers may be useful, such as N-telopeptide of type I collagen (NTX) and bone alkaline phosphatase (BALP), which are associated with higher rates of death and SREs in PC bone metastases [15][16]. Further studies would be useful to stratify the risk of SREs in different types of bone metastases.

The field exploring potential biomarkers of bone metastases deserves special attention, and researchers have investigated new strategies and approaches with different biomarkers.

Yu and colleagues retrospectively analyzed data from 150 PC patients and found that patients with bone metastases had significantly elevated serum levels of carcinoembyonic antigen 125 (CA125), total prostate-specific antigen (T-PSA), free PSA (F-PSA), cytokeratin-19 fragment (CYFRA 21-1) and pro-gastrin-releasing peptide (ProGRP). The ROC curves indicated that T-PSA, F-PSA and ProGRP could effectively aid in discriminating between patients with bone metastases and those without. The area under the curves for the combination of these parameters was 0.941 with 90% sensitivity and gave better results than with each biomarker alone or with two biomarkers combined [17]. Instead, Aufderklamm and colleagues investigated the utility of serum c-terminal telopeptide of type I collagen (1CTP) and n-terminal propeptide of type I procollagen (P1NP) in the diagnosis of bone metastases and in the prognosis of patients. These peptides are markers of bone formation which are increased in PC patients and bone metastases. They analyzed serum samples of 186 patients with prostatic hyperplasia or PC, with or without metastases. Increased levels of 1CTP were found in PC patients compared with others, while no significant difference was shown for P1NP levels. Instead, both markers were altered in metastatic patients compared with non-metastatic ones. Cancer prognosis was significantly worse in metastatic PC patients with higher 1CTP concentration [18]. Moreover, to improve the capability of detecting for the risk of bone metastases, Windrichova and colleagues compared the performance of 16 biomarkers and suggested a mathematical model, the Bone Risk Score (BRS), by combining three of the biomarkers. They compared serum biomarkers levels in patients with different primary tumors, using scintigraphy to detect those with bone metastases (56 patients) or those without (75 patients). The best performance was obtained with the BRS combining P1NP, growth differentiation factor-15 (GDF15) and osteonectin [19]. In addition, Ku et al. carried out comprehensive expression profiling of tissue samples of bone metastasis from different types of cancer, revealing their proteome landscape and four significant proteins with the potential capability to differentiate tumor primaries [20]. Further studies are required to confirm these findings with a larger number of patients, and the clinical relevance of these markers.

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