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Advances in the Therapy of Prostate Cancer–Induced Bone Disease: Current Insights and Future Perspectives on the RANK/RANKL Pathways

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Abstract

Context: Prostate cancer (PCa) cells are characterised by an exquisite tropism for the bone, which translates into one of the highest rates of bone metastases and skeletal morbidity. New, effective treatments have emerged from a better understanding of the physiopathology of bone metastases.
Objective: To summarise current insights and future perspectives in the therapy of PCa-induced bone disease.
Evidence acquisition: This manuscript is based on presentations given at a satellite symposium held at the 2nd World Congress on Controversies in Urology (CURy) in Lisbon, Portugal. Data were retrieved from original and recent review papers on PCa-induced bone disease.
Evidence synthesis: In normal, healthy bone, there is a balance between bone resorption and bone formation through the coordinated activity of osteoclasts and osteoblasts. The receptor activator of nuclear factor-κB ligand (RANKL) is an essential mediator of osteoclast formation, function, and survival. The RANKL pathway represents a therapeutic target for osteoclast-induced bone destruction in pathologic conditions, including treatment-induced bone loss and metastatic cancer. Based on a multicentre, randomised, open-label, active-controlled phase 2 trial, denosumab, a fully human monoclonal antibody against RANKL, reduced the incidence of skeletal morbidity in patients with bone metastases from PCa, breast cancer, or other neoplasms.
Conclusions: In a phase 2 clinical study, denosumab reduced skeletal-related events in patients with bone metastases from PCa. In addition, the potential role of denosumab in the management of treatment-induced bone loss and the prevention of bone metastases is currently under investigation.

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1. Introduction

Prostate cancer (PCa) is the most common cancer and the third leading cause of cancer death among men in economically developed countries [1,2]. In 2007, nearly 782 647 new cases of PCa were diagnosed worldwide, resulting in an estimated 253 906 deaths [3]. The major source of morbidity in advanced PCa results from the exquisite tropism of PCa cells spreading out of the prostate to bone, a phenomenon known as *osteotropism* [4]. In men who progressed under hormone therapy, bone is indeed the primary metastatic site in 80% of patients [5]. Later on, in end-stage disease, ≥90% of patients will have bone metastases [6–8]. Bone metastases can alter the normal composition of bone, change the physiologic bone remodelling processes, and invade the surrounding structures, resulting in complications such as pathologic fractures, pain, spinal cord compression, and anaemia. These complications are also known as *skeletal-related events* (SREs) [9]. SREs are common in osteotropic cancers, such as breast and lung cancer. In PCa, however, bone metastases and SREs occur mainly in an abnormal osteopenic environment caused by the chronic use of androgen-deprivation therapy (ADT) as a mainstay treatment of advanced and metastatic disease. Because testosterone is critical for normal bone physiology, ADT causes rapid and profound bone loss, a process called *cancer treatment–induced bone loss* (CTIBL) [10]. This unique interaction between a selective osteotropism of PCa and a profound alteration of the bone composition creates a newly recognised "bone paradigm." A proper understanding of the key steps involved in the development of bone metastases and CTIBL in PCa is necessary and will be critical for considering the development of new or more effective therapies for PCa-induced bone diseases.

2. Evidence acquisition

This paper was based on presentations given at a satellite symposium on advances in the therapy of PCa-induced bone disease that was held during the 2nd World Congress on Controversies in Urology (CURy) on 7 February 2009 in Lisbon, Portugal. Data were retrieved from original and recent review articles on PCa-induced bone disease.

3. Evidence synthesis

3.1. The RANK/RANKL/–osteoprotegerin pathway in cancer treatment–induced bone loss and the pathogenesis of the "vicious circle" of bone metastases

In normal, healthy bone, bone formation and bone resorption occur in a balanced remodelling sequence through the coordinated activity of two types of specialised cells: osteoclasts and osteoblasts. Osteoclasts are responsible for bone resorption, whereas osteoblasts are responsible for bone formation. Osteoblasts and osteoclasts communicate via local paracrine factors. The receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which is produced by osteoblasts and progenitor cells, plays a central role in this communication process. The binding of RANKL to RANK induces the maturation of preosteoclasts into mature osteoclasts, resulting in resorption of bone tissue and the release of growth factors such as transforming growth factor-β1 (TGF-β1), which in turn stimulate osteoblast formation. Osteoclast-induced bone resorption also leads to degradation of the nuclear matrix consisting of collagen. Degraded proteins such as urinary N-telopeptide (uNtx) can be traced, measured, and used as markers of bone resorption.

Several hormones, cytokines, and growth factors can stimulate the expression of RANKL by osteoblasts. To keep the bone formation and bone resorption in physiologic balance, osteoblasts and stromal cells also produce osteoprotegerin (OPG), which acts as a decoy receptor for RANKL. OPG prevents binding of RANKL to RANK and stimulates osteoclasts to induce apoptosis (Fig. 1). An imbalance of the RANKL-to-OPG ratio plays a critical role in the pathogenesis of bone diseases [11–15]. Indeed, studies in transgenic animals showed that mice lacking the OPG gene are severely osteoporotic, while those lacking the RANK gene develop severe osteopetrosis, a condition in which bone is deposited in excess[1].

The RANKL pathway has been implicated in many bone diseases associated with increased bone resorption, such as postmenopausal osteoporosis, hypogonadism, ADT-induced bone loss, and rheumatoid arthritis. In addition, the RANKL pathway is of critical importance in the selective tropisms of PCa metastases [11,13,15,16]. RANKL is one of the candidate chemokines that attract PCa cells and favours landing in the bone microenvironment [17]. Further, tumour cells alter the natural balance between bone resorption and bone formation. Cancer cells with a high tropism for the bone secrete parathyroid hormone-related protein (PTHrP), which increases RANKL-mediated osteoclast activity, leading to osteolytic metastases. In turn, growth factors released from the bone matrix (eg, TGF-β1) stimulate the growth of the cancer cells, creating a cross-fertilisation mechanism known as the "vicious circle" of bone metastases (Fig. 2). This mechanism is typical, for instance, in breast cancer metastases. In contrast, PCa cells secrete growth factors, such as endothelin-1 (ET-1) and bone morphogenic proteins that selectively stimulate osteoblastic proliferation. Hypothetically, the osteoblastic phenotypes result also from the secretion of a series of proteases, including prostate-specific antigen (PSA), that inactivate PTHrP and other pro-osteoclastic features.

Although PCa bone metastases are mainly osteoblastic, they contain an important osteoclastic component. From histologic evidence, it was demonstrated that PCa metastases are a heterogeneous mixture of osteolytic and osteoblastic lesions [18,19]. In addition, the importance of the osteolytic activity has been demonstrated in clinical studies evaluating the efficacy of bisphosphonates in blocking osteoclast-mediated bone resorption. In a randomised, placebo-controlled trial in patients with hormone-refractory metastatic PCa [20,21], zoledronic acid

[1] Data on file, Amgen.