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

Kurt Miller[a,*], *Arnulf Stenzl*[b], *Bertrand Tombal*[c]

[a] *Department of Urology, Charité Universitätsmedizin Berlin, Berlin, Germany*
[b] *Department of Urology, Uniklinikum Tubingen, Tubingen, Germany*
[c] *Department of Urology, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Belgium*

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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.

* Corresponding author. Department of Urology, Charité Universitätsmedizin Berlin, Hindenburgdamm 30, 12200 Berlin, Germany. Tel.: +49 30 84452575; Fax: +49 30 84454448.
E-mail address: kurt.miller@charite.de (K. Miller).

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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.

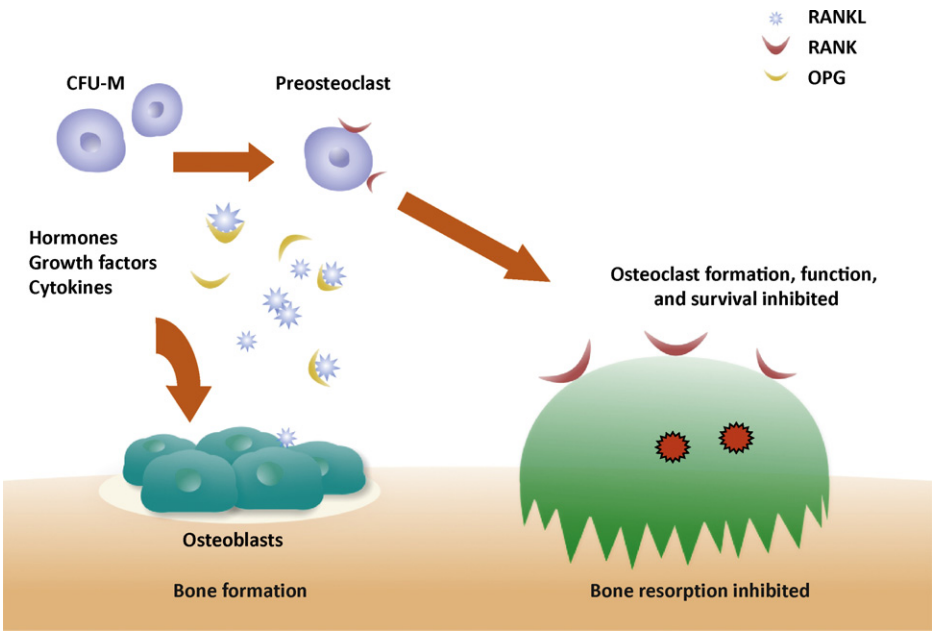

Fig. 1 – An overview of the physiologic balance between bone resorption and bone formation in normal healthy bone.
CFU-M = colony-forming unit-macrophage; RANKL = receptor activator of nuclear factor-κB ligand; RANK = receptor activator of nuclear factor-κB; OPG = osteoprotegerin.

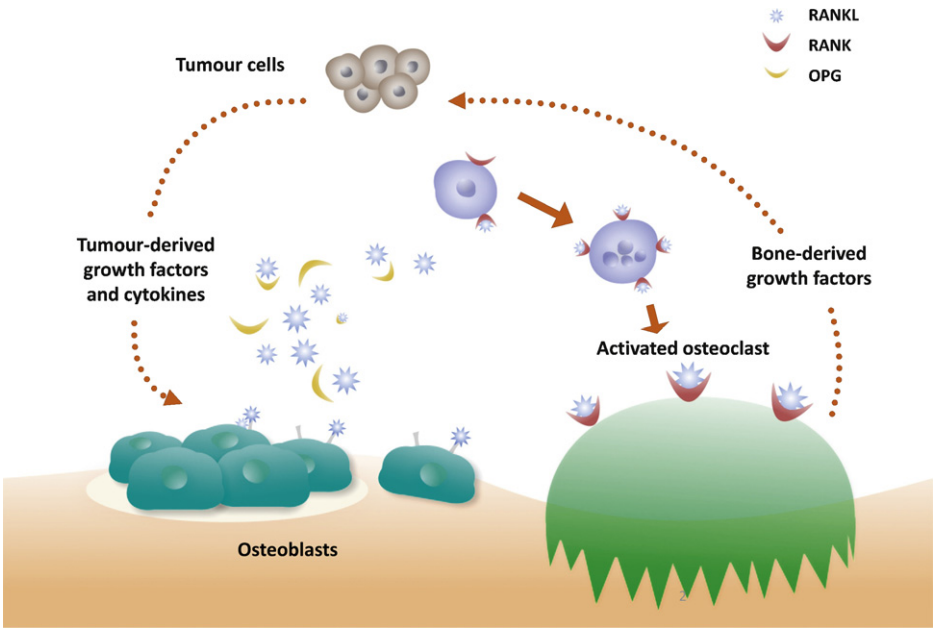

Fig. 2 – An overview of the vicious circle of bone destruction and tumour growth in osteolytic metastases.
RANKL = receptor activator of nuclear factor-κB ligand; RANK = receptor activator of nuclear factor-κB; OPG = osteoprotegerin.

significantly reduced the proportion of patients with SREs, prolonged the time to the first SRE, and reduced the ongoing risk of developing SREs. These findings support the concept that osteoclast activation plays an important role in metastatic PCa.

3.2. RANK/RANKL inhibition as a therapeutic target

The potential of RANKL as a therapeutic target for osteoclast-mediated bone destruction is under investigation. Denosumab is an investigational fully human monoclonal antibody that specifically inhibits RANKL. Based on findings in postmenopausal women with osteoporosis, injection of denosumab resulted in a prolonged inhibition of bone resorption [22,23]. In a preclinical animal model, RANKL inhibition using a RANK fusion protein blocked osteoclast-mediated bone resorption and diminished PCa progression in bone [24]. Blockade of RANKL using RANKL antibodies or RANK fusion proteins may thus emerge as a therapeutic goal for the treatment of patients with PCa-induced bone disease.

3.3. RANKL inhibition in men with prostate cancer

Recently, the final results of a multicentre, randomised, open-label, active-controlled phase 2 trial evaluating the effect of denosumab in patients with bone metastases from advanced cancer after bisphosphonate therapy were reported [25]. Eligible patients had bone metastases from PCa, breast cancer, or other solid tumours and elevated (>50 nM bone collagen equivalents [BCE]/mM creatinine) uNtx levels despite intravenous bisphosphonate therapy for at least 8 wk. Elevated uNtx serum levels are predictive of SREs, cancer progression, and death in patients with bone metastases [26]. Patients were stratified by tumour type and screening uNtx levels and randomly assigned to continue intravenous bisphosphonates every 4 wk ($n = 37$) or to receive 180 mg of subcutaneous denosumab every 4 wk ($n = 38$) or every 12 wk ($n = 36$). All patients took supplemental calcium and vitamin D. A total of 111 patients were enrolled between 2004 and 2007.

Among all patients, the primary end point of reducing uNtx to levels <50 nM BCE/mM creatinine at week 13 was achieved in 71% of patients in the denosumab arms compared with 29% of patients in the bisphosphonate arm ($p < 0.001$). Among a subgroup of patients with PCa ($n = 50$), 69% of denosumab patients compared with 19% of bisphosphonates patients reached uNtx levels <50 nM BCE/mM creatinine. The proportion of PCa patients with uNtx <50 nM BCE/mM creatinine was maintained at week 25 (69% of patients treated with denosumab; 31% of patients treated with bisphosphonates). The median time to reduction of uNtx <50 nM BCE/mM creatinine was 9 d for denosumab compared with 65 d for bisphosphonates ($p < 0.001$). The incidence of SREs during the 25-wk treatment period was 8% and 18% of patients in the denosumab group and the bisphosphonate group, respectively. Moreover, in the subgroup of patients with PCa, only 3% of patients on denosumab had SREs, compared with 19% of patients on bisphosphonates (Fig. 3) [27]. Rates of adverse events at week 25 were similar between the treatment groups. Denosumab given every 4 wk or 12 wk resulted in overall similar response rates. These data provide a strong rationale for further evaluation of denosumab in patients with bone metastases from advanced cancer in phase 3 trials. In addition, denosumab is being investigated for use in the prevention of bone metastases and the management of treatment-induced bone loss.

3.4. Case study

During the symposium, a case study was presented to draw attention to the importance of bone health in the treatment of PCa patients. A 65-yr-old man had a PSA of 8.3 ng/ml and was diagnosed with stage T1c PCa. After a prostate biopsy, Gleason score of 7 (4 + 3) was revealed in both lobes. In September 2005, the patient underwent a radical prostatectomy. Histopathologically, he was diagnosed with pT3c, pN1, R0 PCa. The Gleason score was upgraded to 8 (4 + 4). Subsequently, he received adjuvant therapy with luteinising hormone-releasing hormone agonists. After 2 mo, his PSA level was undetectable. It was mentioned that this patient was at risk for CTIBL. PCa patients are at higher risk because many of them already present with osteoporosis before initiation of ADT [28]. Normal bone remodelling is rapidly altered after induction of ADT, and bone loss accumulates over time, leading to a significant proportion of patients with osteoporosis and at risk of pathologic fractures [29–34]. Physicians should be aware of CTIBL, learn how to recognise additional risk factors, and properly monitor bone mineral density (BMD) during treatment. Assessment of BMD by dual energy x-ray absorptiometry (DEXA) scan is highly recommended before treatment in the presence of risk factors and after 1 yr of treatment, and then annually or biannually. Proper treatment should be administered when osteoporosis is demonstrated [35].

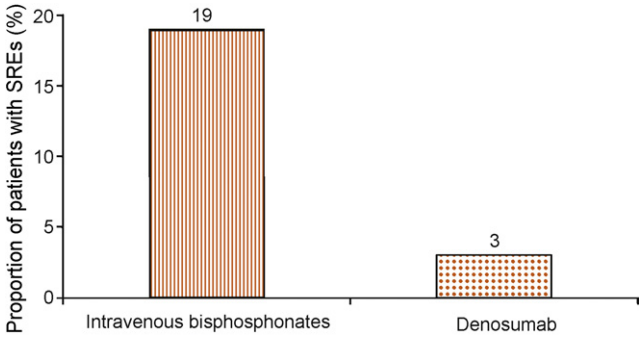

Fig. 3 – The incidence of skeletal-related events (SREs) during a 25-week treatment period among patients with bone metastases from prostate cancer after intravenous bisphosphonates who received denosumab or further bisphosphonate therapy in a multicentre, randomised, open-label, active-controlled phase 2 trial [27].

The patient's PSA was 0.08 ng/ml in November 2006 and increased to 0.2 ng/ml in January 2007. The man was further treated with bicalutamide and flutamide. However, his PSA was 1.3 ng/ml in October 2007 and rose to 35 ng/ml after 1 yr. He had severe back pain, and a bone scan revealed bone metastases. Consequently, he received radiation therapy for local pain control and systemic therapy with bisphosphonates to prevent further SREs. During the discussion, it seems that the role of the simultaneous use of bisphosphonates with chemotherapy needs to be addressed. In addition, the potential of new agents, such as denosumab, in the management of treatment-induced bone loss and the prevention and treatment of PCa-induced bone metastases is currently under investigation in phase 3 trials.

4. Conclusions

Prevention and treatment of bone metastases and ADT-induced bone loss is essential for the management of men with aggressive PCa. Bone metastases and SREs are the first metastatic site and source of morbidity, respectively. RANKL signalling is a key regulator for osteoclast-mediated bone destruction in both normal bone remodelling and pathologic conditions. In addition, RANKL contributes

to the vicious cycle of bone destruction and tumour growth in PCa. Inhibition of RANKL using RANKL antibodies or RANK fusion proteins resulted in a prolonged inhibition of bone resorption and diminished PCa progression in bone in postmenopausal women and a preclinical animal model, respectively. Recently, a multicentre, randomised, open-label, active-controlled phase 2 study demonstrated that denosumab, a fully human monoclonal antibody against RANKL, reduced the incidence of SREs. The role of denosumab in the management of treatment-induced bone loss and the prevention and treatment of PCa-induced metastases is currently under investigation in phase 3 trials.

Conflicts of interest

Kurt Miller is an advisor for Amgen and Novartis. Arnulf Stenzl is an advisor for Amgen. Bertrand Tombal is an advisor and an investigator for Amgen and Novartis.

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