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Academia–Pharma Intersect: Genitourinary Cancer: Prostate

The Role of RANK-Ligand Inhibition in Cancer: The Story of Denosumab

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ABSTRACT

The diagnosis of bone metastases is an event with certain consequences for the patient. They often mean pain and can also mean pathological fractures, hypercalcemia, and spinal cord compression, all synonymous with a diminished quality of life and often also hospitalization. Since the advent of the intravenous bisphosphonates, things began to look a bit brighter for patients with bone metastases—bone destruction was kept at bay a little longer. The next generation of bone metastasis treatments is well on its way in clinical development, and among them, the most advanced drug is denosumab. Denosumab is a fully human monoclonal antibody that inhibits osteoclast maturation, activation, and function by binding to receptor activator of nuclear factor kappa B ligand, with the final result being a reduced rate of bone resorption. In this review, we give an overview of relevant preclinical and clinical data regarding the use of denosumab in patients with solid tumors in general and prostate cancer in particular. ***The Oncologist*** 2011;16:136–145

INTRODUCTION

The bone is a very common site of metastasis in patients with advanced cancer. Skeletal metastases are most common in breast and prostate cancer, but virtually any advanced cancer may disseminate to the bone. Multiple myeloma patients also frequently develop bone lesions. Bone metastases can cause a wide range of symptoms and complications, such as pain, hypercalcemia, pathologic fractures, and spinal cord compression, which may all severely affect the quality of life of the patient. Skeletal metastases are commonly classified as either osteolytic—when the destruction of normal bone is the predominant feature—or osteoblastic—when the deposition of new bone predominates, although this distinction is not absolute. Many lesions are mixed or impossible to classify on radiological images, and bone markers often reveal that

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both processes are ongoing (especially in prostate cancer). In the two types of lesions, there is a dysregulation of the normal bone remodeling process.

The bone is commonly affected both in localized and advanced prostate cancer, in the former mainly as a result of prolonged androgen deprivation therapy (ADT) for locally advanced disease, which causes cancer treatment–induced bone loss (CTIBL), and in the latter by metastatic bone destruction with or without CTIBL caused by prolonged ADT. Bone is the most common site of metastasis in prostate cancer, affecting 85%–90% of men with advanced disease [1, 2]. It is a cause of significant morbidity such as pain, pathologic fractures, nerve compression, and hypercalcemia. Once the disease has spread to the bone, prostate cancer is incurable. Osteoporotic fractures induced by bone metastases and CITBL are also a real clinical problem. Clearly, new approaches and novel therapies are required to alter the course of aggressive metastatic disease and ameliorate the effects of ADT on bone mineral density (BMD).

The main therapeutic alternatives directed at treating bone metastases in prostate cancer have been external beam radiotherapy, radioisotope treatment, and intravenous bisphosphonates (i.v. BPs), often in conjunction with ADT or chemotherapy. Up to now, none of these treatments is curative, but they are aimed to reduce the risk of skeletal-related events (SREs), which in turn can increase quality of life and life expectancy. Regarding CITBL prevention, no approved therapeutic alternatives are available, but it is expected that some of the treatments indicated for bone metastases will also help reduce bone loss. Strontium-89 ($_{89}$Sr) is the prototypic example of a bone-targeted radioisotope, which functions as a calcium analogue preferentially taken up at areas of increased bone turnover. In a phase III trial, radioisotope treatment was associated with decreased opioid usage and increased quality of life, but no survival benefit or appreciable antitumor activity was observed [3]. BPs are synthetic analogues of pyrophosphate, a physiologic constituent of the bone matrix. They have the capacity to inhibit, directly and indirectly, osteoclast activity, resulting in decreased bone resorption [4]. Zoledronic acid was the first BP to demonstrate efficacy in a phase III trial in reducing SREs in men with prostate cancer and bone metastases [5], leading to approval in this indication by the European Medicines Agency (EMA) in 2001 and the U.S. Food and Drug Administration (FDA) in 2002.

Preclinical and clinical studies have provided increasing insight into the physiopathology of bone metastases and osteoporosis, providing new potential therapeutic strategies. On the basis of recent advances in the understanding of the bone microenvironment and cancer cell interactions, the development of new targeted therapies, capable of disrupting these interactions, is being tested. One molecule that has proven central to osteoclast formation, function, and survival is the receptor activator of nuclear factor kappa B ligand (RANK-L). Denosumab is a fully human monoclonal antibody against RANK-L that is being investigated in a variety of tumors. In the last year, results from several phase III trials with denosumab in different clinical settings have been presented. Here, we review present knowledge of the role of RANK-L in bone physiopathology and the latest clinical data on denosumab in prostate cancer and other tumors.

The Role of RANK and RANK-L in the Control of Normal Bone Remodeling

Preclinical studies have discovered a complex system of multiple interacting proteins and pathways that contribute to the development of bone metastases. The activity of osteoclasts and osteoblasts is intricately coordinated to continually remodel the adult skeleton. There is a well-balanced remodeling sequence in normal bone: bone is first resorbed by osteoclasts and then regenerated by osteoblasts to mature bone.

Osteoclasts arise from the monocyte-macrophage lineage and, when they are activated, reabsorb bone and eventually undergo apoptosis. Locally produced cytokines and systemic hormones regulate this physiological process. Bone resorption is dependent on a cytokine known as RANK-L, a TNF (tumor necrosis factor) family member that is expressed on the surface of osteoblasts and is released by activated T-cells. Most osteotropic factors, such as 1,25-dihydroxivitamin D3 or parathyroid hormone, increase the expression of RANK-L, making it a key stimulator of bone resorption. When RANK, expressed by both osteoclasts and their precursors, binds to RANK-L, it stimulates osteoclast formation [6], activation [7], adherence [8], and survival [9], ultimately leading to increased bone resorption. The catabolic effects of RANK-L are counteracted by osteoprotegerin (OPG), a TNF receptor family member that binds RANK-L and thereby prevents activation of its single cognate receptor, RANK [10]. Osteoclast activity is likely to depend, at least in part, on the relative balance of RANK-L and OPG. Studies in numerous animal models of bone disease show that RANK-L inhibition leads to marked suppression of bone resorption and increases in cortical and cancellous bone volume, density, and strength [11–13].

There are at least three forms of RANK-L, two of which possess a transmembrane domain that positions the biologically active carboxy-terminus in the extracellular domain. One of these forms, RANK-L2, is a shorter alternative splicing variant of RANK-L1 [14]. Both variants can re-

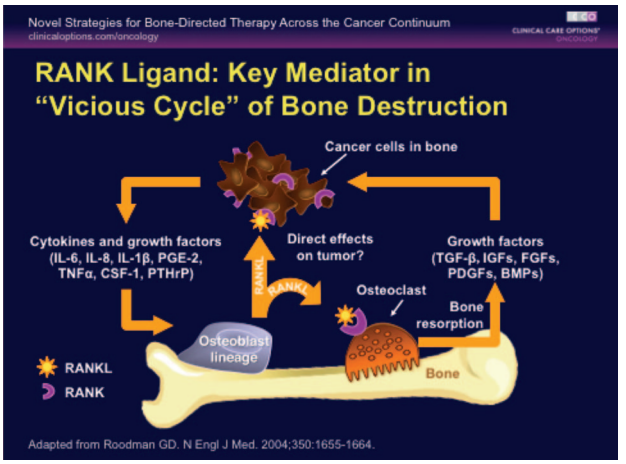

Figure 1. The role of RANK-L in bone formation and resorption. Adapted from Roodman, GD. Mechanisms of bone metastasis. N Engl J Med 2004;350:1655–1664 with permission. Copyright ©2004 Massachusetts Medical Society. All rights reserved.

Abbreviations: BMP, bone morphogenic protein; CSF, colony-stimulated factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; IL, interleukin; PDGF, platelet-derived growth factor; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor-kappa B; RANKL, receptor activator of nuclear factor-kappa B ligand; TGF, transforming growth factor; TNF-α, tumor necrosis factor-α.

main on cell surfaces or can be proteolytically cleaved into soluble forms that possess osteoclast-stimulating activities within their TNF-homology domains [15, 16]. Numerous cell types including cells of the osteoblast lineage [17] and activated T cells [18] produce RANK-L. T cells express both soluble and membrane-bound forms of RANK-L [19], and both forms are implicated in focal bone erosions associated with inflammatory arthritis. Cells of the osteoblast lineage can express RANK-L on their surface in a manner that facilitates osteoclastogenesis in vitro via cell-to-cell contact with osteoclast precursors [20]. In most situations, RANK-L probably relies on macrophage colony-stimulated factor as a cofactor for osteoclast differentiation [21].

The expression of RANK-L is controlled by numerous cytokines and hormones, commonly known as regulators of the immune system and calcium homeostasis (Fig 1). Among the proresorptive factors are $1,25(OH)_2$ vitamin D_3, parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP), prostaglandin E2, interleukin-1 and -6, TNF, prolactin, and corticosteroids (Fig. 2). However, estrogens, calcitonin, transforming growth factor-β, platelet-derived growth factor, and calcium induce OPG expression, leading to neutralization of RANK-L and thereby inhibition of osteoclastogenesis and resorption [22].

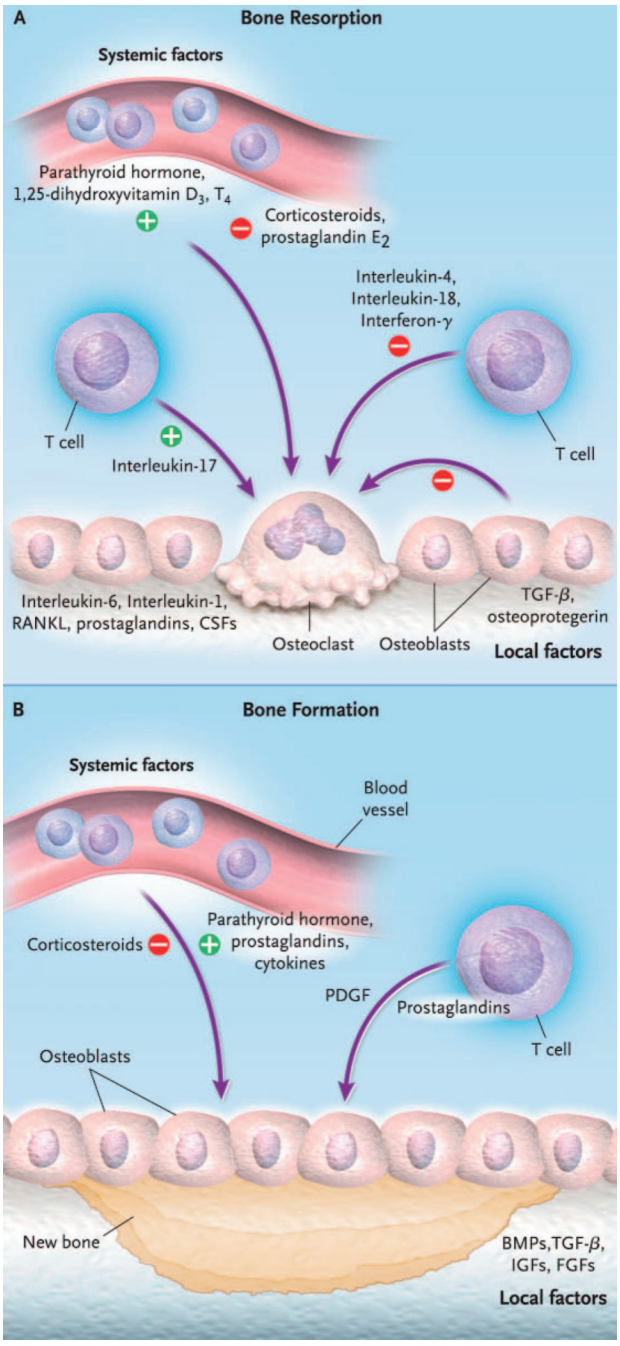

Figure 2. Factors implicated in bone resorption **(A)** and formation **(B)**.

Abbreviations: BMP, bone morphogenic protein; CSF, colony-stimulated factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor; RANKL, receptor activator of nuclear factor-kappa B ligand.

RANK is the receptor that mediates all activities of RANK-L. The binding and activation of RANK involves direct interactions between the extracellular receptor binding domain of RANK-L and the extracellular cysteine-rich domains of RANK. This interaction causes oligomerization

of RANK and the subsequent activation of several signal transduction pathways, especially protein kinase pathways and transcription factors such as nuclear factor-kappa B (NF-κB). Activated NF-κB upregulates the expression of c-fos to induce the transcription of osteoclastogenic genes [23].

The Role of RANK and RANK-L in the Development of Bone Metastases

Recent evidence indicates that osteoblastic metastases form on trabecular bone at sites of previous osteoclast resorption. In fact, such resorption is necessary for subsequent osteoblastic bone formation [24, 25]. These findings suggest that prostate cancer cells induce bone production through an overall increase of bone remodeling [26]. In fact, animal models of prostate cancer metastasis have shown that skeletal lesions frequently exhibit increased osteoclast activation and osteolysis, although bone metastases radiologically have an osteoblastic appearance [27]. When neoplastic cells from prostate cancer metastasize to bone, they initially induce osteoclastogenesis and bone resorption. RANK, RANK-L, and its soluble decoy receptor OPG play an essential role in the regulation of this process [28]. It has been shown that metastatic prostate cancer cells in bone (and not at other sites) express both RANK-L and its "antagonist" OPG. OPG, however, seems to have a primarily nuclear localization in these cells, whereas normally it is expressed in the cytoplasm. This could affect the bioavailability of this protein [29]. Similar findings have been made in in vitro experiments with multiple myeloma cells [30]. Breast cancer cells have been shown not only to express RANK [31] but also to upregulate RANK-L expression by osteoblasts and bone marrow stromal cells [32]. Prostate cancer cells can also upregulate RANK-L expression in osteoblasts [33].

Preclinical and Early Clinical Data on Denosumab

Denosumab is a fully human monoclonal antibody with a high affinity and specificity for RANK-L and can thus bind and thereby neutralize the activity of RANK-L in a similar fashion as OPG. Denosumab, as other fully human therapeutic antibodies, has been produced in transgenic mice, by deleting their murine immunoglobulin genes and replacing them with human orthologs [34]. The activity of denosumab is primate-specific, and it cannot be tested in rat models of bone metastasis. However, because OPG and denosumab have similar mechanisms of action, OPG has been used as a surrogate for the study of RANK-L inhibition in animal models. These experiments have shown that OPG markedly reduces osteoclast numbers in bone lesions that resulted from direct intratibial injection of human prostate cancer cells into immunodeficient mice [35]. Experiments in rats have shown that a single injection of OPG resulted in a rapid (within 12 hours) and deep (up to 95%) reduction in the percentage of bone surfaces occupied by osteoclasts, which then gradually returned to normal from days 10–30 after injection as the drug is cleared from the circulation. Osteoblast surface and biochemical markers of osteoblast activity were more modestly suppressed. These changes were associated with a progressive increase in bone mineral density at day 30 compared with controls [36].

The marked suppression of bone turnover associated with RANK-L inhibition raises the question of the possible consequences of long-term therapy to bone strength and bone quality. Non-human primates represent the most appropriate preclinical species for evaluating the skeletal response to therapeutic intervention. In young gonad-intact monkeys, three months of OPG treatment led to significant reductions in biochemical markers of bone turnover [37]. OPG treatment was associated with decreases in serum ionized calcium and phosphorus levels, an expected consequence of suppressed bone resorption, and a secondary increase in serum PTH levels. In this study, the treatment increased BMD. There were no treatment-related clinical observations and no treatment-related histopathologic findings in animals treated for 1 or 3 months with OPG. Similarly, 12 months of denosumab treatment in cynomolgus monkeys was associated with significant increases in bone strength [38].

Moving into clinical trials in humans, two phase I trials have been conducted with denosumab in cancer patients. Body et al. [39] developed a phase I study looking at safety, pharmacokinetics, and pharmacodynamics of a single subcutaneous injection in patients with breast cancer or multiple myeloma. Patients received a single dose of either denosumab (0.1, 0.3, 1.0, or 3.0 mg/kg) or pamidronate (90 mg iv). The most common adverse events were fatigue and asthenia, and no serious drug-related adverse events were reported. Pharmacokinetics studies showed a rapid and prolonged absorption, starting 1 hour postdose and reaching maximum serum levels as late as 21 days later. Effects on bone resorption were assessed by changes in urinary and serum *N*-telopeptide (NTX) levels. In patients treated with denosumab, levels decreased within 1 day and this effect lasted through day 84 in the higher dose levels, whereas the effect of pamidronate reached a maximum at 3 days and started to rise again on day 28. The other phase I trial was carried out in 18 Japanese patients who received a single subcutaneous injection of 60 or 180 mg or three doses of 180 mg every 4 weeks. No major safety concerns or dose-limiting toxicities were noted in any cohort. Denosumab

Table 1. Ongoing trials of denosumab for breast cancer, multiple myeloma, and prostate cancer (http://www.clinicaltrials.gov)

Study/design	*N*	Study population	Arms	Primary endpoint
Prostate cancer				
NCT00321620/phase III	1901	Hormone refractory nonmetastatic prostate cancer	Denosumab vs zoledronic acid	Time to first on-study SRE (noninferiority test)
NCT00089674/phase III	1468	Androgen deprivation therapy for nonmetastasic prostate cancer	Denosumab vs placebo	% change from baseline in lumbar spine BMD
NCT00286091/phase III	1435	Hormone refractory prostate cancer without bone metastases	Denosumab vs placebo	Time to first ocurrance of bone metastasis or death
Breast cancer				
NCT00321464/phase III	2046	Advanced breast cancer	Denosumab vs zoledronic acid	Time to first on-study SRE
NCT00556374/phase III	2800	Nonmetastatic breast cancer receiving AI	Denosumab vs placebo	Time to first clinical fracture
Other solid tumors and multiple myeloma				
NCT00259740/phase II	96	Relapsed or plateau-phase MM	Denosumab	CR or PR to treatment (serum M protein)
NCT00330759/phase III	1776	Advanced cancer (excluding breast and prostate) and MM	Denosumab vs zoledronic acid	Time to first on-study SRE (noninferiority test)

Abbreviations: AI, aromatase inhibitors; BMD, bone mass density; CR, complete response; MM, multiple myeloma; PR, partial response; SRE, skeletal-related event.

caused rapid, substantial, and sustained suppression of urine NTX (uNTX). The median change of UNTX corrected for urine creatinine (uNTx/Cr) from baseline ranged from −61.9% to −90.8% [40].

The optimal dose regimen has been studied in a phase II trial evaluating five dose regimens of denosumab in 255 patients with bone metastases not previously treated with i.v. BPs. Patients were randomized to receive either denosumab or i.v. BP. Denosumab was administered subcutaneously either every 4 weeks (30, 120, or 180 mg) or every 12 weeks (60 or 180 mg), and the i.v. BP was administered every 4 weeks. The primary endpoint was median percent change in uNTX/Cr from baseline to week 13. Overall, 74% of denosumab-treated patients achieved a reduction in uNTx of >65%, compared with 63% of i.v. BP treated patients without any unexpected serious adverse events related to study treatment. The dose regimen showing the greatest suppression of bone resorption seems to be 120 mg every 4 weeks, according to this study. The authors conclude that these data suggest that denosumab may be similar to i.v. BP in both efficacy and safety [41].

Recently published results from a randomized phase II trial of denosumab versus continued i.v. BP provide insights on the effect of denosumab in patients previously treated with an i.v. BP. The trial included 111 patients with bone metastases from prostate cancer, breast cancer, multiple myeloma, or other solid neoplasms currently receiving i.v. BP. Eligible patients for this study had at least 1 bone metastasis, and uNTx levels > 50 nmol/L bone collagen equivalents/mM creatinine despite ongoing i.v. BP therapy. The primary endpoint of the study was the percentage of patients with an uNTx < 50 at week 13 and was reached by 71% of the patients on the denosumab arm and 29% in the i.v. BP arm ($p < .001$). This difference diminished slightly over time: at 25 weeks of follow-up, 64% versus 37% ($p = .01$), respectively, of patients maintained an uNTx <50. There was also a nonsignificant trend toward fewer SREs in the denosumab group versus the i.v. BP group (8% versus 17%, respectively). The study shows that denosumab normalized uNTx levels more frequently than continued i.v. BP therapy, whereas the rate of adverse events was similar between the two groups [42].

Several other phase II trials are being conducted, and there are at present 23 phase III trials registered with denosumab in http://www.clinicaltrials.gov, 10 of which are in the oncological setting. The rest of this review will focus on the most important trials with this compound in cancer patients, including recently presented results.

Clinical Studies of Denosumab in Prostate Cancer

Three phase III trials are currently ongoing to determine the efficacy of denosumab in men with prostate cancer (Table 1).

There is no approved therapy for the prevention of bone

Table 2. Time to first on-study skeletal-related event in the three pivotal phase III trials [47, 52, 59]

Study/design	Hazard ratio		*p*-value
	Point estimate	95% CI	
Breast cancer ($N = 2046$)	0.82	(0.71, 0.95)	.01
Prostate cancer ($N = 1901$)	0.82	(0.71, 0.95)	.008
Other solid tumors or multiple myeloma ($N = 1776$)	0.84	(0.71, 0.98)	.06

Hazard ratio <1 favors denosumab.
Abbreviations: CI, confidence interval; SRE, skeletal-related event.

loss induced by hormonal treatment of prostate cancer, although by extrapolation of data from studies in osteoporosis, many physicians use both oral and i.v. BPs in this setting. Several phase III clinical trials with denosumab address its use in the setting of postmenopausal osteoporosis, confirming its capacity to increase BMD, decrease bone turnover, and reduce fracture in this population [43–45]. Recent results have also confirmed its efficacy in reducing CTIBL in both prostate and breast cancer, as follows.

NCT00089674, also known as the HALT-prostate cancer trial, was a randomized double-blind, placebo-controlled phase III trial that accrued 1468 men with nonmetastatic prostate cancer receiving ADT. The purpose was to evaluate denosumab in the prevention of bone loss in this group of patients. The subjects were randomized to either 60 mg of denosumab by subcutaneous injection every 6 months or placebo, together with calcium and vitamin D supplements. The primary endpoint was percent change of BMD in the lumbar spine after 24 months of treatment, and fracture rate was a secondary endpoint. The results indicated a significant difference between the two treatment arms, with a 5.6% increase in BMD in the denosumab group and a 1.0% decrease in the placebo group ($p < .001$). There was also a significant difference in vertebral fracture rate at 36 months in favor of denosumab: 1.5% versus 3.9% ($p = .006$). Rates of adverse events were similar between the two groups, and no cases of osteonecrosis of the jaw (ONJ) were reported [46].

Trial NCT00321620 was a phase III randomized double-blind, double-dummy trial that compared the efficacy and safety of denosumab versus zoledronic acid in 1901 men with prostate cancer, bone metastasis, and disease progression despite ADT (without prior i.v. BP use). The primary endpoint was time to first on-study SRE, defined as pathological fracture, radiation to bone, surgery to bone, or spinal cord compression. Patients were randomized to receive either subcutaneous denosumab 120 mg and i.v. placebo ($n = 950$), or subcutaneous placebo and i.v. zoledronic acid 4 mg ($n = 951$). Denosumab significantly delayed the time to first on-study SRE (median of 20.7 months versus 17.1 months with zoledronic acid; $p = .008$) (Table 2), as well as the time to first and subsequent on-study SRE ($p = .004$). A greater suppression of the bone turnover markers uNTx and bone-specific alkaline phosphatase was also observed in denosumab patients compared with zoledronic acid ($p < .0001$ for both). Adverse event rates were similar, irrespective of potential relationship to study drugs. Hypocalcemia was reported in 13% and 6% of denosumab and zoledronic acid patients. Overall survival ($p = .65$) and time to cancer progression ($p = .30$) were similar between the two arms. These results demonstrated the superiority of denosumab over zoledronic acid in delaying or preventing SREs in patients with bone metastases from hormone-refractory prostate cancer [47].

NCT00286091 is a trial with a slightly different aim: to study a possible metastasis-preventive effect of denosumab. It is a randomized double-blind, placebo-controlled phase III trial of 1435 patients with hormone refractory prostate cancer with no bone metastases at baseline but a rising prostate-specific antigen (PSA) despite ADT. Only patients at high risk for development of bone metastasis based on PSA > 8 ngs/dl and/or PSA doubling time < 10 months are included. The primary endpoint is bone metastasis-free survival. Enrollment has concluded, and first results are awaited soon (http://clinicaltrials.gov).

Clinical Studies of Denosumab in Breast Cancer

Breast cancer can induce several osteotropic factors that in turn induce RANK-L production by stromal cells in bone marrow. In experimental models, breast cancer cells increase stromal cell expression of RANK-L [48], probably through the effects of PTHrP [49]. In stromal tissue surrounding a breast cancer, the levels of stromal RANK-L are increased, although with no effect on circulating levels. As a response to high RANK-L levels, OPG also rises and binds excess RANK-L [50].

In the clinical setting, the effects of denosumab in breast cancer patients have been extensively studied during the last several years. One patient population of special interest is women with hormone receptor-positive breast cancer receiving adjuvant aromatase inhibitors, due to the increased risk of developing osteopenia and osteoporosis. Results have been published from a randomized phase III study (NCT00089661, also known as the HALT-BC trial) including 252 patients in this clinical setting. They were randomly assigned to receive either 60 mg of subcutaneous deno-

sumab every 6 months (127 patients) or placebo (125 patients), and all received supplementary vitamin D and calcium. The primary outcome measure was change in BMD. At 12 and 24 months, lumbar spine BMD had increased by 5.5% and 7.6%, respectively, in the denosumab arm versus placebo ($p < .0001$), with decreased bone turnover markers in the denosumab group. No differences in adverse events were found between the two groups [51]. Another phase III study (NCT00556374, the ABCSG-18 trial) in this population is currently recruiting patients for randomization to either denosumab treatment or placebo in conjunction with the aromatase inhibitors treatment. The primary endpoint in this trial, however, is time to first clinical fracture. Accrual is ongoing with the goal of including 2800 patients.

The trial NCT00321464 is a randomized phase III trial comparing denosumab with zoledronic acid in patients with metastatic breast cancer. The primary endpoint is time to first on-study SRE. The first results were recently presented confirming the superiority of denosumab in delaying or preventing the onset of the first on-study SRE (hazard ratio [HR] 0.82; 95% confidence interval [CI]: 0.71–0.95; $p = .01$), as well as subsequent SREs (HR 0.77; 95% CI: 0.66–0.89; $p = .001$) (Table 2). There were no significant differences in the frequency of adverse events, including some cases of ONJ in both treatment arms [52].

Clinical Studies of Denosumab in Other Solid Tumors and Multiple Myeloma

In multiple myeloma, >80% of patients develop osteopenia or osteolytic lesions due to increased bone resorption caused by stimulation of osteoclast formation and activity [53–55]. This increased osteoclast activity is accompanied by decreased or absent osteoblast function. Several studies have identified potential novel targets for treating bone disease in multiple myeloma including the Wingless-type and the RANK-L pathways [56]. Focusing on the latter, Giuliani et al. [57] and other authors have reported that there is an imbalance between OPG and RANK-L levels in the bone marrow environment of patients with multiple myeloma, although the cell source for RANK-L production in the microenvironment remains controversial. Vij et al. [58] recently reported the results of a phase II trial in patients with plateau-phase or progressive multiple myeloma, demonstrating that denosumab significantly inhibited the RANK-L pathway as demonstrated by decreased levels of bone turnover markers, although the principal hypothesis of the study—a possible cytotoxic effect of RANK-L inhibition—could not be confirmed.

The results from a randomized, double-blind phase III trial (NCT00330759), comparing denosumab with zoledronic acid in the treatment of bone metastases in 1776 patients with advanced cancer or multiple myeloma and no previous i.v. BP therapy, were also recently presented. The patients were randomized to receive either 120 mg of denosumab or 4 mg of zoledronic acid every 4 weeks, and all were recommended to take vitamin D and calcium supplements. Denosumab delayed the time to first on-study SRE (pathologic fracture, radiation therapy or surgery to bone, or spinal cord compression) and was noninferior to zoledronic acid (HR 0.84; 95% CI: 0.71–0.98; $p = .0007$). The median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for zoledronic acid. Although numerically greater, the delay in time to first on-study SRE with denosumab was not superior to zoledronic acid based upon the statistical testing strategy (adjusted $p = .06$) (Table 2). Time to first and subsequent SRE was numerically greater for denosumab (HR 0.90; 95% CI: 0.77–1.04; $p = .14$). The overall incidence of adverse events was similar between the two groups, including the reported rate of ONJ: 1.1% and 1.3% in the denosumab and zoledronic acid arms, respectively [59]. Although this study showed a trend toward superiority of denosumab versus zoledronic acid in delaying the time to first on-study SRE in patients with advanced solid tumors and multiple myeloma, further trials in myeloma patients are needed to support the use of denosumab in this population. A subset analysis of the same study presented at the American Society of Clinical Oncology (ASCO) 2010 meeting compared the treatment effects in only patients with solid tumors and bone metastases ($n = 1597$) [60]. Denosumab significantly delayed the time to the first on-study SRE compared with zoledronic acid (HR 0.81; 95% CI: 0.68–0.96; $p < .02$) and also delayed the time to first and subsequent SREs (HR 0.85; 95% CI: 0.72–1.00; $p < .05$). These results support that denosumab is more effective than zoledronic acid in patients with solid tumors and bone metastases.

Safety Profile

Generally speaking, denosumab is well tolerated. Perhaps the most comprehensive safety analysis that is publicly available is the FDA's analysis of the currently available evidence in relation to its evaluation of this drug for treatment of postmenopausal women who have a high risk for osteoporotic fractures (60 mg dose administered every 6 months) [61]. Looking at placebo-controlled phase III trials, there are few adverse events that differ clearly in incidence between denosumab and placebo groups. Some of the most frequently reported adverse events are arthralgia, back pain, pain in extremity, musculoskeletal pain, peripheral edemas, cough, and dizziness. The most commonly altered laboratory value is serum calcium levels, where

denosumab can cause hypocalcemia that is, however, usually transient and rarely symptomatic. Nadir for serum calcium after a dose of denosumab is reached around day 10. There are currently no indications that treatment with denosumab may lead to impaired renal function.

In terms of possible serious drug-related adverse events, there has been a concern that denosumab may increase the risk of serious infections or immune reactions, due to the fact that RANK-L is expressed on T and B cells as well. Although according to the FDA report patients treated with 60 mg of denosumab every 6 months had a slightly increased incidence of serious infections (4.1% for denosumab versus 3.3% for placebo), the incidence of overall infections and opportunistic infections did not differ between groups.

Another concern is the possibility of ONJ. A preplanned integrated analysis of the three trials comparing denosumab with zoledronic acid for preventing skeletal-related events in cancer patients with bone metastases [62] found that, among 5673 patients who received at least one treatment dose, ONJ occurred in 1.8% ($n = 52$) of denosumab-treated patients and 1.3% ($n = 37$) of zoledronic acid–treated patients ($p = .13$). The majority of these patients experienced at least one known risk factor (81% in both arms had undergone tooth extraction, had poor oral hygiene, or used a dental appliance; 67% and 73%, respectively, had received chemotherapy; and 10% and 22% had received prior antiangiogenic therapy). ONJ resolution during the study occurred in 35% of denosumab- and 27% of zoledronic acid–treated patients. These data suggest that ONJ risk with denosumab is the same as with zoledronic acid and that some preventive actions should be undertaken prior to and during treatment.

Conclusions and Future Directions

Metastatic disease to the bone had, during the whole history of cancer treatment, been a cruelly crippling complication of the tumor, leaving many patients bedridden or wheelchair-bound. With the advent of the iv BPs this changed radically, by progressively reducing the risk of SREs with increasing potency of the drugs [63]. As clinical experience with these drugs increased, however, awareness also increased regarding their safety profile and the potential risk of ONJ. This occasionally disfiguring and mutilating complication, the real incidence of which is not quite ascertained, changed the risk-benefit ratio for the use of i.v. BP in metastatic disease. Great effort has been put into discovering the pathophysiology of ONJ and possible ways to prevent it, and progress has been made, which once again shifts the scale toward the benefit side. The inclusion of new pharmacological alternatives in the treatment of bone metastases will most probably be the best way to further tilt the risk-benefit scale in the right direction for these patients.

Denosumab represents a new therapeutic approach by targeting the RANK-L pathway essential for osteoclast differentiation, activation, and function, and whose expression seems to be induced by cancer cells. In oncology it is being developed in two specific areas: prevention and treatment of CTIBL, and treatment of bone metastases. Recent clinical data demonstrate that denosumab is well tolerated and effective in increasing BMD and reducing bone turnover and fracture rates versus placebo. Phase III data also confirm its efficacy in preventing or delaying SREs in patients with metastatic disease of the bone. In terms of efficacy, it is as good as, and perhaps better than, zoledronic acid. The subcutaneous route of administration adds convenience to patients as well. The overall safety profile seems to be clearly manageable, although treatment with denosumab is still associated with a low risk of ONJ, similar to that observed with i.v. BPs. Prevention of this entity in denosumab-treated patients is recommended. Prior to initiating therapy, a routine dental clinical examination should be performed. All patients should be instructed to avoid elective invasive dental procedures, and routine oral assessments during treatment should be scheduled.

In conclusion, denosumab has added benefits that may help in the search for the optimal treatment of metastatic disease to the bone. Most of the phase II and III trials with denosumab in oncology have completed accrual but have yet to present their results. Much new information will be gained about RANK-L inhibition in general and denosumab in particular, to further improve quality of life in cancer patients.

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