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RANK Ligand Inhibition: A Novel Strategy for the Treatment of Bone Metastases

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Abstract

Context: Prostate cancer (PCa) is associated with bone metastases, which lead to disruption in the normally well-controlled process of bone remodelling. This disruption may lead to bone pain and fractures. Improvements in the assessment and management of bone metastases are therefore required.
Objective: To assess the value of bone turnover markers, particularly *N*-telopeptide in urine (uNTx), in predicting skeletal events and the potential of the novel agent denosumab to reduce the secondary disruption to bone in men with PCa.
Evidence acquisition: This article is based on a presentation at an Amgen satellite symposium held at the European Association of Urology Congress in Stockholm, Sweden, in March 2009.
Evidence synthesis: High levels of uNTx in patients with bone metastases secondary to a range of cancers, including PCa, are associated with an increased risk of skeletal-related events (SRE) and death. Denosumab is a fully human monoclonal antibody that binds to and inhibits RANK Ligand, currently under development as a potential new treatment for bone metastases associated with a broad range of tumours. Denosumab has been shown to reduce the level of uNTx in patients with bone metastases resulting from breast cancer. Treatment with denosumab also has beneficial effects on other bone markers and the incidence of SRE in these patients. Similarly, denosumab reduces uNTx levels and the risk of SRE in patients with other primary tumours, including PCa. Evidence from an active-comparator study involving patients previously unresponsive to bisphosphonates suggests a benefit of denosumab over continued bisphosphonate treatment.
Conclusions: Measurement of uNTx levels may be a useful marker for identifying patients most at risk of skeletal complications. Denosumab suppresses uNTx levels, and trials evaluating the efficacy of denosumab in preventing and treating complications caused by bone metastases are continuing.

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1. Introduction

Prostate cancer (PCa) has the tendency to metastasize to bone, leading to disruption in the normally well-controlled process of bone remodelling [1]. The mechanisms responsible for tumour growth in bone are complex and may involve stimulation of both osteoblasts and osteoclasts, even when the radiographic appearance of the lesions is osteoblastic (as is often the case in PCa) [1]. The risk of skeletal complications is strongly related to the rate of bone

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resorption in both breast and prostate cancer [2,3]. Bone lesions give rise to skeletal-related events (SREs), including pathological fractures, pain requiring palliative radiation therapy, spinal cord compression, hypercalcaemia and severe bone pain, all leading to a reduced quality of life, surgery, increased morbidity and burden on health care resources [4].

Improved methods of identifying and monitoring bone metastases are needed now that new treatments for bone metastases are being developed (eg, RANK Ligand). Radiography is not a convenient method for frequent assessment of disease progression, so measurement of bone markers is being investigated. In the future, the altered bone remodelling activity observed in patients with PCa could be assessed by analysing markers of bone formation and resorption in serum or urine samples.

2. Evidence acquisition

This article is based on a presentation at an Amgen-sponsored satellite symposium held at the European Association of Urology Congress in Stockholm, Sweden, in March 2009.

3. Evidence synthesis

3.1. *Bone markers in patients with bone metastases*

Numerous biomarkers of bone remodelling have been assessed. Bone formation can be assessed in the early phase of osteoblastic proliferation using the serum enzyme marker bone-specific alkaline phosphatase (BSAP) and a metabolic indicator amino-terminal propeptide of type 1 procollagen (P1NP). Osteocalcin, a noncollagenous protein secreted by osteoblasts during the later phase of bone formation, can also be used [5]. Mature type 1 bone collagen contains cross-linking amino acid derivatives (pyridinium cross-links) that add tensile strength to bone. Pyridinium cross-links are released into the circulation both in a free state and bound to peptide during the process of bone collagen breakdown and are not metabolised further.

The degree of bone resorption can be assessed by measuring by-products of bone collagen breakdown, including two different telopeptide fragments of mature type 1 collagen [6]: a peptide of the N-terminus, called *N*-telopeptide (NTx), is usually measured in urine samples (uNTx) by immunoassay, whereas the C-terminus peptide (*C*-telopeptide [CTx]) is measured using assays that usually require serum samples (sCTx) [6]. The monoclonal antibody in the uNTx immunoassay was raised against the $\alpha 2$ chain of type I bone collagen fibrils and does not recognise the attached pyridinium cross-link [7]. Tartrate-resistant acid phosphatase 5b (TRAP-5b) is another marker of bone resorption shown to be a useful predictor of survival in patients with PCa and bone metastases [5,8].

Several studies have assessed the diagnostic efficacy of bone turnover markers for the detection of bone metastases in patients with cancer. Levels of the bone resorption marker uNTx discriminated between cancer patients with and without bone metastases [7]. In addition, levels of uNTx and serum BSAP in cancer patients with bone metastases showed a significant correlation ($p < 0.05$) with the number of skeletal sites involved with bone metastasis [6]. Furthermore, monthly measurement of uNTx levels during treatment with bisphosphonates in 121 cancer patients with metastatic bone disease indicated a strong correlation between the rate of bone resorption and the frequency of skeletal complications [3]. In another study, levels of uNTx and BSAP were assessed every 3 mo in patients with PCa or other tumours. Overall, levels of uNTx were a more consistent indicator of SREs, time to first SRE and occurrence of disease progression and death than were levels of BSAP for all tumour types [2]. For the group with PCa, a high uNTx level during the study was associated with a >3-fold increased risk of an SRE compared with a low uNTx level (Fig. 1). Thus, measurement of uNTx may be a particularly useful marker of outcomes in these patients. Further studies in breast cancer were recently reviewed, indicating that measurement of uNTx is increasingly useful in the management and understanding of breast cancer [9].

More recently, a study investigated whether reductions in uNTx levels correlated with improved clinical outcomes in men with bone metastases associated with PCa [10]. In this randomised, placebo-controlled trial of zoledronic acid (a third-generation bisphosphonate [11]), patients were stratified by baseline uNTx (normal: <64 nmol/mmol of creatinine; elevated: ≥64 nmol/mmol of creatinine). Levels of uNTx were normalised (ie, <64 nmol/mmol of creatinine) at 3 mo in about 70% of the elevated-uNTx group treated with zoledronic acid, regardless of the degree to which uNTx levels were elevated at baseline. Among patients in the normal group who were alive at 3 mo, normal levels of uNTx were maintained in 117 of 121 patients (96.7%) treated with zoledronic acid compared with only 39 of 59 patients (66%) who received placebo.

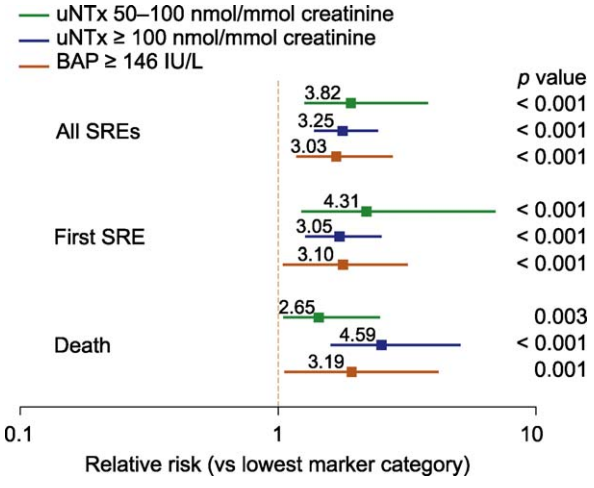

Fig. 1 – Association between bone markers and outcomes in men with metastatic prostate cancer. Adapted from Brown et al [2].
uNTx = urinary *N*-telopeptide; BAP = bone-specific alkaline phosphate; SRE = skeletal-related event.

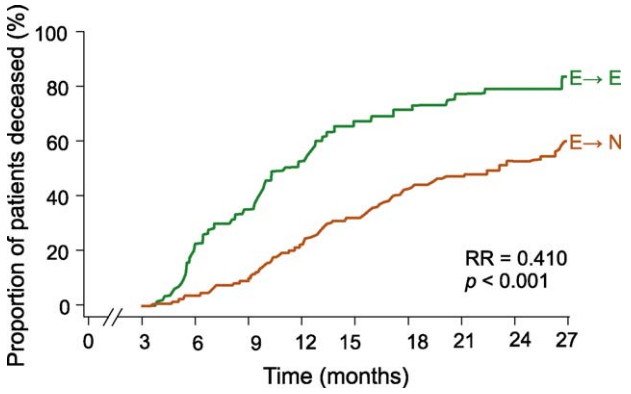

Fig. 2 – Normalisation of urinary *N*-telopeptide (uNTx) at 3 mo correlates with improved survival.
E = elevated baseline uNTx (≥64 nmol/mmol of creatinine); N = normal baseline uNTx (<64 nmol/mmol of creatinine); RR = relative risk of death.

Normalisation of elevated baseline uNTx levels mediated by zoledronic acid was associated with a 59% reduction in the risk of death compared with patients in whom uNTx levels remained persistently elevated at 3 mo (Fig. 2). Similar patterns were observed among placebo recipients with reductions from elevated uNTx at baseline, suggesting that changes in uNTx are truly indicative of a change in risk.

Correlations between uNTx normalisation during treatment and clinical outcomes in three large trials have been analysed retrospectively. In this pooled analysis, levels of uNTx were measured at baseline and at 3 mo in patients with bone metastases from breast cancer ($n = 578$), hormone-refractory PCa ($n = 472$), or non–small-cell lung cancer and other solid tumours ($n = 291$), all of whom received either zoledronic acid or placebo. Normalisation of uNTx within 3 mo of treatment was associated with reduced risks of skeletal complications and death compared with persistently elevated uNTx [12].

Bone markers, in particular uNTx, may indicate risk of bone-related morbidity and mortality in patients with a range of tumours that metastasize to bone. In addition, measurement of uNTx levels may provide a convenient method of assessing the need for and response to therapy.

3.2. Inhibition of RANK Ligand in the treatment of bone metastases

Bone architecture is determined by the balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. The formation, function, and survival of osteoclasts depend on RANK Ligand, which binds to RANK on preosteoclasts and mature osteoclasts. Denosumab is a fully human monoclonal antibody that binds to and inhibits RANK Ligand, thereby suppressing bone resorption by osteoclasts [13,14].

A recent trial evaluated the efficacy and safety of five dosing regimens of denosumab in patients with breast cancer–induced bone metastases not previously treated with intravenous (IV) bisphosphonates [15]. Denosumab was administered subcutaneously every 4 wk (30, 120, or 180 mg) or every 12 wk (60 or 180 mg) for 21 wk (Fig. 3). A sixth cohort received open-label IV bisphosphonates every 4 wk. The percentage changes in uNTx from baseline to week 13 (primary endpoint) [15] and to week 25 were evaluated [16]. The proportion of patients in whom uNTx was reduced by >65% and the percentage experiencing one or more SRE were also determined at both time points [16].

All doses of denosumab resulted in rapid reduction of uNTx. This reduction was seen at the first study visit after the initial dose (week 2) and continued throughout the 25 wk of treatment (Fig. 4). The median percentage change from baseline in uNTx was similar in the pooled denosumab and bisphosphonate groups at week 13. A reduction in uNTx >65% occurred in 74% of denosumab-treated patients and 63% of bisphosphonate-treated patients at week 13, but this difference was not statistically significant. The level of suppression of uNTx remained similar in the pooled denosumab group and bisphosphonate group after 25 wk of treatment. Levels of other bone-turnover markers (sCTx, BSAP, TRAP-5b, P1NP, and osteocalcin) were also similarly suppressed by denosumab and IV bisphosphonates.

During the first 13 wk of the study, SREs were experienced by 9% of denosumab-treated patients (20 of 211) compared with 16% of bisphosphonate-treated patients (7 of 43), with fracture being the most common SRE. At week 25, these values were 12% and 16%, respectively. Overall, these data suggest a potential benefit of denosumab in reducing the incidence of SREs. Adverse events were as expected in

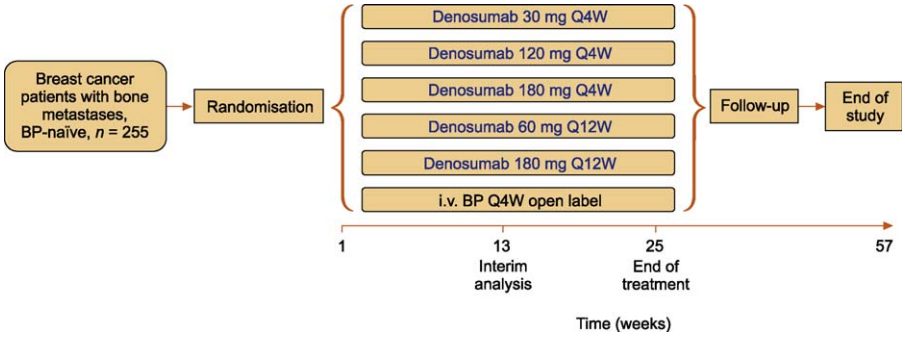

Fig. 3 – Design for phase 2 study of denosumab in patients with breast cancer and bone metastases not previously treated with intravenous bisphosphonates [15].
BP = bisphosphonate; Q4W = every 4 wk; Q12W = every 12 wk; i.v. = intravenous.

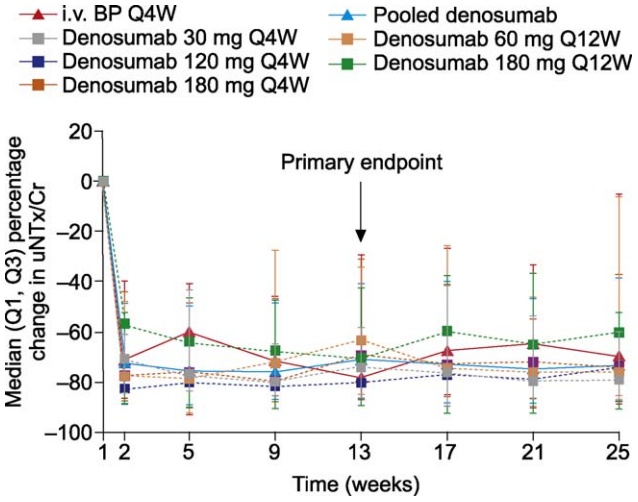

Fig. 4 – Effect of denosumab given every 4 wk or every 12 wk on urinary *N*-telopeptide corrected for creatinine in a phase 2 study in patients with breast cancer and bone metastases not previously treated with bisphosphonates. Redrawn with permission from Lipton et al [16].
i.v. = intravenous; BP = bisphosphonate; Q4W = every 4 wk; Q12W = every 12 wk; uNTx/Cr = urinary *N*-telopeptide corrected for creatinine.

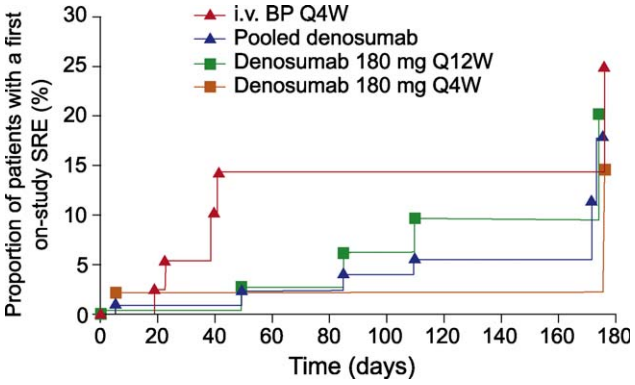

Fig. 5 – Kaplan-Meier estimate of time to first skeletal-related event in patients with bone metastases associated with different cancers who were treated with denosumab every 4 wk or every 12 wk or intravenous bisphosphonates every 4 wk. Redrawn with permission from Fizazi et al [17].
SRE = skeletal-related event; BP = bisphosphonate; Q4W = every 4 wk; Q12W = every 12 wk; i.v. = intravenous.

patients with advanced cancer receiving systemic chemotherapy or hormone therapy [16]. These data support the further investigation of denosumab as a potential treatment for bone destruction associated with metastatic cancer.

A recent study assessing this potential included patients with bone metastases associated with PCa ($n = 50$), breast cancer ($n = 46$), multiple myeloma ($n = 9$), or other neoplasms ($n = 6$) who had elevated uNTx levels despite ongoing IV bisphosphonate therapy [17]. Eligible patients were stratified by tumour type and screening uNTx levels, and then randomly assigned to receive subcutaneous injections of denosumab 180 mg (either every 4 wk or every 12 wk) or continued IV bisphosphonates every 4 wk for 25 wk. The primary endpoint was normalisation of uNTx levels (defined in this study as uNTx levels <50 nmol/mmol of creatinine) at week 13, which was achieved by significantly more patients (49 of 69; 71%) in the pooled denosumab group than in patients who continued on IV bisphosphonates (10 of 35 patients; 29%; $p < 0.001$). The uNTx level decreased within 2 wk of the first denosumab dose, and the overall decrease in uNTx at week 13 was greater with denosumab than with ongoing IV bisphosphonates. These results were consistent across tumour types and screening uNTx levels. The extent of uNTx reduction was generally maintained over 25 wk, and a higher proportion of patients treated with denosumab (64%) maintained normalised levels of uNTx over 25 wk compared with those who continued to receive IV bisphosphonates (37%). In patients in whom uNTx levels remained elevated while on bisphosphonate therapy, the odds of achieving normalised uNTx levels were significantly greater with denosumab than with IV bisphosphonates at week 13 (odds ratio [OR], 7.6; 95% confidence interval [CI], 2.8–20.5) and week 25 (OR, 3.0; 95% CI, 1.3–6.9).

Use of denosumab resulted in a 2.5-fold greater suppression of TRAP-5b levels than with continued IV bisphosphonates, further demonstrating that denosumab actively inhibited osteoclast formation in these patients. Levels of sCTx and the bone formation markers BSAP, P1NP, and osteocalcin were reduced at the first visit after the initial dose of denosumab, and these reductions were sustained over 25 wk.

Importantly, the positive effects on bone markers translated into a positive effect on SREs (Fig. 5). The percentage of patients experiencing a first SRE during the 25-wk treatment period was 8% (6 of 73) for the pooled denosumab group compared with 17% (6 of 35) for the bisphosphonate group (OR, 0.31; 95% CI, 0.08–1.18). The safety profile of denosumab was as expected in a population with cancer receiving antineoplastic treatment [17].

One may anticipate that denosumab, because of its effect on bone resorption, would have a beneficial effect in breast cancer–induced bone metastases, as these metastases tend to be osteolytic in nature [1]. Data from current phase 2 studies indicate that denosumab may have benefits in other types of bone metastases, including those from PCa [15,17]. From these studies, treatment with denosumab 120 mg every 4 wk was selected for use in ongoing phase 3 clinical trials, evaluating its efficacy in preventing and treating complications caused by bone metastases associated with breast cancer, PCa, and multiple myeloma.

In summary, levels of uNTx were normalised with denosumab in the majority of patients with bone metastases who had elevated uNTx despite IV bisphosphonate therapy. A large phase 3 clinical trial programme evaluating the efficacy of denosumab in the prevention and treatment of complications caused by bone metastases is in progress.

4. Conclusions

Men with PCa that has metastasized to bone are at high risk for SREs. The measurement of uNTx levels appears to be an excellent marker of SRE risk, with reductions in uNTx

correlating with improved outcomes. This biomarker may therefore represent a convenient alternative to repeated radiography in the assessment of bone metastases and their treatment.

Levels of uNTx have tended to normalise in trials to date of patients with bone metastases receiving denosumab, suggesting that denosumab reduces the risk of SREs. Large-scale studies assessing denosumab in the prevention and treatment of bone metastases are underway.

Conflicts of interest

Fred Saad is a member of the advisory boards for Amgen and for Novartis and has conducted research with both companies.

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