Cancer Biology & Therapy 13:2, 69–70; January 15, 2012; © 2012 Landes Bioscience

Significant addition to treatment options for bone metastasis in prostate cancer

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Pathologic fractures, spinal compression and pain take a great toll on the healthcare costs and well-being of men with prostate cancer metastatic to the bone. For almost 10 years, the only drug proven to prevent these skeletal-related adverse events was the bisphosphonate zoledronic acid. In a study published by Fizazi et al. in *The Lancet*, the monoclonal antibody to RANKL, denosumab, is shown to be superior to zoledronic acid in the prevention of these events. The only notable adverse event more frequent in either arm was increased hypocalcemia in the denosumab arm. There was a greater frequency of osteonecrosis of the jaw in the denosumab treatment group that did not reach statistical significance, but is of great concern. While further analysis is needed to determine the value of denosumab in preventing adverse events and improving quality of life, this new therapy is a significant addition to the treatment of men living with metastatic prostate cancer.

Keywords: prostate cancer, bone metastasis, denosumab, bisphosphonates, osteonecrosis of the jaw

Abbreviations: SRE, skeletal-related event; CRPC, castration-resistant prostate cancer; ONJ, osteonecrosis of the jaw

Submitted: 09/30/11

Accepted: 10/16/11

http://dx.doi.org/10.4161/cbt.13.2.18441

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Prostate cancer is the most frequently diagnosed cancer in men in the United States.[1] Up to 70% of men with advanced prostate cancer have metastasis to the bone.[2] This takes a high toll both on patients' quality of life and their healthcare costs. In 2002, a randomized phase III study determined that zoledronic acid was effective in reducing skeletal-related events (SREs). It became the first and only bisphosphonate approved to treat men with prostate cancer metastatic to the bone.[3,4]

Denosumab is a humanized monoclonal antibody to the receptor activator of NF-κB ligand, or RANKL, which regulates osteoclast growth and activity.[5] It inhibits osteoclastogenesis extracellularly by keeping RANKL from binding to the RANK receptor. Its effects are upstream of zoledronic acid, which primarily acts intracellularly after being taken up by osteoclasts at the site of bone resorption.[6]

The results of a phase I study of denosumab (formerly AMG-162) in postmenopausal women were published in 2004, with the intention of treating osteoporosis in later trials.[7] In 2006, a phase I study of denosumab in breast cancer and multiple myeloma was published, the first to study cancer-related bone lesions.[8] Absorption was found to be nonlinear, and there was a dose-response curve in activity as measured by the decrease in urine-N-Telopeptide/Creatinine, a biomarker of bone resorption and osteoclast activity.[8] It was shown that after a single dose (3 mg/kg), denosumab remained detectable in blood for at least 80 d. Unlike zoledronic acid, denosumab is "cleared" from the body by the phagocytic cells of the immune system.[6] Since it is a humanized antibody, denosumab may evade the immune system, possibly explaining why it is detectable months after a single dose.[8]

The phase III trial described in *The Lancet* by Fizazi et al.[5] was designed to test denosumab in men with castration resistant prostate cancer (CRPC) and bone metastasis against zoledronic acid in the prevention of SREs. Nine-hundred and fifty patients were randomized to receive denosumab and 951 received zoledronic acid in this double-blind study. No patients had previously received bisphosphonates

for treatment of bone metastases. The randomization was stratified so that both arms had similar numbers of prior skeletal events, range in PSA, and number of men who received chemotherapy in the previous 6 weeks. This trial was one of three pivotal studies of denosumab; the other two were in breast cancer[9] and multiple myeloma.[10]

Denosumab significantly extended time to first skeletal-event (17.1 mo on zoledronic acid to 20.7 mo on denosumab, p = 0.008 for superiority), and was associated with a greater decrease in bone-turnover markers. Still, there was no significant difference between the two treatments in any of the exploratory endpoints, which included overall survival, disease progression, and change in PSA.

The incidence of adverse-events in most categories was not significantly different between the two arms. However, there was a significant increase in hypocalcaemia in the denosumab treatment group, including more grade 3 or 4 events, despite a 90% patient-reported use of at least 500 mg/day calcium supplementation in the denosumab arm (vs. 87% in zoledronic acid). This is of some concern, and all patients' calcium levels should be monitored.

The investigators do not address the significantly higher incidence of any grade 3 or 4 adverse event in the denosumab treatment group (72–66%, p = 0.01). Since therapy is intended to prevent procedures and hospital stays associated with SREs, important comparisons lacking in this analysis are the categories of adverse events grade 3 or higher that were most prevalent in both arms, and the frequency of adverse events leading to hospitalization.

A concerning risk with the use of bisphosphonates is osteonecrosis of the jaw (ONJ). For both groups there was a fortunate but surprisingly low incidence—1 and 2% of patients in the zoledronic acid and denosumab arm, respectively. Although this difference did not reach statistical significance, it is of clinical concern that the incidence of ONJ in the denosumab arm was nearly twice that of zoledronic acid (12–22 patients, p = 0.09). Furthermore, in Amgen's study of denosumab in men with CRPC at high risk for developing bone metastasis, the incidence of ONJ was 4.6% (vs. 0% in placebo arm).[11] In a review of four studies on the incidence of ONJ in prostate cancer patients receiving bisphosphonates, the overall incidence was 2.9–18.6%.[12] Therefore the incidence of ONJ in both arms was lower than expected. With longer times on treatment and follow-up, there may be more cases of ONJ. At the primary analysis cutoff, the median times on study for patients on denosumab and zoledronic acid were 12.2 and 11.2 mo, respectively. However, in a review of cases, the mean time to zoledronic-acid-related ONJ was 21.6 mo.[13]

The authors concede a drawback of the study was the double-blind set-up limiting them from measuring how the subcutaneous administration of denosumab improved quality of life. Avoiding monthly infusions might indeed be an advantage of denosumab treatment for patients. Another is that denosumab is not associated with the flu-like acute phase reaction that can be caused by zoledronic acid. Providers may appreciate that denosumab does not require the monitoring of renal function that is necessary with zoledronic acid, and for which 22% of patients in that arm has doses held or adjusted.

Denosumab is the only drug proven to be superior to zoledronic acid in the prevention of skeletal-related events in men with prostate cancer bone metastases, and only the second drug proven to be better than placebo in this setting. Although the double-blind study design could not support this speculation, this new treatment option will likely be welcomed by patients wishing to avoid monthly infusions. Comparison of the frequencies of grade 3 or higher adverse events requiring procedures or hospitalization is necessary to judge denosumab's value in quality of life. Still, this new treatment option and evidence of superiority is an important advance in the prevention of serious skeletal-related events and the improvement of life in patients living with metastatic prostate cancer.

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