Research Highlight

Denosumab: Delay of bone metastasis in men with nonmetastatic castrate-resistant prostate cancer

Jules P. Manger, Tracey L. Krupski

University of Virginia Department of Urology, Charlottesville, Virginia

Correspondence to: Jules P. Manger, MD. University of Virginia Health System, Department of Urology. Email: jmanger@virginia.edu.

Submitted Apr 27, 2012. Accepted for publication May 17, 2012.

doi: 10.3978/j.issn.2223-4683.2012.05.08

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In a large multicenter phase 3 randomized controlled trial published in *Lancet*, Smith and colleagues highlight a potential new indication for denosumab for patients with hormone refractory prostate cancer (1). Already approved for prevention of skeletal-related events in the setting of bone metastases in solid tumors (Xgeva) and prevention of androgen deprivation therapy (ADT) induced bone loss (Prolia), the authors theorized that denosumab administered prior to bone metastasis might stabilize the bone microenvironment thus delaying time to first bone metastasis. Men with castrate-resistant nonmetastatic prostate cancer treated with denosumab showed improved bone-metastasis-free survival and delayed time to first bone metastasis compared to those dosed with placebo.

Denosumab is a fully human monoclonal antibody that selectively binds and neutralizes receptor activator of nuclear factor kappa-B ligand (RANKL). This inhibits RANKL activation of osteoclasts in the vicious cycle of bone turnover. While the FDA-approved indications of denosumab fit intuitively into this mechanism, the delay of onset of bone metastasis with denosumab is rooted in the "seed and soil" hypothesis of metastasis of Paget and Fuchs. Denosumab demonstrates antitumor and antimetastatic properties independent of its osteoclast inhibition. In a mouse xenograft model of prostate cancer, Fc-RANK (a RANKL inhibitor) delays bone metastasis, inhibits osteolysis, and preserves bone architecture with decreased bony tumor burden (2). Similarly, in a mouse mammary cancer model, RANKL inhibition delays non-osseous metastasis and decreases metastatic tumor burden (3).

In the *Lancet* article, investigators performed a placebo-controlled, randomized trial in 319 centers in 30 countries. They enrolled 1,432 men with castration-resistant prostate cancer defined as three consecutive PSA rises despite castrate testosterone. Men with metastatic disease or recent antiresorptive therapy were excluded from this study. Based on premature study closure due to low event rate in similar intravenous bisphosphonate studies (4), this study targeted high risk prostate cancer. PSA of 8 ng/dL or greater and/or PSA doubling time of 10 months or less was deemed high risk for bone metastasis. The study was open label to any chemotherapeutic agents. A centralized computer randomization maintained allocation concealment. Patients were randomized to 120 mg denosumab subcutaneously monthly versus saline placebo. Patients, investigators, and radiologists were all blinded to treatment intervention. Bone scans, and confrirmatory studies based on suspicious bone scans, were obtained every 4 months to assess for bone metastasis with central radiology review. Results were analyzed by intention to treat for efficacy outcomes and per protocol for safety outcomes (four patients in the control group were accidentally dosed with denosumab). The primary endpoint was bone-metastasis-free survival. Secondary outcomes included time to bone metastasis, symptomatic bone metastasis, and overall survival (OS).

The enrollees were overwhelmingly white heptagenarians with good functional status. Half of the men had undergone local therapy with prostatectomy, radiation or both. The study group found an improvement in bone-metastasis-free survival from 25.2 months in the placebo group to 29.5 months in the denosumab cohort for a 4.2 month improvement and a similar delay in time to first bone metastasis. There was a greater rate of symptomatic bone metastases in the placebo cohort than those treated with

denosumab, 13% versus 10%.

With regards to safety, there was no significant difference in study discontinuation due to adverse event or grade 3 or higher adverse events as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3. Hypocalcemia was rare in both groups and symptomatic hypocalcemia only occurred in one patient randomized to denosumab who was not taking his supplemental calcium and vitamin D. Osteonecrosis of the jaw (ONJ) occurred exclusively in the denosumab cohort in 33 men (5%). The majority of these men had risk factors such as dentures or poor dentition. Two-thirds of men who developed ONJ required at least minor debridement for treatment. The percentage of patients ONJ is higher in this than in other studies evaluating denosumab in cancer metastatic to bone; nevertheless the length of treatment and follow up is longer in this study making the incidence in line with prior studies. This rate of ONJ was worrisome to the food and Drug Administration. In February 2012, the FDA's Oncologic Drugs Advisory Committee voted 12-1 to deny an expanded indication for denosumab in preventing bone metastasis. In part, the committee stated that the 5% risk of ONJ did not justify a four-month potential delay in prostate cancer metastasis (5).

Bony metastasis is a dreaded yet inevitable consequence of castrate-resistant prostate cancer that is costly in terms of patient quality of life and societal economic burden. Similar to the controversy of when to initiate ADT in the setting of recurrence after local treatment, this study calls into question when to initiate denosumab in the setting of castrate-resistant prostate cancer. Is it best to initiate therapy in the setting of impending bony metastasis to prolong bone-metastasis-free survival or better to stabilize the bone to minimize skeletal related events with denosumab once clinical or radiographic bone disease develops? The FDA felt this study was insufficient to justify approval of denosumab for this indication. They were concerned about the clinical relevance of the endpoint of bone-metastasis-free survival or time to first bone metastasis. Additionally, they were underwhelmed with the magnitude of the effect of 4.2 months, optimistically expecting results in the 6 to 12 month range. They felt a better study design would focus on outcomes of SRE and OS in castrate-resistant prostate cancer patients treated in an early (prior to bony metastasis) versus delayed (after imaging confirmation of metastasis) strategy (5). Certainly, 4 month overall survival advantage has been robust enough to justify approval of other prostate cancer drugs such as abiraterone and sipuleucel-T.

Manipulation of the bone microenvironment in the clinical scenario of high-risk nonmetastatic castrate-resistant prostate cancer has the potential to improve not only quality of life but overall survival. Innovative agents, such as selective estrogen receptor modulators (SERMs), or new combinations of existing agents will continue to be vigorously pursued.

Cite this article as: Manger JP, Krupski TL. Denosumab: Delay of bone metastasis in men with nonmetastatic castrate-resistant prostate cancer. Transl Androl Urol 2012;1(2):113-114. doi: 10.3978/j.issn.2223-4683.2012.05.08

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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