Asian Journal of Andrology (2011) 13, 612–613

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RESEARCH HIGHLIGHT

# Denosumab in bone-metastatic prostate cancer: known effects on skeletal-related events but unknown effects on quality of life

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*Asian Journal of Andrology* (2011) **13,** 612–613; doi:10.1038/aja.2011.33; Published online: 18 April 2011

The purpose of new pharmaceuticals is to improve how patients feel, function or survive. Exceptions exist when surrogates are developed and we know that those surrogates correlate well with one of the above. Hypercholesterolemia is a well-accepted example. We know that high cholesterol is a reasonable indicator that results in increased risk of strokes and heart attacks. Thus, we treat hypercholesterolemia in hopes that our patients' health will improve.

That being said, let us move on to more germane topics for this editorial, skeletal-related events (SREs); what are they and what do they mean? It is important to answer the question, if a patient has a SRE, does it affect the way a patient feels, functions or survives?

The definition of an SRE in prostate cancer is somewhat arbitrary. The definition that was promulgated in the initial zoledronic acid/placebo trial (and accepted by some regulators) includes bone fracture (vertebral or non-vertebral), spinal cord compression, surgery to bone, radiation therapy to bone (including radioisotopes) or a change of antineoplastic therapy to treat bone pain.[1] A new vertebral compression fracture was defined as a decrease in total, anterior or posterior vertebral height of at least 25% from baseline. This SRE definition has been used since 2002 when zoledronic acid was the first (and only) bisphosphonate approved by the US Food and Drug Administration for use in bone-metastatic castrate-resistant prostate cancer (CRPC).

So back to question at hand, how does an SRE relate to the 'feel, function, or survive' standard that drugs are typically assessed by? The answer is, not very well. A more straight forward definition of benefit would be a reduction in pain, analgesic consumption or improvement in quality of life (QoL). Though patient reported that outcomes are not easy to assess, particularly because of the risk of unintentional unblinding associated with drug-induced adverse events,[2] they are important to assess. So far, the drugs that are US Food and Drug Administration-approved for the treatment of SREs in prostate cancer have not clearly improved pain, analgesic consumption or QoL.[1,3] Though one may argue that radiation to bone and fractures are associated with decreased QoL, a formal assessment of QoL performed with the initial zoledronic acid/placebo trial[2] demonstrated no differences in the various treatment groups when using two QoL scales (FACT-G QoL and EURO-QoL).

The use of radiographic 'skeletal surveys' and assessment of asymptomatic vertebral fractures are part of this issue. Though vertebral fractures are surrogates for increased risk of more significant fractures in the non-cancerous literature, patients with bone-metastatic CRPC have a much more limited life expectancy than non-cancer patients. Consequently, an asymptomatic event linked to a future adverse event is less meaningful in a patient with metastatic CRPC. It is also noteworthy that vertebral fractures even in CRPC patients may be related to osteoporosis rather than an underlying cancer-associated pathological fracture. It is not often noted, but true, that in era of the original bisphosphonate trials in CRPC that osteopenia/osteoporosis was rarely addressed in men receiving androgen deprivation. Had osteopenia/osteoporosis been addressed, the vertebral fracture rate may have been considerably diminished.

There are now new data on SREs in patients with bone-metastatic CRPC.[3] This time a new drug, denosumab at 120 mg by subcutaneous injection every 4 weeks, was evaluated against zoledronic acid at 4 mg intravenously every 4 weeks, in a head-to-head randomized trial using time to first on-study SRE as the primary end point. Denosumab is a monoclonal antibody against the receptor activator of NF-κB (RANK) ligand. Skeletal surveys were done at baseline and every 12 weeks. These radiographs were performed of the skull, spine, chest, pelvis, arm from shoulder to elbow, and leg from hip to knee. A SRE was defined as a 'pathological fracture' (excluding fractures from severe trauma), radiation therapy to bone (including use of radioisotopes), surgery to bone or spinal cord compression. Survival, overall progression-free survival and prostate-specific antigen were assessed as secondary end points. Pain was assessed only as an adverse event. Analgesic consumption was not reported. QoL was not mentioned in the manuscript.

In this recently reported trial,[3] which randomized over 1900 patients, median time on study was 12.2 months for the denosumab-treated patients and 11.2 months for the zoledronic acid-treated patients. Values of survival, time to disease progression and prostate-specific antigen changes were similar between the two arms. Values of median survival were 19.4 and 19.8 months in the denosumab and zoledronic acid arms, respectively. Pain reported as an adverse event was equal between the two arms (back pain was reported in approximately 30% of patients on each arm and bone pain was reported in approximately 25% of each arm). Median time to first on-study SRE was 20.7 months with denosumab compared with 17.1 months for zoledronic acid (hazard ratio: 0.82; $P=0.008$). Note that the time to SRE was longer than the median survival in the

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denosumab arm. Vertebral fractures were not separated from non-vertebral fractures. Symptomatic events were not distinguished from asymptomatic events. Total SRE events were 386 (41%) in the zoledronic acid arm and 341 (36%) in the denosumab arm. The first SRE events were broken down in the zoledronic acid and denosumab arms as follows: radiation to bone: 203 (21%) versus 177 (19%); pathological fracture: 143 (15%) versus 137 (14%); spinal cord compression: 36 (4%) versus 26 (3%); and surgery to bone: 4 (<1%) versus 1 (<1%). Comparisons between individual components of the SREs were not analyzed.

In terms of adverse events, grade 3 or higher hypocalcemia occurred in 48 patients (5%) receiving denosumab and 13 patients (1%) receiving zoledronic acid. Osteonecrosis of the jaw occurred in 22 (2%) and 12 (1%) of the denosumab- and zoledronic acid-treated patients, respectively. Adverse events potentially associated with acute phase reactions occurred in 79 patients (8%) on denosumab and 168 patients (18%) on zoledronic acid.

So what do we conclude? A large trial has now shown that SREs can be more effectively reduced in bone-metastatic CRPC patients by denosumab as compared to zoledronic acid. Hypocalcemia and osteonecrosis of the jaw are risks that clinicians should be apprised of going forward. Denosumab does not necessitate obtaining creatinine level predosing which is a significant advantage. Subcutaneous administration (available with denosumab) is preferable to intravenous access (required for zoledronate) in terms of both ease of administration and patient preference. That being said, it is troublesome that we do not know if denosumab helps a patient feel or function better. The lack of effect of bisphosphonates or denosumab on patient-reported outcomes including QoL, pain or analgesic consumption continues to be a disappointment for this entire field.

Do bisphosphonates and the new RANK-ligand monoclonal have a place in the treatment of bone-metastatic CRPC patients? Will these drugs continue to be used? The answer to both questions is 'Yes', but that does not mean that clinicians will know that our treated patients will feel or function any better than before.

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2 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf (accessed 20 March 2011).
3 Fizazi K, Carducci M, Smith M, Damião R, Brown J *et al*. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011; **377**: 813–22.