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PROSTATE CANCER

Does denosumab have a role in metastasis prevention?

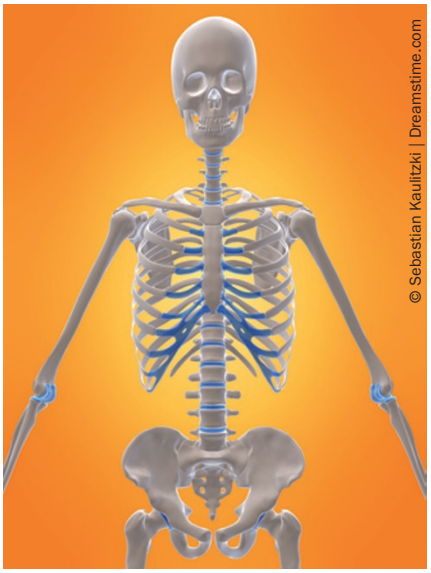
Results of a large phase III randomized controlled trial—recently published online in the *Lancet*—have shown that denosumab can delay the onset of bone metastasis in patients with castration-resistant prostate cancer (CRPC). The question now is how this finding should be translated into clinical practice—could denosumab be administered as a preventative agent in patients who have CRPC that has not yet spread to bone?

Denosumab is a human monoclonal antibody raised against the receptor activator of nuclear factor κB ligand (RANKL). It was approved by the FDA for the prevention of bone-related events in patients with metastatic prostate cancer based on phase III trial data published earlier this year, which demonstrated that denosumab could delay such events for longer than zoledronic acid in men with confirmed bone metastasis.

The current study, reported by Smith and colleagues, was designed to assess the role of denosumab in the premetastatic setting. 1,432 men with nonmetastatic CRPC were enrolled from 319 centers across 30 countries. All patients were considered at high risk of developing metastases, according to either a PSA level ≥8 ng/ml in the 3 months prior to randomization, a PSA doubling time ≤10 months, or both, but had no evidence of previous or current bone metastases on radiography.

Patients were randomized to receive an injection of either denosumab (120 mg; $n = 716$) or placebo (sterile saline; $n = 716$) every 4 weeks. Follow up included a radioisotope bone scan every 4 months and a radiographic skeletal survey every year. As soon as metastasis was detected (and confirmed by a second imaging modality) denosumab was discontinued, so that patients could receive the standard treatment for metastatic CRPC instead.

Denosumab treatment significantly improved bone-metastasis-free survival compared to placebo (by a median



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of 4.2 months; HR 0.85; $P = 0.028$), and significantly extended the time to detection of first bone metastasis (33.2 months for denosumab versus 29.5 months for placebo; HR 0.84; $P = 0.032$). No difference was found in overall survival (HR 1.01; $P = 0.91$).

Denosumab is the first drug that has been demonstrated to delay the onset of bone metastasis in patients with CRPC, and although some experts are hailing a paradigm shift, others are more cautious about these findings. In an accompanying editorial for the *Lancet*, Christopher Logothetis states his opinion that the data are not sufficient to support the use of denosumab for prevention of bone metastasis. His main concern is that the metastatic process might have already started in the patients selected for this study. He also draws attention to the fact that the duration of benefit (around 4 months) is similar to that observed previously in the metastatic setting. Given that there was no survival benefit associated with denosumab in this study, there is no reason to consider premetastatic administration over the current approach.

Unfortunately, Smith *et al.* were unable to evaluate the effect of denosumab on overall survival, because treatment was discontinued as soon as metastasis was confirmed. Approximately 80% of deaths in the total cohort occurred in patients who had stopped taking denosumab.

Regardless of whether these data justify the use of denosumab as a preventative agent, it is important to note that this study provides the first direct clinical evidence that RANKL signaling and the bone microenvironment are important in the spread of prostate cancer to bone in men with CRPC.

Preclinical studies have previously elucidated a complex reciprocal relationship between prostate cancer cells and the bone microenvironment, which is integral to the metastatic process. Growth factors secreted by tumor cells induce RANKL expression in stromal cells and osteoblasts, and RANKL then activates osteoclasts, leading to an increase in bone turnover. In experimental models of prostate cancer, osteoclast inhibition has been shown to prevent metastasis. Thus, it might be predicted that using denosumab therapy to inhibit RANKL would prevent bone turnover and, therefore, metastasis in men with CRPC.

Indeed, Smith *et al.* evaluated a number of markers of bone turnover in their study, and found that denosumab treatment was associated with a significant reduction of each marker ($P < 0.001$). For example, the concentration of bone-specific alkaline phosphatase decreased by 49% between baseline and 22 months after randomization in men who received denosumab, compared to a reduction of only 7% in the placebo group.

If nothing else, it is hoped that the results of this study might inspire researchers to gain a better understanding of the complex mechanisms involved in the spread of prostate cancer to bone.

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Original article Smith, M. R. *et al.* Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* doi:10.1016/S0140-6736(11)61226-9