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LETTER TO THE EDITOR

De-escalation of bone-targeted agents for metastatic prostate cancer

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Despite advances in therapy, bone remains the most common site of prostate cancer recurrence. Once cancer has spread to bone, it is incurable and can be associated with pain, decreased quality of life, reduced mobility, and skeletal related events (SREs). Given that more than half of all prostate cancer patients with bone metastases experience SREs (for example, radiotherapy or surgery to bone, pathologic fractures, or spinal cord compression), reducing the occurrence of those events is an important therapeutic goal[1]. Currently, based on the results of several randomized trials, patients with bone metastases from castrate-resistant prostate cancer (mCRPC) are often treated with bone-targeted agents such as bisphosphonates or denosumab every 3–4 weeks.

Historically, the dosing frequency for bone-targeted agents was adopted from data for the management of hypercalcemia of malignancy and for convenience (3- to 4-weekly dosing allowed clinicians to deliver the drugs at the same time that patients were receiving chemotherapy)[1]. However, that rationale ignores studies of biomarkers of bone turnover (a surrogate marker of SRE risk), which have consistently shown, for both zoledronate and denosumab, rapid and sustained falls in turnover at significantly lower doses and for significantly longer than 3–4 weeks[2]. The question about the optimal dosing interval is particularly important given that the toxicity of bone-targeted agents is related to both the potency of the agent and the cumulative dose.

A meta-analysis of de-escalated bone-targeted therapy (that is, treatment every 12 weeks instead of every 4 weeks) in patients with metastatic breast cancer was recently published. The results show no difference in SREs or pain with de-escalated therapy[3]. Interest in similar de-escalated therapy for patients with mCRPC is now increasing. If de-escalated treatment is as efficacious as 3–4-weekly dosing, then not only would costs to both patients and the health care system be significantly reduced, but drug side effects could also potentially be reduced.

In view of the findings in the breast cancer population, we conducted a systematic review to answer the question "Does 12-weekly bone-targeted agent use in mCRPC patients with bone metastases provide a benefit similar to that with 4-weekly treatment?" We were interested in randomized trials that had evaluated de-escalation of any established bone-targeted agent (for example, zoledronate and denosumab) against the standard 4-weekly treatment. Our systematic review was conducted as outlined in the Cochrane handbook, and only two studies met our inclusion criteria[4,5].

The study by Fizazi *et al.*[4] was a phase II open-label randomized trial in which 33 patients with mCRPC were randomized to either subcutaneous denosumab 180 mg every 4 weeks (n = 17) or every 12 weeks (n = 16). All patients randomized to denosumab had received treatment with zoledronic acid before randomization. Twenty-seven patients receiving denosumab completed the study. Biomarkers (urinary N-telopeptide) were assessed at week 13 and week 25. There was no significant difference between the 12-weekly and 4-weekly denosumab arms in terms of on-study biomarker changes, pain, or occurrence of SREs. Those results are clearly interesting and similar to the findings in a similar population of breast cancer patients[4]; however, they are limited by the small sample size.

The ongoing phase III open-label randomized noninferiority REDUSE trial[5] is comparing 4-weekly denosumab 120 mg with 12-weekly denosumab 120 mg in patients with bone metastases from breast cancer and mCRPC. The primary endpoint is time to first on-study symptomatic SRE. The secondary endpoints include safety, time to subsequent on-study SRE, quality of life, health economics, and bone turnover markers. Target accrual is 1380 patients; no data from the study are yet available.

We have identified a knowledge gap in the existing literature that compares de-escalated with standard schedules of bone-targeted therapies in patients with bone metastases from CRPC. More randomized trials are needed to compare the benefits and safety of de-escalated treatment. The study endpoints should include symptomatic SRE rates, pain control, health-related quality of life, and safety, as well as health care costs. While waiting for the results of the REDUSE trial, researchers have a unique opportunity to perform additional practice-changing trials to identify the optimal schedule of denosumab dosing.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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