Re: A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients with Hormone-Refractory Metastatic Prostate Carcinoma

The article by Saad et al. (1) indicated clinical benefit for the use of zoledronic acid in the treatment of bone metastases and androgen-independent prostate cancer. However, the precise nature and biologic implication of the clinical benefit deserves further scrutiny.

The endpoint used to determine clinical benefit was “skeletal-related events.” However, only “pathologic bone fracture” was statistically significantly improved in patients who received zoledronic acid (4 mg). Other events, such as nonvertebral fractures, radiation therapy to bone, surgery to bone, spinal cord compressions, and change in antineoplastic treatments were not statistically significantly altered. Thus, although the findings demonstrated benefit to patients treated with androgen ablation, they did not provide any indication whether this benefit resulted from a direct effect on the bone and/or the cancer.

From our perspective, it would be useful to distinguish the effect of zoledronic acid on the bone (i.e., osteoporosis) from an effect on the cancer (2,3). Distinguishing between the two effects will be difficult given the complexities of the stromal–epithelial interactions after prostate cancer metastasizes to the bone. However, a rational development of therapy requires further understanding of this interaction. Improved understanding of the role of bone cells such as osteoclasts and osteoblasts and their response to zoledronic acid in the context of prostate cancer bone metastases will form the basis of future studies. Given the absence of any detectable antitumor activity, we interpret the results from Saad et al. (1) to be more suggestive of an effect of zoledronic acid on osteoporosis rather than on the tumor.

The final arbiter of clinical benefit is increased survival time. Unfortunately, treating only the osteoclastic or the osteoblastic components (with zoledronic acid and strontium-89, respectively) of bone metastases has not provided any survival advantage for patients with androgen-independent prostate cancer (1,4). Although there are no phase III data indicating a survival advantage, we have reported encouraging results from an initial study of bone-targeted therapy in advanced prostate cancer (5). The patients in our study (5) were selected by their initial response to chemotherapy and thus the results might not be applicable to all patients with androgen-independent prostate cancer and bone metastases. An updated survival time of the three categories of patients reported continues to demonstrate a longer survival time for those patients who received combination treatment involving induction chemotherapy and consolidation strontium-89 that targeted both the tumor and osteoblastic components (5) (Fig. 1). A confirmatory randomized phase III trial (MDA-3410) using this strategy is currently open for patient accrual at the Community Clinical Oncology Program (CCOP) and the Cancer Treatment Support Unit (CTSU) of the National Cancer Institute.

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DOI: 10.1093/jnci/djg020

RESPONSE

Tu et al. asked about the nature of clinical benefit of zoledronic acid and stated that only “pathological bone fracture” was statistically significantly improved. We noted, however, that the primary endpoint was the proportion of patients with any skeletal-related events (SREs), which has been accepted as the standard endpoint to determine clinical benefit of bisphosphonates in clinical studies. SRE is a composite endpoint consisting of not only fractures, but also of radiation therapy for bone pain or impending fractures, spinal cord compression, surgery, hypercalcemia, and in our study with prostate cancer, change of antineoplastic therapy for bone pain. Obviously, the study is powered to show difference in the primary endpoint, so we do not expect to show statistical significance in each individual type of SREs. In any case, we also analyzed the data excluding all non-symptomatic fractures as well as all fractures, and the primary endpoint remained statistically significant, indicating that the clinical benefit of zoledronic acid is beyond reduction of risk of fractures.

We concur with Dr. Tu that it is very difficult to distinguish between the effects of zoledronic acid on bone and on cancer cells because zoledronic acid was shown to have effects on both types of cells in preclinical studies. It is well understood that bone metastases occur as a result of the interaction between the tumor cells and the bone tissues that perpetuates a vicious cycle, which is interrupted by a bisphosphonate such as zoledronic acid. In addition, zoledronic acid has demonstrated antitumor and antiangiogenic properties in preclinical studies (1).

Dr. Tu also suggested that the efficacy of zoledronic acid may be interpreted as a result of anti-osteoporotic effect. However, the benefit of zoledronic acid remains even after fractures are excluded from the analysis, strongly arguing against the notion that the benefit of zoledronic acid is simply because of its anti-osteoporotic effects. Although it is not possible to differentiate what proportion of fractures result from osteoporosis or from bone metastases, it is more important to know that zoledronic acid has demonstrated efficacy in reducing the bone complications regardless of the underlying causes, thereby providing clinical significant benefit to patients.

The objective of bisphosphonate treatment in advanced cancer metastatic to bone is to improve the patients’ quality of life by reducing the number of bone complications that lead to morbidity and mortality. In hormone refractory prostate cancer, no agent has shown a survival benefit. Although Dr. Tu and colleagues have shown interesting findings on a regimen of chemotherapy in combination with strontium-89, these preliminary results need to be confirmed in the ongoing randomized phase III study.

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DOI: 10.1093/jnci/djg021