Re: Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients With Metastatic Hormone-Refractory Prostate Cancer

I was interested to read the updated results of the Zoledronic Acid Prostate Cancer Study Group’s randomized placebo-controlled trial in men with bone metastases from hormone-refractory prostate cancer (HRPC) (1). This was a positive trial, in the sense that zoledronic acid demonstrated statistically significant reductions in skeletal complications. However, there are several reasons why I question whether the reported reduction in skeletal complications, particularly in the absence of any impact on either overall survival or quality of life, should be regarded as sufficient evidence to change clinical practice.

First, statistical significance does not equal clinical significance. Saad et al. (1) reported that zoledronic acid had a statistically significant effect on pain control at 24 months, in that patients who received 4 mg of zoledronic acid had a smaller increase in their Brief Pain Inventory (BPI) scores than patients who received placebo (0.58 versus 1.05; P = .024). Given that BPI is measured on an 11-point scale (ranging from 0 to 10), the clinical significance of a difference of 0.47 points (95% confidence interval = 0.06 to 0.88 points) is doubtful.

Second, not all skeletal complications are created equal. Some skeletal complications, such as spinal cord compression, can be devastating, whereas others, such as asymptomatic fractures, are of little or no relevance to the patient. The authors acknowledge this point by presenting data for the effect of zoledronic acid on skeletal complications excluding asymptomatic fractures. However, radiation therapy to bone, which is the single most common “skeletal complication,” is also of debatable clinical significance. For example, two randomized studies of pamidronate in HRPC considered palliative radiotherapy as part of routine care, not as a skeletal complication (2). It would be interesting to know the magnitude of the benefit of zoledronic acid on skeletal complications when both asymptomatic fractures and radiation to bone are excluded. In their original analysis of the trial data, Saad et al. (3) reported that 29.3% of patients in the placebo group received radiation to bone within 15 months of randomization, compared with 22.9% of those in 4-mg zoledronic acid group and 24.0% of those in the 8/4-mg zoledronic acid group. Whether or not radiation to bone is classified as a skeletal complication, I question the utility of regular intravenous infusions every 3 weeks for up to 15 months in order to reduce the need for a single fraction of radiation by approximately 6%.

Third, zoledronic acid is not without adverse effects. Saad et al. (2) reported that, compared with patients receiving placebo, those receiving 4 mg of zoledronic acid had increased risks of fatigue (32.7% versus 25.5%), anemia (26.6% versus 17.8%), malaise (24.8% versus 17.8%), fever (20.1% versus 13.0%), edema (19.2% versus 13.0%), and weight loss (16.8% versus 12.5%). In considering the clinical role of zoledronic acid in patients with HRPC, it is important to take into account the balance between the risks of adverse effects and the potential benefits of reducing skeletal events. The lack of any published quality-of-life data from the Saad et al. study is an important omission. In the absence of such data, and given the range of adverse effects listed above, one could speculate that zoledronic acid might have a detrimental, rather than a beneficial, effect on the quality of life of men with HRPC.

Christopher C. Parker

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Dr. Parker stated that in our trial (1) “zoledronic acid demonstrated statistically significant reductions in skeletal complications”; however, he questioned whether such reductions should be regarded as sufficient evidence to change clinical practice. First, he doubted the clinical significance of the statistically significant 0.47-point reduction in bone pain we observed in the mean Brief Pain Inventory score (where 0 = no pain and 10 = worst pain) at 24 months among patients treated with zoledronic acid versus patients in the placebo group. Although this change in mean pain score may not appear great, certainly some patients experienced much larger decreases in pain scores. Moreover, the decreased incidence of radiation to bone among patients treated with zoledronic acid suggests that they experienced a decrease in severe bone pain. It is important to keep in mind that pain is a difficult clinical endpoint to assess and that this is the first randomized, placebo-controlled bisphosphonate trial in patients with prostate cancer to show a statistically significant and durable decrease in pain scores among patients treated with zoledronic acid compared with placebo. Neither intravenous pamidronate nor intravenous clodronate have demonstrated such a benefit (2,3).

Second, Dr. Parker stated that radiation therapy to bone “is also of debatable clinical significance” and suggested that radiation therapy should not be included in the composite endpoint as a skeletal-related event. He cited two randomized studies (3) of pamidronate in hormone-refractory prostate cancer as examples of studies that considered palliative radiotherapy to be part of routine care, not a skeletal complication. This statement is incorrect. Those studies (3) did include radiation to bone as a skeletal-related event and used a definition for skeletal-related events that was very similar to that used in our trial. Radiation to bone is an important indicator of
the incidence of severe bone pain and has been shown to be associated with a statistically significant decrease in health-related quality of life (4). Therefore, it is appropriate to include palliative radiotherapy in the composite definition of a skeletal-related event.

Third, Dr. Parker stated that “zoledronic acid is not without adverse effects.” However, if one considers the risk–benefit equation, the evidence supports the routine use of zoledronic acid in prostate cancer patients. The adverse events that occurred more frequently in the zoledronic acid group than in the placebo group were primarily mild-to-moderate flu-like symptoms, which occurred mainly after the first infusion and only rarely after later infusions. These adverse events would not be expected to affect quality of life to the same extent as skeletal complications. The skeletal-related events that are prevented by treatment with zoledronic acid, such as pathologic fractures and severe bone pain requiring palliative radiotherapy, are associated with clinically significant decrements in multiple domains of health-related quality of life (4). Fractures have also been shown to be an independent adverse predictor of survival in patients with prostate cancer (5). Pathologic fractures, in particular, can be devastating events in patients’ lives because they signal skeletal disease progression and can lead to substantial morbidity and mortality (6,7). Therefore, I submit that there is a sound clinical rationale for proactive treatment with zoledronic acid in patients with bone metastases from advanced prostate cancer and that the potential benefit of maintaining bone health outweighs the risks associated with intravenous bisphosphonate therapy.

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