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

Saad et al. (1) report a reduction in “skeletal-related events” in patients with hormone-refractory metastatic prostate cancer who received zoledronic acid every 3 weeks. This included a reduction in pathologic fractures and radiation therapy to bone. However, the protocol required bone surveys every 3 months, and vertebral fractures were defined only as a 25% reduction in vertebral height, without any requirement for clinical correlation. This raises the possibility that asymptomatic fractures of limited clinical relevance were counted as skeletal events. The authors noted that nonvertebral fractures are generally accompanied by acute clinical symptoms (emphasis mine) and that such fractures were also reduced. However, the reduction in nonvertebral fractures was not statistically significant, and we may well question whether routine skeletal surveys would have demonstrated such fractures that were asymptomatic. Furthermore, although only one event was counted in any 3-week interval, is it not possible that an asymptomatic fracture was counted as an event during one interval and, because of this finding, the patient was then given radiation therapy in the next interval, leading to an inappropriate count of two events for one clinically insignificant episode?

Because the authors showed no statistically significant changes in pain or quality of life among the treatment groups, I question whether zoledronic acid treatment results in any clinically relevant benefit for patients with hormone-refractory prostate cancer metastatic to bone. The authors should first assure us that radiation therapy to bone was not counted as an additional event in patients with a pathologic fracture within the treatment field. They must then show that treatment results in an overall reduction in clinically relevant skeletal-related events by excluding asymptomatic fractures. Assuming they can do so, we must still question whether the requirement for surgery or radiation therapy to bone for 7.5% fewer patients is sufficient justification for the administration of zoledronic acid intra-venously every 3 weeks to all patients with prostate cancer metastatic to bone.

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Bisphosphonates such as zoledronic acid have an increasing role in the treatment of patients with bone metastases. The study by Saad et al. (1) suggests that zoledronic acid reduces skeletal-related events in patients with metastatic prostate cancer.

Although Saad et al. (1) clearly define “skeletal-related events,” the authors do not indicate clinical relevance. The only skeletal-related event to achieve a statistically significant difference was that of pathologic fracture. However, it is unknown how many of these pathologic bone fractures had a clinically significant impact. Indeed, the equivalent incidence of radiation therapy to bone across the treatment arms suggests that not all fractures were clinically relevant. Similarly, the other primary endpoints suggesting a therapeutic response to the clinical problem of pathologic fracture, such as change in neoplastic treatment and surgery to bone, were not different between treatment arms. In addition, the incidence of spinal cord compression was unaltered between treatment arms, further suggesting that pathologic fractures did not necessarily result in clinically important complications.

The study by Saad et al. (1) also clearly demonstrates that zoledronic acid has no effect on other important clinical parameters, including quality of life, progression-free survival, and overall survival. The authors highlight the statistically significant effect of zoledronic acid on pain scores but do not address the paradox that there was no concurrent increase in the analgesics required by those patients with worse pain.

In conclusion, the study by Saad et al. (1) documents that zoledronic acid can provide statistically significant radiologic benefits to patients with metastatic prostate cancer. However, there is little, if any, demonstrable clinical benefit identified for the same patients, raising the question of whether zoledronic acid should become a standard of care for patients with metastatic prostate cancer.

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We read with interest the article by Saad et al. (1) showing that the administration of zoledronic acid can substantially decrease the risk of skeletal-related complications in hormone-refractory prostate cancer patients with bony metastases. The monitoring of bone turnover markers stimulates questions that were not addressed by the authors in the discussion and suggest some further analyses. As expected, zoledronic acid administration led not only to a prompt reduction in bone collagen breakdown markers (N-telopeptide of type 1 collagen [NTX]) but also to a decrease in bone alkaline phosphatase (BALP), with the lowest levels attained after 3 months. Because the target of bisphosphonates is not osteoblasts, the delayed BALP reduction with respect to urinary NTX suggests a maintenance, at least to a certain degree, of the coupling phenomenon (osteoclastic bone resorption followed by osteoblastic bone formation) in metastatic...
involved with the tumor. Recently, it was activity at sites distant from those in parathyroidism may stimulate osteoclast action. The transient rise in serum BALP in a number of cases could have delayed the decrease in mean BALP values with respect to urinary NTX levels. If this hypothesis is true, monitoring BALP serum levels could be useful in predicting early who would benefit from zoledronic acid. This raises two questions: 1) how many patients who received zoledronic acid had a transient rise in BALP levels within the first 2 months? and 2) was this transient rise related to the probability of subsequent skeletal-related complications?

Saad et al. (1) also showed that zoledronic acid administration led to a rise in parathyroid hormone (PTH) serum levels, which persisted throughout the study. The osteoblastic nature of bone lesions from prostate cancer and the high potency of zoledronic acid could have contributed to the increased levels. It is important to note that a proportion of prostate cancer patients with bone metastases already have elevated PTH values before the zoledronic acid administration, resulting from an increased calcium demand related to increased bone formation (5). Secondary hyperparathyroidism may stimulate osteoclast activity at sites distant from those involved with the tumor. Recently, it was suggested (5) that the administration of bisphosphonates in prostate cancer patients with bone metastases may be contraindicated because these drugs may potentially worsen the pre-existing hyperparathyroidism. This hypothesis is not supported by our results obtained with pamidronate in a prostate cancer patient with bone metastases and associated hypocalcemia and hyperparathyroidism (6). Pamidronate treatment achieved an improvement in bone metabolism, leading to a reduction in bone remodelling markers. The reduction in bone formation improved the hyperparathyroidism (PTH serum levels decreased after an initial rise and serum calcium increased). In the study by Saad et al. (1), BALP significantly decreased, as in our experience, but serum PTH still remained elevated after many months, probably because zoledronic acid is 1000 times more potent than pamidronate. It would be interesting to know how many patients in the study by Saad et al. (1) had baseline elevated PTH and what the outcome of these patients was according to the randomization arms in terms of incidence of adverse skeletal events, bone pain, changes in bone turnover markers, and PTH.

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RESPONSE

Atkins and Rosenthal suggest that the reductions in skeletal-related events and in clinical interventions for the events observed in patients who received zoledronic acid in our study (1) are of limited clinical meaning. They questioned why quality of life, bone pain, analgesic use, progression-free survival, and survival were not improved in patients who received zoledronic acid compared with those who received placebo.

The types of skeletal-related events evaluated in our study can cause serious morbidity and may affect survival. Indeed, Oefelein et al. (2) suggest that there is a negative correlation between fractures and overall survival in a similar patient population. Atkins and Rosenthal also question how many of the bone fractures had a significant clinical impact. We determined that approximately 3% and 10% of patients who received 4 mg of zoledronic acid and placebo, respectively, had a bone fracture that required medical intervention. When only these bone fractures are included in the analysis of the proportion of patients having at least one skeletal-related event, the benefit of 4 mg of zoledronic acid remains statistically signifi- cant (P = .029).

Dr. Atkins expressed a concern that there might be double counting of the skeletal events in the efficacy analysis. For analyses of the proportion of pa- tients having at least one skeletal-related event and for the time to the first skeletal-related event, only information pertaining to the first event was used. Thus, additional events had no impact on the results of these two analyses. For subse- quent events, we counted all events occurring in close proximity in a patient as a single event to prevent “double counting.” Two additional multiple events analyses to address Dr. Atkins’s concern on the double counting of the skeletal-related events were done. Each analysis excludes one of the two most frequently occurring types of skeletal-related events (i.e., pathologic fractures and radiation therapy to bone). The compar- isons of treatment effect in reducing the skeletal-related event occurrences between the 4 mg of zoledronic acid and placebo groups remain statistically signifi- cant in both analyses (P = .026 and P = .004, respectively). No conclusive evidence on spinal cord compression and surgery to bone was available from the study because of the low incidences of these events. The incremental bene- fits of each component of the skeletal-related event contributed to the aggre- gate statistically significant clinical benefits observed with zoledronic acid.

There were no statistically significant
differences in quality-of-life assessments between the groups. These assessment instruments, however, have not been validated for the purpose of detecting the quality-of-life benefits associated with the prevention of skeletal-related events. Survival was also similar in the groups. We note that no clinical study to date has provided evidence of improved survival with any medical intervention in this patient population.

Better control of pain without a higher level of analgesic use, as observed in our study, is one criterion of treatment benefit when palliating bone pain. Management of bone pain in our study also included use of radiation therapy, which was used more frequently in the placebo group and could have partially obfuscated differences in analgesic scores between those in the zoledronic and placebo groups.

In summary, zoledronic acid statistically significantly reduced the incidence of clinically relevant skeletal-related complications, delayed the onset of all skeletal-related events, and helped reduce the inevitable increase in bone pain. We therefore believe that zoledronic acid provides a clinically meaningful benefit to patients with metastatic prostate cancer.

Berruti et al. raised interesting questions regarding the levels of bone alkaline phosphates (BALP) and parathyroid hormone (PTH) in patients in our study. We found that 73% of patients in the placebo arm and 48% of patients in the zoledronic acid-treated group (4 mg and 8/4 mg groups) had a transient rise in BALP over 15 months. However, the effects of zoledronic acid did not appear to be different in patients with a transient rise in BALP (proportion of patients with any skeletal-related event was 40%, 34%, and 40%, in placebo, 4 mg zoledronic acid, and 8/4 mg zoledronic acid groups, respectively) compared with those without a transient rise in BALP (proportion of patients with any skeletal-related event was 44%, 35%, and 44%, in placebo, 4 mg zoledronic acid, and 8/4 mg zoledronic acid groups, respectively). However, the sample size for each subgroup is small, and no definitive conclusions should be drawn on the basis of this analysis.

With regard to baseline PTH levels, there was no statistically significant difference in response to zoledronic acid between patients with normal PTH levels and those with elevated PTH levels. The response to 4 mg zoledronic acid was better than that to placebo in both PTH groups but may favor patients with normal baseline PTH levels. For patients with normal baseline PTH levels, the proportion of patients with any skeletal-related event was 43% and 33% for placebo and 4 mg zoledronic acid groups, respectively. For patients with elevated PTH levels, the proportion of patients with any skeletal-related event was 41% and 35% for placebo and 4 mg zoledronic acid, respectively. However, the sample size for each subgroup is small, with only 32 patients in the placebo group and 40 patients in the zoledronic acid-treated group having elevated baseline PTH levels.

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