In the placebo arm of the trial because all men in this situation were primarily mild-to-moderate adverse events, there is not adequate rationale for routine use of bisphosphonates in patients with bone metastases from advanced prostate cancer. However, we believe that the evidence supports the routine use of zoledronic acid in these patients. After 24 months of follow-up, 49% of patients in the placebo arm had experienced at least one SRE (2), suggesting that patients with bone metastases from advanced prostate cancer are at substantial risk of skeletal complications. In fact, the risk is similar to that observed in patients with stage III multiple myeloma (51% incidence at 21 months) (3), for which intravenous bisphosphonate therapy has been the standard of care for years. Moreover, the mean annual incidence of SREs among prostate cancer patients in the placebo arm is approximately 1.5 events per year (2), indicating that patients often have multiple events each year. Because these patients have a median survival of 12–53 months from the time of diagnosis of bone metastases (4), the likelihood that any given patient will experience a skeletal complication is high. More important, skeletal complications are associated with decreased quality of life (5) and survival (6). Therefore, we believe there is sound clinical rationale for proactive treatment with zoledronic acid in patients with bone metastases from advanced prostate cancer and that the potential benefits outweigh the risks associated with bisphosphonate therapy. Adverse events associated with zoledronic acid were primarily mild-to-moderate flu-like symptoms and would not be expected to affect quality of life to the same extent as skeletal complications.

Drs. Winquist and Berry also point out subtle differences in the treatment groups, such as differences in the percentage of patients with an SRE before study entry, and suggest that these differences may have influenced the outcome of the trial. Exploratory analyses have shown that this imbalance, which was not statistically significant, did not affect the outcome of the trial. Before study entry, 30.8% of patients in the 4 mg of zoledronic acid group and 37.5% in the placebo group had experienced an SRE. After adjusting for prior SRE, compared with patients in the placebo group, the percentage of patients with an SRE was lower for patients in the zoledronic acid group ($P = .037$, logistic regression analysis), and the time to
first SRE was longer for patients in the zoledronic acid group (adjusted hazard ratio = 0.684, 95% confidence interval = 0.510 to 0.918; \( P = .011 \)). A stratified analysis showed that zoledronic acid was associated with an absolute 10% reduction in the percentage of patients with at least one SRE, regardless of whether patients did or did not have an SRE before study entry (2).

Finally, Drs. Winquist and Berry ask if there are any data on prognostic factors that might predict the risk of SREs and that could be used to guide treatment decisions. Although there are data to suggest that some patients are at higher risk of SREs than others, to date, there is no way to predict with any degree of certainty who will experience skeletal complications. Two factors that appear to predict a higher risk for skeletal complications include previous SRE and high levels of the bone resorption marker N-telopeptide (NTX). Patients who experienced an SRE before study entry were slightly more likely to experience a subsequent SRE (2); however, the urinary NTX/creatinine ratio may be the strongest predictor of the risk of SREs. A detailed retrospective analysis of prostate cancer patients’ most recent NTX levels before an SRE indicated that patients with the highest levels of NTX excretion (≥100 nmol/mmol of creatinine) had a fivefold increased risk of SREs (7). Moreover, high NTX excretion was associated with disease progression in bone and was indicative of immediate risk of an event. Although bone resorption markers may be useful for monitoring disease progression and response to bisphosphonate therapy, they should not be used to determine when to initiate treatment with bisphosphonates. The use of biochemical markers of bone resorption for making treatment decisions is not supported by American Society of Clinical Oncology guidelines for the treatment of bone metastases from breast cancer. This would require prospective clinical trials.

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REFERENCES


NOTES

F. Saad currently conducts research sponsored by Novartis and is a member of the advisory board for Novartis.

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