Economic Evaluation of Denosumab Compared with Zoledronic Acid in Hormone-Refractory Prostate Cancer Patients with Bone Metastases

The recent analysis by Xie et al. was intended to delineate the cost-effectiveness of denosumab (Xgeva) versus zoledronic acid (Zometa) for prevention of skeletal-related events (SREs) in patients with castrate-resistant prostate cancer (CRPC) and bone metastases. The authors conclude that denosumab is a “costly alternative” to zoledronic acid. Their conclusions, however, are based on methods that we believe are flawed in a number of respects. Like all scientific studies, cost-effectiveness analyses (CEA) must be critically evaluated based on the methods used, data collected, assumptions made, and conclusions drawn. The Xie et al. CEA oversimplifies a complex area of research and likely understates the seriousness and true prevalence of skeletal complications in oncology, which led them to their conclusion that less costly, less effective treatments are acceptable for these patients.

The Xie et al. CEA was specified to be from the perspective of a U.S. third party payer. However, the Xie et al. model used SRE rates from clinical trial data, which are not consistent with published real-world SRE rates in the United States. An analysis of a commercial claims database of patients with at least 1 SRE receiving zoledronic acid demonstrated an average rate of 0.29 SREs per month (3.48 SREs per year), notably greater than that reported from clinical trials. Lower SRE rates observed in clinical trials may be because of the patient eligibility criteria, such as better performance status (83% or more of patients in these trials had an Eastern Cooperative Oncology Group [ECOG] status of 0 or 1) and higher levels of treatment compliance than in the real-world setting.

The Xie et al. CEA model structure model required multiple inappropriate assumptions to derive the transition probabilities between Markov health states that were not based on information included in the Fizazi et al. study. Notably, the authors assumed that all patients entering the Markov cohort model were SRE-naive, yet nearly one-quarter of patients enrolled in the denosumab versus zoledronic acid phase 3 trial had a prior SRE. Secondly, the hazards of experiencing a first SRE and disease progression were assumed to be constant, but as a patient’s disease progresses, they may be at an even greater risk of experiencing an SRE. Finally, the transitional probability to first-or-subsequent SRE among patients without disease progression used the risk reported in Tchekmedjian et al., which reflected the risk for first SREs only. Taken together, these assumptions undoubtedly yield downwardly biased estimates of the incidence of SREs in patients with metastatic disease.

Xie et al. used a cycle length of 12 weeks, which only allows for 1 SRE per cycle, and is inconsistent with the previously published cost-effectiveness models evaluating bone-modifying agents in the treatment of bone metastases.

For CEA “The time horizon…should extend far enough into the future to capture the major health and economic outcomes,” yet a very short time horizon was selected for this CEA. Results from Fizazi et al. showed that the difference in efficacy between denosumab and zoledronic acid continued to diverge over the duration of the study, and the median survival of patients enrolled in this study was approximately 1.7 years, indicating that a number of patients are surviving well past the model’s 1-year time horizon. Consequently, by implementing a 1-year time horizon the benefit of denosumab versus zoledronic acid for prevention of SREs was truncated and the occurrences of SREs and associated economic outcomes were not fully captured. This is reflected in the lower cost per SRE avoided in the sensitivity analyses which extended the time horizon. A lifetime model is more appropriate since SREs occur throughout the entire remaining life span of people with metastatic cancer.

SRE costs were derived from Lage et al. (2008), which reported 1-year cumulative costs associated with SREs in aggregate to describe the burden of SREs. These values are not appropriate for use in Markov-event CEA models. Instead, costs of individual SRE types using an episode-based approach are more appropriate as they allow attribution of cost for each occurrence of a SRE. There is a large discrepancy in costs using these different methods. The Lage et al. analysis notes that the total annual inpatient costs associated with SREs is $5,641, whereas an episode-based approach using data from a large commercial claims database estimates the total reimbursed amounts of SRE-associated hospitalizations were $22,390 to $59,788, depending on the SRE type. The underestimation of SRE management costs diminishes the economic benefit of treatment for preventing SREs.

Moreover, the cost per quality-adjusted life-year (QALY), rather than the cost per SRE avoided (which accords no weight or importance to the impact of SREs on patients’ lives), is generally accepted to be a more appropriate metric for economic evaluations. Although Xie et al. mention QALYs in their discussion, the estimates they cite cannot be accorded much weight in light of the limited details provided.

Overall, the study by Xie et al. has a number of critical flaws that call into question the basis for and validity of their conclusions. By not reflecting SRE events in actual clinical practice and not accounting for all events using short time horizons, inappropriately applying and underestimating SRE costs, and not considering the detrimental impact of SREs on patients’ quality-of-life, this model systematically biases against more effective therapies. Moreover, when these biases are combined, the problem is further compounded, making the interpretation difficult at best. When models with critical flaws are used to inform decision making, the ultimate harm is suffered by patients.
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REFERENCES

The Authors Respond:
We admit that any cost-effectiveness analysis (CEA) has limitations, the details of which have been stated in the paper. However, we disagree that the flaws cited by Rader et al.1 lead to biases that will change the study conclusions. We would also like to point out that we have conducted extensive sensitivity analyses to address the limitations, such as uncertainties of data and restrictiveness of base-case assumptions. The results were robust under various scenarios, except for substantial changes in drug prices and relative efficacy between denosumab and zoledronic acid.

With respect to the flaws cited by Rader et al.,1 we have provided the following responses.

Rader et al.1 commented that the model was based on clinical trials instead of real-world rates of skeletal-related events (SREs). CEA based on clinical trials is not uncommon. For example, most of the guidance published by the National Institute for Health and Clinical Excellence is based on the technology appraisals using clinical trial data.2 The real-world comparative effectiveness between denosumab and zoledronic acid has not been reported. Using the same relative efficacy reported by Fizazi et al. (2011),3 when we artificially inflated the number of SREs of patients receiving zoledronic acid to 3.48 for the first year, as suggested by Rader et al., the incremental cost per SRE avoided increased to $78,217. Unless there is solid evidence that the real-world relative effectiveness of denosumab versus zoledronic acid is larger compared with the relative efficacy observed in the trial, using clinical trial data will not bias against denosumab.

Although we did make assumptions in the CEA, the “inappropriate assumptions” cited by Rader et al.1 warrant further discussion. First, we did not assume that patients entering the Markov model were SRE-naive. We specifically mentioned in the methods section that the transition probabilities were “to the first on-study SRE” instead of the first-ever SRE, and the probabilities were calculated based on the results reported by Fizazi et al.3 Second, we had a detailed discussion in the limitations section about the assumption of constant hazard and its effects on the results. We showed that it did not affect our conclusion. Third, we used the risk ratio reported by Tchekmedyian et al. (2010)10 for both first and subsequent SREs because there is no evidence that the impact of disease progression is different between first on-study SREs and subsequent SREs. We have stated this limitation in the published study. Without further evidence, it is difficult to assess whether and how the current assumption biases the incidence of SREs.

The cycle length of 12 weeks was consistent with the mean...
time of 3 months between the first and second types of SREs in prostate cancer patients reported by a study using real-world data. Although the assumption of 1 SRE per cycle is somewhat arbitrary, as stated in the limitations, the proportion of patients with first on-study SREs and the total number of SREs in each arm match well with the numbers reported in the Phase 3 clinical trial.

In the study, we presented the results for both 1- and 3-year time horizons. The reason for not using the longer time horizon is that zoledronic acid (Zometa) is expected to be available in a less expensive generic form by March 2013. Because the model results are sensitive to zoledronic acid drug price, a longer time horizon is not meaningful in this case. With respect to the suggestion of using a lifetime model, we would like to mention that metastatic castration-resistant prostate cancer (mCRPC) patients had a poor survival (median 9-13 months). In our model, 83% of patients died by the end of 3 years. Therefore, even if we used a lifetime model, the results would not be very different compared to the 3-year model.

Regarding the cost estimate for SREs, we have provided detailed information and discussed its limitations in the published study. However, we would like to reiterate that using the 1-year cumulative costs as per event costs would not underestimate the cost of SRE because in the study by Lage et al. (2008), the 1-year costs were estimated among patients experiencing 1 or more episodes of a specific type of SRE. Barlev et al. (2010) reported inpatient costs for only 3 types of SREs: pathologic fracture, surgery to bone, and spinal cord compression. Radiation to bone, which we believe is primarily managed in an outpatient setting, was not estimated in the study, and it accounted for more than 50% of first on-study SREs in both treatment arms in the Phase 3 trial. Therefore, using the costs suggested by Rader et al. will inevitably inflate the mean costs for SREs.

Finally, SRE was the primary endpoint of the Phase 3 trial and was thus used as the effectiveness measure in this CEA. From clinical perspectives, SRE is the most relevant outcome among mCRPC patients with bone metastasis. Therefore, incremental cost per SRE avoided is particularly pertinent to physicians as well as payers. The outcome has been commonly used in the previous economic analyses of treatments that prevent and delay SREs in cancer patients. Although a CEA using cost per quality-adjusted life year (QALY) as the outcome has not been published, another independent study by Snedecor et al. has been presented at the 2011 American Society of Clinical Oncology meeting. Both the current study and the study by Snedecor et al. estimated that the incremental cost per QALY comparing denosumab versus zoledronic acid was more than $1 million.

Overall, despite the limitations, we feel that the results of our study are robust and the conclusion is valid. Denosumab does have better efficacy in preventing and delaying SREs in CRPC patients with bone metastases compared with zoledronic acid but at considerable costs.

**REFERENCES**


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