Journal Watch

Long-Term Efficacy and Safety of Zoledronic Acid in the Treatment of Skeletal Metastases in patients with Nonsmall Cell Lung Carcinoma and Other Solid Tumors.

Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M, et al. Cancer 2004; 100(12):2613-21.

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Abstract

Background: The authors previously reported the efficacy of a dose of 4 mg of zoledronic acid in reducing skeletal complications in patients with bone metastases secondary to lung carcinoma and other solid tumors (except carcinomas of the breast and prostate). In the current study, they update these results and report the long-term efficacy and safety of 21 months of treatment with zoledronic acid in a randomized, placebo-controlled trial.

Methods: A total of 773 patients were randomized to receive zoledronic acid (4 mg or 8 mg) or placebo via a 15-minute infusion every 3 weeks for 21 months. The 8-mg dose later was reduced to 4 mg (8/4-mg group). The primary efficacy endpoint was the percentage of patients at 21 months with ≥ 1 skeletal-related event (SRE) (pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone). Secondary analyses (time to first SRE, annual incidence of SREs, and multiple-event analysis) included hypercalcemia of malignancy.

Results: Fewer patients treated with zoledronic acid developed at least 1 SRE at 21 months compared with patients treated with placebo (39% of those treated at the 4-mg dose [P=0.127] and 36% of those treated at the 8/4-mg dose [P=0.023], compared with 46% of those treated with placebo). Furthermore, 4 mg of zoledronic acid significantly delayed the median time to first SRE (236 days with 4 mg vs. 155 days with placebo; P-0.009) and significantly reduced the annual incidence of SREs (1.74 per year with the 4-mg dose vs. 2.71 per year with placebo; P=0.012). Moreover, the 4-mg dose of zoledronic acid was found to reduce the risk of developing a skeletal event by 31% (hazard ratio of 0.693; P-0.003). Zoledronic acid was found to be well tolerated with long-tem use; the most commonly reported adverse events in all treatment groups included bone pain and the transient, acute-phase reactions of nausea, anemia, and emesis.

Conclusions: To the author's knowledge, zoledronic acid is the first bisphosphonate to demonstrate long-term safety and efficacy in this patient population.

Comments

Strengths/uniqueness:
Randomized, double-blinded trial

Weaknesses:
1. Supported by the pharmaceutical industry (vested interest).
2. The primary endpoint (percentage of patients at 21 months with >1 skeletal-related event) only reached significance when hypercalcemia of malignancy was added, so zoledronic acid likely only helps patients with hypercalcemia.
3. Many patients may die (median of 6 mos. survival), before they experience the benefit of this treatment (since endpoints were measured at 21 months not at 6 months).
4. The number of patients who discontinued zoledronic acid due to adverse events was not provided.
5. The cost of using this agent and measures of improvement of quality of life were not addressed.

Relevance to Palliative Care:
At this time, there is not sufficient evidence to use zoledronic acid prophylactically in patients with bone metastases.