Review: Bisphosphonates are modestly better than placebo for relieving painful bone metastases

Wong R, Shukla VK, Mensinkai S, Wiffen P. **Bisphosphonate agents for the management of pain secondary to bone metastases: a systematic review of effectiveness and safety.** Technology Report no. 45. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); Jan 2004. www.ccohta.ca. **Clinical impact ratings:** GIM/FP/GP ★★★★★★☆ Oncology ★★★★★☆☆

QUESTION

In patients with bone metastases, are bisphosphonates more effective than placebo for relieving pain?

METHODS

Data sources: 7 databases, scientific proceedings, and abstracts of professional associations.

Study selection and assessment: Randomized controlled trials (RCTs) that included patients who had bone metastases with or without pain at enrollment, measured pain as an outcome, allowed antineoplastic therapy or rescue pain medications (if available to all patients), and compared bisphosphonates with a control intervention (placebo, no treatment, different types of bisphosphonates, different doses of the same bisphosphonate, or other treatments). Study quality was assessed using the 5-point Jadad scale.

Outcomes: Pain relief. Secondary outcomes included dose response of bisphosphonates for reducing pain, quality of life (QOL), and adverse effects (AEs).

MAIN RESULTS

51 RCTs (n = 9425) met the selection criteria. Patients had bone metastases (12 RCTs); breast cancer (18 RCTs), multiple myeloma (10 RCTs), or both (3 RCTs); and prostate cancer (8 RCTs). 28 RCTs had quality scores ranging from 3 to 5. 32 RCTs compared bisphosphonates with placebo. Bisphosphonates used were etidronate (3 RCTs), clodronate (18 RCTs), pamidronate (7 RCTs), zoledronate (2 RCTs), and ibandronate (2 RCTs). Using a random-effects model, meta-analysis of 5 RCTs showed greater pain relief with bisphosphonates than with placebo (Table). Pain scores were reduced more in the bisphosphonates group than in the placebo group (weighted mean difference −0.35, 95% CI −0.39 to −0.31). More patients who received bisphosphonates had reduced analgesic use than those who received no intervention (Table). 8 RCTs that reported on QOL showed variable results, and 1 RCT (which was the only trial with 12-mo results) showed no difference between groups for improvement in QOL. Pooling of 4 RCTs that compared low- with high-dose bisphosphonates showed no difference for reducing pain (odds ratio [OR] 1.05, CI 0.57 to 1.92). Of 39 RCTs that reported on AEs, the most common were nausea and vomiting. Gastrointestinal (GI) AEs (diarrhea and constipation) occurred only with clodronate (18 RCTs) (OR 3.67, CI 1.12 to 12.06). Other bisphosphonate-specific AEs were hypocalcemia and local reactions with pamidronate (4 RCTs), and anemia, limb edema, fever, elevations in serum creatinine, and deterioration in renal function with zoledronate (2 RCTs).

CONCLUSIONS

Bisphosphonates are modestly better than placebo for relieving painful bone metastases and reducing analgesic use. The most common adverse events are nausea, vomiting, and fever.

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Bisphosphonates vs control (placebo or no intervention) for bone metastases at 12 weeks*

Outcomes	Number of trials (*n*)	Weighted event rates		RBI (95% CI)	NNT (CI)
		Bisphosphonates	Control		
Pain relief	5 (634)	37%	22%	65% (28 to 111)	7 (4 to 36)
Reduction in analgesic use	3 (182)	34%	23%	49% (4 to 113)	10 (5 to 525)

*Abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

Bone metastases are common and cause substantial suffering that can be reduced by bisphosphonates, although their effects are limited. Bisphosphonates are heavily promoted by their manufacturers and are expensive. Although the estimated effects on bone pain are probably accurate, these effects might be inflated by including open-label trials that are more susceptible to placebo effects. They may also be attenuated by the use of older and less potent bisphosphonates, which may be less effective. Most trials in the review by Wong and colleagues had a background of suitable analgesics and anticancer treatments, and the findings were consistent with other systematic reviews assessing a wider range of outcomes in breast cancer and myeloma (1, 2).

The common AEs of bisphosphonates are mild and vary with the route of administration. Upper GI symptoms are more common with oral bisphosphonates, while fever, rigors, and transient musculoskeletal pain are more common with intravenous bisphosphonates.

The practical implication is that bisphosphonates are a reasonable option for patients with pain from bone metastases that is not controlled by optimal analgesia and anticancer treatment. Optimal analgesia includes regular and adequate doses of acetaminophen (1 g 4 times/d), an opioid (dose titrated to optimize the balance between pain relief and side effects), and a nonsteroidal antiinflammatory drug (if not contraindicated). Optimal anticancer treatment includes radiation for most patients and systemic therapy for those with responsive tumors (e.g., endocrine therapy for breast and prostate, steroids for myeloma and lymphoma, and chemotherapy for these and other tumors). Using bisphosphonates alone is tempting for patients with symptoms limited to their bones. However, most patients have disease elsewhere that does not respond to bisphosphonates. This might explain the lack of effect of bisphosphonates on QOL. Optimal dosing, frequency, and duration of bisphosphonates await further clarification.

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References

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