

Review: Bisphosphonates prevent or delay skeletal events in women with advanced breast cancer and bone metastases

Pavlaklis N, Schmidt RL, Stockler M. **Bisphosphonates for breast cancer.** *Cochrane Database Syst Rev.* 2005;(3):CD003474.

Clinical impact ratings: Oncology ★★★★★☆

QUESTION

In women with early or advanced breast cancer, do bisphosphonates reduce the incidence of skeletal events, decrease bone pain, improve quality of life, and increase survival?

METHODS

Data sources: Cochrane Breast Cancer Group specialized register, EMBASE/Excerpta Medica, CancerLit, selected journals, lists of conference abstracts, bibliographies of relevant studies, pharmaceutical companies, authors of included studies, and other researchers in the field.

Study selection and assessment: Randomized controlled trials (RCTs) that compared a bisphosphonate with placebo or no bisphosphonate (control) or with another bisphosphonate in women with advanced breast cancer, with or without bone metastases, or early breast cancer. Individual study quality was assessed using the 13-item MERGE criteria.

Outcomes: Skeletal events (new bone metastases, pathologic fractures, spinal cord compression, irradiation of or surgery on bone, development or progression of bone pain [and, in some studies, hypercalcemia]), quality of life, and survival.

MAIN RESULTS

21 RCTs met the inclusion criteria: 15 RCTs ($n = 5187$) in women with advanced breast cancer and clinically evident bone metastases

(category 1), 3 RCTs ($n = 320$) in women with advanced breast cancer without bone metastases (category 2), and 3 RCTs ($n = 1670$) in women with early breast cancer (category 3). In category 1, risk for skeletal events was reduced with bisphosphonates (Table) and time to the first event was longer in 7 of 10 RCTs, compared with control. The exclusion of hypercalcemia as a skeletal event and the route of administration (oral or intravenous) did not affect the benefit of treatment. 6 of 10 RCTs showed less bone pain in category 1 women receiving bisphosphonates than in control-group women. Bisphosphonates did not prevent the occurrence of new bone metastases in category

2 or 3 (Table). 2 of 6 RCTs in women with advanced breast cancer showed improved quality of life with bisphosphonate treatment. Survival increased with bisphosphonate use in women with early, but not advanced, breast cancer (Table).

CONCLUSION

In women with advanced breast cancer and clinically evident bone metastases, bisphosphonates reduce the incidence of skeletal events but have no effect on survival.

Source of funding: Not stated.

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Bisphosphonates (treatment) vs placebo or no bisphosphonates (control) in women with breast cancer*

Outcomes	Stages of breast cancer	Number of comparisons (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
			Treatment	Control		
Skeletal events	Advanced, bone metastases	10 (3065)	54%	65%	16% (11 to 21)	10 (8 to 15)
New bone metastases	Advanced, no bone metastases	3 (320)	24%	24%	1% (-47 to 33)	Not significant
	Early	3 (1653)	15%	18%	18% (-1 to 34)	Not significant
Death	Advanced	9 (1968)	62%	64%	2% (-3 to 8)	Not significant
	Early	3 (1653)	21%	26%	18% (3 to 31)	20 (12 to 100)

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

COMMENTARY

Bisphosphonates have a wide spectrum of uses in breast cancer. Pavlaklis and colleagues reviewed the use of bisphosphonates in 3 specific breast cancer-related situations. They noted that the use of bisphosphonates in patients with bone metastases definitely reduces the rate of skeletal-related events (SREs). Zoledronate, the most potent bisphosphonate currently available, is at least as effective as pamidronate in preventing SREs and has a much-reduced infusion time (1).

Considerable interest exists in the use of bisphosphonates in the adjuvant setting, not only to reduce the rate of bone metastases, but to prolong disease-free and overall survival. The findings of available trials conflict, but Pavlaklis and colleagues noted significantly improved survival when the results of these trials were combined. However, meta-analysis of the available trials did not provide evidence that the incidence of bone metastases is reduced by the prophylactic use of bisphosphonates in either early-stage or advanced breast cancer.

So how should medical oncologists use bisphosphonates in their clinical practice? Clearly, patients with bone metastases should be treated with a bisphosphonate to reduce the rate of SREs until their

performance status declines. Either zoledronate or pamidronate given intravenously are reasonable options, and ongoing trials with oral agents will elucidate their role. In patients with early-stage breast cancer, the benefits of bisphosphonates on survival are encouraging but need confirmation before off-trial use can be recommended. Several ongoing studies are exploring this issue. The NSABP B-34 trial, which has completed accrual, randomized patients with early-stage breast cancer to oral clodronate or placebo for 3 years; disease-free survival is the primary endpoint. A current Intergroup trial is randomizing patients with early-stage breast cancer to 3 different bisphosphonates, zoledronate, ibandronate, or clodronate, after adjuvant chemotherapy.

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Reference

- Rosen LS, Gordon DH, Dugan W Jr, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer.* 2004;100:36-43.