EFFICACY OF PAMIDRONATE IN BREAST CANCER WITH BONE METASTASES: A RANDOMIZED DOUBLE-BLIND PLACEBO CONTROLLED MULTICENTER STUDY

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Symptoms and complications from skeletal metastases in advanced breast cancer constitute a quantitative and qualitative challenge in the care of these patients, where introduction of undue toxicity should be avoided.

Bone metastases act on the mineralized tissue via direct digestion, but predominantly by cytokine activation of osteoclast activity. Apart from pain and increased skeletal fragility, hypercalcemia may occur, but the last event has, during the past decade, been effectively treated by use of bisphosphonates.

Several phase II studies have indicated the efficacy of various bisphosphonates in reversing osteolysis and in decreasing pain. To establish the efficacy of orally administered clodronate Elomaa et al. (1) performed a small placebo-controlled randomized study, as Paterson et al. (2) did on a larger scale. Van Holten-Verzantvoort et al. (3) conducted an open randomized study on orally administered pamidronate and recently Conte et al. (4) reported a similar study on parenteral pamidronate. These four studies demonstrate to various extents a decrease in skeletal-related morbidity.

Since most symptoms of skeletal metastases that require palliative radiotherapy are liable to placebo effects, it was considered important to perform a large scale- study using a double-blind placebo-controlled design.

Methods

Eligible patients were women with breast cancer with skeletal metastases. Antitumoral therapy was given at the discretion of the physician. The patients were randomized to receive 60 mg disodiumpamidronate or placebo in 500 ml saline as an intravenous infusion over 1 hour every fourth week for up to two years or until the second sign of skeletal progression occurred.

Evaluation of skeletal-related symptoms, increased pain, hypercalcemia, pathologic fractures, paralysis due to vertebral compression and implicated treatment, i.e. palliative radiotherapy, osteosynthesis and change in basal antitumor therapy was made every third month. Side effects were recorded as with all medication. A separate quality-of-life form including visual analogue scales relating to skeletal pain was also filled in by the patient at each quarterly visit.

Results

Four hundred-and-four women were randomized between 1990 and 1993. The prestudy characteristics were not significantly different.

The median time on allocated treatment was 12.0 and 11.5 months for the pamidronate and placebo groups respectively. The cumulative incidence of all skeletal symptom events was significantly reduced for the pamidronate group. Expressed as progression-free survival, the time period was 11.8 and 8.4 months for the pamidronate and placebo groups respectively ($p < 0.01$) including hypercalcemia.

The incidence of radiotherapy, osteosynthesis and change in antitumour treatment was not different between the treatment groups.

Side effects were few but significantly higher for the pamidronate group at the first follow-up visit. Performance status was significantly improved for the pamidronate group.

The use of analgesics was insignificantly lower in the pamidronate group during follow-up. In conclusion it seems that 60 mg pamidronate iv. q 4 weeks enhances the quality of life in women with bone metastases from breast cancer though not in a reduction of other palliative measures.

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REFERENCES

1. Elomaa I, Blomqvist C, Gröhn P, et al. Long-term controlled trial with diphosphonate in patients with osteolytic bone metastases. Lancet 1983; 22: 146–149.
2. Paterson AHG, Powles TJ, Kanis JA, McCloskey E, Hansson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol 1993; 11: 59–65.
3. van Holten-Verzantvoort ATM, Kroon HM, Bijvoet OLM, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. J Clin Oncol 1993; 11(3): 491–498.
4. Conte PF, Giannessi PG, Latreille J, et al. Delayed progression of bone metastases with pamidronate therapy in breast cancer patients.: A randomized, multicenter phase III trial. Annals of Oncol 1994; 5, suppl: 7: S41–S44.