Bisphosphonates and skeletal morbidity in patients with metastatic cancer

Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SR. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003;327: 469-72.

Background: Metastatic bone disease continues to represent a major challenge to physicians. Cancer patients with bone metastases can suffer from hypercalcemia, pathologic fractures, spinal cord compression, reduced mobility and pain. A completely satisfactory therapeutic option has yet to be found. Recent meta-analyses confirm the efficacy of bisphosphonates — potent medications that inhibit bone resorption — in increasing bone mineral density and reducing fracture rates.[1] Whether these results with bisphosphonates can be extrapolated to patients with metastatic bone disease remains uncertain.

Question: In patients with proven malignant disease and bone metastases, does the use of oral or intravenous bisphosphonate therapy reduce skeletal morbidity (pathological fractures, radiotherapy to bone metastases, hypercalcemia, spinal cord compression and orthopedic surgery)?

Design: The investigators conducted a systematic review and meta-analysis of all available randomized trials evaluating the use of bisphosphonates in cancer patients with metastatic bone disease. Patients with multiple myeloma were included, but those with other hematological cancers were not. The investigators identified potentially relevant trials by searching electronic databases (MEDLINE, CancerLit, EMBASE, Science Citation Index, Cochrane Database), manually searching 3 oncology journals and abstracts from international meetings, scanning reference lists of articles, and consulting experts in the specialty and drug companies for unpublished data. All foreign-language articles were translated in full into English. The reporting of concealment and blinding in each trial was graded by the authors. Data were pooled when appropriate using a random effects model and weighted according to the inverse of their variance. No sensitivity analyses were defined a priori.

Results: Of 95 potentially relevant articles, 47 papers describing 30 studies met the eligibility criteria. Data extracted from 18 studies were eligible for inclusion in the meta-analyses. Patient populations included those with breast cancer, prostate cancer, multiple myeloma and mixed diagnoses. Compared with placebo, in the studies of more than 6 months' duration, bisphosphonates significantly reduced the odds ratio (OR) for vertebral fractures (7 studies [n = 3238], OR 0.69, 95% confidence interval [CI] 0.57–0.84), nonvertebral fractures (9 studies [n = 3376], OR 0.65, 95% CI 0.54–0.79), combined fractures (7 studies [n = 2587], OR 0.65, 95% CI 0.55–0.78), radiotherapy (8 studies [n = 3140], OR 0.67, 95% CI 0.57–0.79) and hypercalcemia (11 studies [n = 3894], OR 0.54, 95% CI 0.36–0.81). Bisphosphonates did not reduce the incidence of spinal cord compression (6 studies [n = 2628], OR 0.71, 95% CI 0.47–1.08). The risk of subsequent orthopedic surgery was reduced with bisphosphonates in the studies of more than 2 years' duration (2 studies [n = 753], OR 0.49, 95% CI 0.28–0.86).

Commentary: In the hierarchy of research design, the results of a meta-analysis of high-quality, homogeneous, randomized controlled trials represents the highest level of evidence to guide patient care.[1–3] Ross and coauthors should be commended for their rigorous systematic review and meta-analysis. The validity of the results from this review are strengthened by the inclusion of randomized controlled trials, a comprehensive search strategy, the inclusion of unpublished reports and non-English-language trials, and homogeneity of results across studies.[1–3] The authors did not report whether searches, assessment of study validity or data abstraction were performed in duplicate. The reproducibility of the methodology (i.e., inter-reviewer agreement statistics) would improve confidence in the validity of the review.

Practice implications: Bisphosphonates are effective in decreasing skeletal morbidity. Although morbidity is decreased and time to first skeletal event is increased, overall survival is not increased. Bisphosphonate therapy should be initiated when skeletal metastases are identified and continued for at least 6 months for clinical benefit. Although no direct comparison between intravenous and oral routes of administration were available, indirect comparisons favour the intravenous route.

Mohit Bhandari
Department of Clinical Epidemiology and Biostatistics
Division of Orthopaedic Surgery
McMaster University
Hamilton, Ont.

References

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