A systematic review of the role of bisphosphonates in metastatic disease

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Executive summary

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Executive summary

Background

Bisphosphonates inhibit osteoclastic bone resorption and are used in malignant disease to treat hypercalcaemia, reduce skeletal morbidity associated with bone metastases and, less often, in the adjuvant setting to delay the development of bone metastases. As there are economic implications for the widespread use of these drugs, it is essential that their use is evidence based.

Objectives

1. To identify evidence for the role of bisphosphonates in malignancy for the
   (a) treatment of hypercalcaemia
   (b) prevention of skeletal morbidity
   (c) use in the adjuvant setting.
2. To perform an economic review of current literature and to model the cost-effectiveness of bisphosphonates in the treatment of hypercalcaemia and prevention of skeletal morbidity

Methods

Data sources

- Electronic databases: MEDLINE, CANCERLIT, EMBASE, Science Citation Index Expanded, pre-MEDLINE, Cochrane Register for Randomised Controlled Trials and Database for Abstracts of Reviews of Effectiveness, Health Economic Evaluations Database, National Health Service Economic Evaluations Database.
- Scanning of reference lists of included studies and key reviews.
- Pharmaceutical companies.
- Experts in the field.
- US Food and Drug Administration website.
- Hand-searching of abstracts from the meeting of American Society Clinical Oncology and European Congress Cancer Oncology 1999–2001; contents pages of *Journal Clinical Oncology* 2001, *European Journal of Cancer* 2001 and *Bone* 2001, together with abstracts printed in these journals 1999–2001.

Study selection

1. Hypercalcaemia review
   (a) randomised controlled trials (RCTs)
   (b) patients with hypercalcaemia of malignancy (elevated corrected serum calcium post-rehydration)
   (c) treated with a bisphosphonate.
2. Skeletal morbidity review
   (a) RCTs
   (b) patients with malignancy and bony metastases
   (c) treated with a bisphosphonate
   (d) studies measuring at least one skeletal-related event (SRE): pathological fractures (non-vertebral, vertebral, combined), radiotherapy, spinal cord compression, orthopaedic surgery, hypercalcaemia.
3. Adjuvant review
   (a) RCTs
   (b) patients with malignancy and no bony metastases
   (c) treated with a bisphosphonate.
4. Economic review
   (a) all studies included (not limited to RCTs)
   (b) information regarding cost/cost-benefit of bisphosphonate therapy.

Data extraction

All studies were assessed for inclusion then data extracted by two independent reviewers. Consensus was reached, with a third reviewer's decision being final. Studies were graded according to blinding and allocation concealment.

Data synthesis

Where possible, overall event rates were calculated by meta-analysis and pooled odds ratios (OR) given with 95% confidence intervals (CIs). Where data could not be combined, studies were reported individually and proportions compared using chi-squared analysis. Cost and cost-effectiveness were assessed by a decision analytic model comparing different bisphosphonate regimens for the treatment of hypercalcaemia; Markov models were employed to evaluate the use of bisphosphonates to prevent SRE in patients with breast cancer and multiple myeloma. ▶

Results

Hypercalcaemia review

Owing to the heterogeneity of studies, results could not be combined in a meta-analysis. Pamidronate was more effective than control, etidronate, mithramycin and low-dose clodronate (600 mg) in achieving normocalcaemia. Pamidronate 90 mg was as effective as higher dose clodronate (1500 mg) and demonstrates a dose response from 30–60–90 mg. Pamidronate prolongs (doubles) the median time to relapse compared with clodronate and etidronate. Alendronate has similar efficacy to clodronate but is superior to etidronate in achieving normocalcaemia. A dose response is seen with ibandronate (up to 4 mg) and alendronate. Mean time to normocalcaemia for all bisphosphonates ranges from 2 to 6 days.

Skeletal morbidity review

Primary analysis

On meta-analysis, bisphosphonates, compared with placebo, significantly reduced the OR for vertebral fractures, non-vertebral fractures, combined fractures, radiotherapy and hypercalcaemia but not orthopaedic surgery or spinal cord compression. OR (95% CI): vertebral fractures, 0.692 (0.570 to 0.840), $p < 0.0001$; non-vertebral fractures, 0.653 (0.540 to 0.791), $p < 0.0001$; combined fractures, 0.653 (0.547 to 0.780), $p < 0.0001$; radiotherapy, 0.674 (0.573 to 0.791), $p < 0.0001$; spinal cord compression, 0.714 (0.470 to 1.083), $p = 0.113$; orthopaedic surgery, 0.698 (0.463 to 1.052), $p = 0.086$; and hypercalcaemia, 0.544 (0.364 to 0.814), $p = 0.003$.

Time to first SRE

Bisphosphonates (intravenous pamidronate and intravenous zoledronate) significantly increase the time to first SRE. The evidence for oral clodronate is conflicting.

Sub-analysis over time

The OR for radiotherapy was significantly reduced at all time points. Orthopaedic surgery showed a progressive reduction in OR with narrowing of the CI, reaching significance at 24 months. For hypercalcaemia, the reduction in the OR was significant at all time points except 18–24 months.

Sub-analysis of disease groups

Two results contrasted strongly with the primary analysis. Vertebral fractures were not significantly reduced in patients with breast cancer, OR (95% CI) 0.870 (0.656 to 1.154), $p = 0.334$. Hypercalcaemia was not significantly reduced in patients with myeloma, OR (95% CI) 0.968 (0.687 to 1.365), $p = 0.852$.

Sub-analysis of drugs

All outcomes except spinal cord compression reached significance with pamidronate, including orthopaedic surgery, $p = 0.009$. Clodronate significantly reduced the OR for vertebral fractures, non-vertebral fractures and hypercalcaemia. Zoledronate significantly reduced the OR for all outcomes except spinal cord compression and orthopaedic surgery. There was no difference, for any outcome, in trials directly comparing zoledronate with pamidronate.

Sub-analysis of route

Oral bisphosphonates significantly reduced the OR for vertebral fractures and non-vertebral fractures. Intravenous bisphosphonates significantly reduced the OR for all outcomes except spinal cord compression.

Survival

There was no survival benefit.

Adjuvant review

Clodronate significantly reduces the number of patients with primary operable breast cancer developing bone metastases. This benefit was not maintained once regular administration had been discontinued. Two trials reported significant survival advantages in the treated groups. These findings were not seen in trials of patients with advanced disease.

Toxicity

Bisphosphonates are well tolerated with a low incidence of side-effects

Economic review

Hypercalcaemia

Drugs with the longest cumulative duration of normocalcaemia were most cost-effective. Zoledronate 4 mg was the most costly but most cost-effective treatment (approximately £22,900 per life year gained). The estimates of cost-effectiveness were sensitive to amount of time in hospital.

Skeletal morbidity

The overall cost of bisphosphonate therapy to prevent an SRE was estimated at £250 and £1500 per event for patients with breast cancer and multiple myeloma, respectively. The model suggested that bisphosphonate treatment is sometimes cost-saving in breast cancer patients where fractures are prevented. The models were sensitive to the probability of averting an SRE, the unit cost of an SRE and the price of bisphosphonate treatment. ▶

Conclusions

Bisphosphonates normalise serum calcium in >70% of patients with hypercalcaemia of malignancy within 2–6 days; pamidronate doubles the time to relapse compared with non-aminobisphosphonates. They significantly reduce SREs and delay the time to first SRE in patients with bony metastatic breast cancer and multiple myeloma. Benefit is seen at different time points for different SREs. Bisphosphonates do not affect survival. The current evidence is strongest for the efficacy of pamidronate and for the intravenous over the oral route of administration. In primary operable breast cancer, oral clodronate reduces the number of patients developing bone metastases.

Implications for healthcare

Bisphosphonate therapy appears cost-effective in the treatment of hypercalcaemia and for the prevention of skeletal morbidity, particularly for patients with breast cancer. The economic evidence reviewed was of limited quality, therefore any conclusions based on this evidence need to be interpreted with caution.

Recommendations for research

Hypercalcaemia

- RCT of bisphosphonate maintenance therapy to delay time to relapse in patients following first episode of hypercalcaemia
- trial of parathyroid hormone-related protein (PTHrP) blocker in combination with bisphosphonate in patients with very high levels of PTHrP.

Skeletal morbidity

- RCT using bisphosphonates for prevention of skeletal morbidity in patients with prostate cancer metastatic to bone
- trials to determine the optimum time to commence bisphosphonate therapy: at diagnosis of asymptomatic bone metastases or at first SRE?
- trial to compare efficacy of oral versus intravenous bisphosphonate
- a study to determine current clinical practice with respect to bisphosphonate use in UK oncology centres.

Adjuvant use

- extended use of bisphosphonates (>3 years) for primary prevention of bone metastases from breast cancer
- adjuvant use of bisphosphonates in patients with prostate cancer at high risk of developing bone metastases.

Economic analyses

The evidence base for estimating cost and cost-effectiveness is limited. Further cost and quality of life data are required to identify cost-effectiveness associated with reductions in SREs and delayed time to first SRE. Data on cumulative length of stay and response to successive treatments for patients with hypercalcaemia are needed.

Publication

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The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure was replaced in 2000 by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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