Economic evaluation of zoledronic acid versus pamidronate for the prevention of skeletal-related events in metastatic breast cancer and multiple myeloma

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of a 4-mg infusion of zoledronic acid every 3 to 4 weeks to prevent skeletal-related events in patients with metastatic breast cancer or multiple myeloma.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with advanced breast cancer who had osteolytic or mixed bone metastases and patients with advanced multiple myeloma with osteolytic bone metastases.

Setting
The setting was secondary care. The study took place in 20 countries including the USA, Canada and the UK.

Dates to which data relate
The dates to which the effectiveness and resource use data referred were not reported in this paper. The price year was 2000 for all costs, except for study drugs which used 2002 as the price year.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The cost data were collected prospectively from a sub-sample of the patient sample that provided the clinical effectiveness data.

Study sample
A total of 1,648 patients were recruited, of which 1,116 were randomised to receive either zoledronic acid (561 patients) or pamidronate (555 patients). No sample size or power calculations were presented in the paper. The paper also did not provide any details of how the patient sample was identified, although the authors mentioned that further details of the study had already been published (Coleman et al. 2001 and Rosen et al. 2001, see 'Other Publications of Related Interest' below for bibliographic details). There was no evidence that the study sample was representative of the study population.
Study design
The study was a double-blind, multi-centred randomised controlled trial (the trial involved 248 centres in 20 countries). No details of the randomisation method used in the trial were reported. The patients were followed up for 13 months. Loss to follow-up and details of blinding were not reported in this paper.

Analysis of effectiveness
It would appear that the clinical effectiveness data were analysed on an intention to treat basis. The primary health outcomes used in the analysis were the percentage of patients experiencing skeletal-related events and median time to skeletal-related events (i.e. pathological bone fractures, spinal cord compression, surgery to bone, radiation therapy to bone and hypercalcaemia). Other effectiveness outcomes assessed were patient-reported pain scores and skeletal morbidity rate for radiation therapy to bone. Sub-group analyses were also performed, in which patients with breast cancer were considered independently from those with multiple myeloma. The paper did not show whether the study groups for which effectiveness outcomes were assessed were comparable at analysis.

Effectiveness results
Forty-four per cent of the patients in the zoledronic acid group and 46% of those in the pamidronate group had a skeletal-related event, (p=0.461).

There was no statistically significant difference, either in median time to skeletal-related events or in the overall skeletal morbidity rate, in the two patients groups. The authors reported that both treatment groups experienced a decrease in the pain scores.

In patients with multiple myeloma, there was no statistical difference in the risk of developing a skeletal-related event between the two treatment groups, (p=0.593).

Patients with breast cancer had a 20% lower risk of a skeletal-related event in the zoledronic acid group than in the pamidronate group, (p=0.025).

Clinical conclusions
There were no significant differences in the clinical effectiveness of zoledronic acid, compared with pamidronate, for the prevention of skeletal-related events overall and in patients with multiple myeloma. However, zoledronic acid significantly reduced the risk of developing a skeletal-related event in patients with metastatic breast cancer.

Measure of benefits used in the economic analysis
No summary measure of health benefit was considered in the economic analysis. In effect, a cost-consequences analysis was performed.

Direct costs
The direct costs of the health payer were identified in this study. The resource use data were collected using a case report form that was completed at each study visit. Data were collected on hospitalisation, outpatient use, chemotherapy treatment, radiation treatment, imaging procedures and non acute institutional care. The unit costs of these items were taken from country-specific estimates. The costs incurred in each of the countries included in the study were combined to provide a single estimate of the costs for the two patient groups. When the unit costs were not available, a market-basket based approach was used to impute country-specific estimates. Some of the sources of the unit cost data were the US Medicare reimbursement rates, wholesale prices reported in the Red Book, and unit costs provided by local analysts. The authors estimated the number of doses of the study medication (zoledronic acid or pamidronate) on the basis of the number of days between randomisation and the last day of the study. The costs of administering these drugs were taken from a microcosting study undertaken in the USA. Country-specific drug costs in 2002 were used. Several authors' assumptions were formulated for the cost estimation. The resource quantities were reported separately,
although the unit costs were not provided. With the exception of study drugs, which corresponded to 2002 prices, all costs were adjusted to 2000. The costs were not discounted as the study period was 13 months.

**Statistical analysis of costs**
The statistical significance of differences between the costs incurred by the two patient groups was tested using 95% confidence intervals (CIs) around the difference in the point estimates.

**Indirect Costs**
No indirect costs were included in the study.

**Currency**
US dollars ($). Purchasing power parity currency conversion rates from the Organisation for Economic Cooperation and Development were used to convert all costs to US dollars.

**Sensitivity analysis**
Two one-way sensitivity analyses were undertaken to assess variability in the cost of the study drugs (zoledronic acid and pamidronate). One analysis considered the impact of pamidronate losing patent protection, by reducing the wholesale price of this drug by 5% to 25%. The other analysis varied the cost of the study medications to the wholesale prices listed in the 2002 Red Book and wholesale prices listed for other countries.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The total cost for patients was $16,434 in the zoledronic acid group compared with $15,735 in the pamidronate group. This gives a cost-difference of $699 (95% CI: -1,047 to 2,163).

The cost of medications and their administration were significantly higher for the zoledronic acid group ($5,716) than for the pamidronate group ($5,222), with a cost-difference of $495 (95% CI: 144 to 820). When these costs were excluded from the cost estimation, the difference in mean total direct costs between the two treatment groups was not significant (95% CI: -1,290 to 1,774).

**Synthesis of costs and benefits**
The sensitivity analysis showed that varying the cost of the study medication to wholesale prices did not alter the finding that there was no statistical difference in total costs between the two patient groups. Discounting the cost of pamidronate by 25% resulted in the total cost for patients in the zoledronic acid group being $2,088 higher than that for the pamidronate group.

**Authors' conclusions**
There were no significant differences in the clinical outcomes and costs incurred by patients with breast cancer and multiple myeloma receiving zoledronic acid and those receiving pamidronate.

**CRD COMMENTARY - Selection of comparators**
The authors compared the prevention of skeletal-related events using zoledronic acid in comparison with pamidronate. This was implicitly justified on the basis that both are bisphosphonates, which are the standard therapy for patients with breast cancer or multiple myeloma in the authors' setting. Zoledronic acid is a third-generation bisphosphonate and
pamidronate a second-generation bisphosphonate. You should consider how these two treatments compare with current practice in your own setting.

**Validity of estimate of measure of effectiveness**

The clinical effectiveness data were taken from a randomised controlled trial, which was appropriate to the study question. The analysis of the trial data appears to have been undertaken on an intention to treat basis. The authors did not compare their patient sample with the wider patient population. In addition, they did not directly consider in this paper whether the baseline characteristics of the two patient groups were comparable and, therefore, whether any adjustment for confounding factors should have been taken into account. Few details of the clinical trial were reported as they had been published elsewhere.

**Validity of estimate of measure of benefit**

No measure of health benefit was used in the economic analysis, thus a cost-consequences study was conducted. The reader is therefore referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

**Validity of estimate of costs**

The perspective of the health care payer appears to have been adopted. The study did not include the costs of vitamin D and multiple vitamin supplements for both treatment groups. This was justified on the grounds that they were assumed to be similar in both groups and the costs involved are relatively small. This assumption is unlikely to have altered the findings of the study. Some other costs that were excluded and were stated not to have an impact on the study results were the physician fees for inpatient care provided to US patients. A comprehensive breakdown of resource use with statistical comparisons was provided in the paper. This increases the generalisability of the study. However, no unit costs were reported. The study combined cost data from several countries to provide a single estimate of the costs of the two treatments, thus providing a single estimate of the total costs incurred by the two patient groups, which sought to represent a range of countries.

Appropriate currency conversions (to combine the cost data from several countries) and adjustments to a single price year were undertaken. A clear price year was reported, which enables future reflation exercises. The authors acknowledged that the use of two different price years limits their study. They indicated that this was necessary as zoledronic acid was not available in 2000 and appropriate indices to convert all study costs across all the countries involved to 2002 prices were not available. In addition, the estimated costs of zoledronic acid might have been overestimated since overhead costs were not included in the study and they were implicitly stated to be higher for pamidronate.

**Other issues**

The authors compared their clinical findings with those from a 25 month-follow up study that consistently found that zoledronic acid may have some additional benefits over pamidronate. The authors did not present their results in a selective manner and their conclusions reflected their analysis. The authors suggested that limiting their economic analysis to the core phrase of the trial (13 months) might have resulted in an underestimation of the long-term impact of the two treatments.

**Implications of the study**

The authors did not make any recommendations for changes to policy or further research.

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Other publications of related interest


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