Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases

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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 study compared five types of bisphosphonates with no treatment (i.e. placebo) for the management of patients with breast cancer with bone metastases. The bisphosphonates compared were oral ibandronate (OI), intravenous (i.v.) ibandronate (IBN), zoledronic acid (ZA), generic pamidronate (PA) and generic oral clodronate (OC).

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-utility analysis and cost-benefit analysis.

Study population
As this was a modelling study, the target population comprised six hypothetical cohorts of patients suffering from breast cancer with bone metastases. Each of the cohorts received one of the five types of bisphosphonates, and there was also a "no treatment" cohort. No further inclusion or exclusion criteria were reported.

Setting
The setting was primary and secondary care. The economic study was conducted in the UK.

Dates to which data relate
The demographic and effectiveness data were derived from sources published between 1987 and 2005. The resource use data were derived from sources published in 2001 and 2004. The cost data were derived from sources published in 2004 and 2005. The price year was not explicitly reported.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
The authors constructed a decision analytic model to compare the six strategies in terms of their costs and quality-adjusted life-years (QALYs). The time horizon of the model was 10 years. Health states included in the model were based on whether the patient received therapy (first-line or second-line) or not and whether he/she suffered from SREs or not (i.e. two categories). The health states were not explicitly described. The duration of each cycle was one month, after which patients could transit to the next health state or remain in the same health state according to transition probabilities.
Outcomes assessed in the review
The following parameters were used in the model:

- median survival of the patients;
- the annual rate of SREs in patients not receiving treatment;
- the efficacy of bisphosphonates in preventing SREs, expressed as the Anderson-Gill multiple event hazard ratio and the skeletal morbidity rate (SMR) ratio for each treatment option; and
- the number of SREs per patient-year for each therapy.

For compliance with treatment, the parameters included were:

- the monthly probability of discontinuation of initial i.v. therapy due to adverse events;
- the monthly discontinuation rate of oral therapies at 6 months; and
- the discontinuation rate of OI due to gastrointestinal adverse events.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Overall, 15 primary studies were included in the review.

Methods of combining primary studies
The authors used narrative methods (pooled average estimates) to combine data from the individual studies.

Investigation of differences between primary studies
The authors do not appear to have investigated differences between the primary studies.

Results of the review
Median survival of the patients was 18.8 months.

Patients not receiving treatment had an average of 3.05 SREs per year.

The Anderson-Gill hazard ratio was 0.70 (95% confidence interval, CI: 0.58 to 0.85) for PA, 0.56 (95% CI: 0.36 to 0.87) for ZA, 0.71 (95% CI: 0.53 to 0.94) for IBN and 0.62 (95% CI: 0.51 to 0.75) for OI.
The SMR ratio was 0.625 for PA, 0.57 for ZA, 0.74 for IBN and 0.73 for OC.

The number of SREs per patient-year for each therapy was estimated by multiplying the Anderson Gill statistic and the SMR ratio with the baseline pooled SREs per patient-year in the no treatment group.

The monthly probability of discontinuation of initial i.v. therapy due to adverse events was 0.79% (95% CI: 0.68 to 0.92).

The monthly discontinuation rate of oral therapies at 6 months was 74% (20.11% per month, 95% CI: 16.63 to 24.56).

The discontinuation rate of OI due to gastrointestinal adverse events was 0.95% per month (95% CI: 0.61 to 1.30).

Measure of benefits used in the economic analysis
Health utility (QALYs) was the measure of benefit used in the economic analysis. The utility values were derived from a published study (Dranitsaris and Hsu 1999, see 'Other Publications of Related Interest' below for bibliographic details). The benefits of i.v. bisphosphonates were assumed to start after the first month of treatment. The benefits of OI were assumed to be similar to those of i.v. bisphosphonates but started after 12 weeks of treatment. Finally, it was assumed that the benefits from OC treatment would be half those of other therapies. The authors also used the net monetary benefit (NMB), using a willingness-to-pay of 30,000 per QALY gained (threshold set by the National Institute for Clinical Excellence).

Direct costs
Health service costs were included in the analysis. SRE-related costs included the costs of vertebral fracture, nonvertebral fracture, hypercalcaemia, radiotherapy and orthopaedic surgery. Community costs incurred for 3 months were the monthly cost of bone pain and the cost of long-bone fractures (including medical consultant, palliative care nurse, district nurse and social work assistant). The cost of bisphosphonate treatment included the time (minutes) of the physician, pharmacy technician and nurse time, and the costs of needle, gauze, alcohol swab, syringe, set of gloves, medical tape, sample tubes, disposable i.v. set, piggyback connector, 250 mL of 5% dextrose solution, thermometer cover and serum creatinine test. Summary procedural costs were reported for SRE-related inpatient costs. The community costs and quantities were reported separately. The costs and quantities of resource use were derived from published sources. Although it was reported that the costs were appropriately adjusted for inflation, the price year was not explicitly reported. All costs incurred for more than one year were appropriately discounted.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
UK pounds sterling (€).

Sensitivity analysis
One-way sensitivity analyses were conducted to assess the robustness of the results to variability in key parameters. The parameters tested were the SMR in no treatment, the cost of SRE, median survival, the proportion of patients switching to second-line therapy due to adverse events, OI monthly discontinuation rate, IBN administration time and cost of i.v. therapy administration.

The authors also conducted a probabilistic sensitivity analysis by performing 1,000 Monte Carlo simulations in which
parameters were varied simultaneously over probability distributions. The parameters investigated were median survival, SMR without treatment (events per person year), Andersen-Gill ratio (for OI, IBN, ZA and PA), monthly discontinuation probability (for OC, OI, IBN, ZA, PA), the proportion of patients switching to second-line therapy, the cost per SRE (varying inpatient and outpatient cost), the cost of i.v. treatment administration, SMR ratio, and OC impact on quality of life. Probability distributions for each parameter were explicitly reported.

**Estimated benefits used in the economic analysis**
The primary analysis was conducted using the Andersen-Gill multiple event hazard ratio and OC was excluded. In a secondary analysis the SMR was used and OI was excluded.

An incremental analysis was performed and each therapy was compared against no therapy.

In the primary analysis, compared with no therapy, ZA resulted in 0.205 QALYs gained, PA in 0.194 QALYs gained, IBN in 0.193 QALYs gained and OI in 0.185 QALYs gained.

In the secondary analysis, compared with 'no therapy', ZA resulted in 0.190 QALYs gained, PA in 0.186 QALYs gained, IBN in 0.177 QALYs gained and OC in 0.104 QALYs gained.

**Cost results**
The incremental total costs were reported, where each strategy was compared against no therapy.

In the primary analysis, compared with no therapy, ZA resulted in net costs of -2,267, PA in net costs of 113, IBN in net costs of 458 and OI in net costs of -2,114.

In the secondary analysis, compared with no therapy, ZA resulted in net costs of -1,949, PA in net costs of -883, IBN in net costs of 1,085 and OC in net costs of -450.

The minus sign indicates that the treatment option was cheaper than the no therapy option.

**Synthesis of costs and benefits**
In the primary analysis, compared with no therapy, ZA and OI were the dominant strategies. PA resulted in a cost of 584 per QALY gained and IBN in a cost of 2,370 per QALY gained. Based on the cost per QALY gained and on NMB methods, ZA was the most cost-effective strategy followed by OI, PA and IBN.

In the secondary analysis, compared with no therapy, ZA, PA and OI were the dominant strategies. IBN resulted in a cost of 6,126 per QALY gained. ZA was found to be the most cost-effective and cheapest strategy, followed by PA, IBN and OC.

One-way sensitivity analyses concentrated mainly on the NMB and demonstrated the robustness of the results to variability in the input parameters. The most sensitive parameters were SMR in no treatment, the cost of SRE and median survival. The ranking remained unaffected apart from two cases. In the primary analysis, when administration time for IBN equalled that of ZA, IBN was more cost-effective than PA. Similarly, in the secondary analysis, OC became more cost-effective than IBN when the proportion of patients switching to second line therapy was assumed to be 100%.

The probabilistic sensitivity analysis demonstrated that, at a willingness-to-pay of 30,000 per QALY, ZA would be the preferred therapy in 51% of the 1,000 Monte Carlo simulations, OI in 33%, IBN in 10% and PA in 4%. At a willingness-to-pay of 0, ZA resulted in a maximum NMB in 44% of model simulations, OI in 37%, IBN in 7%, PA in 4% and no therapy in 9%.

**Authors’ conclusions**
Zoledronic acid (ZA) would appear to be the most cost-effective option in comparison with no treatment and all other
bisphosphonate types. The authors concluded that "the use of bisphosphonates in breast cancer patients with bone metastases should lead to improved patient outcomes and cost savings to the NHS (National Health Service)."

**CRD COMMENTARY - Selection of comparators**

In their analysis, the authors accounted for all commonly used bisphosphonates for the treatment of breast cancer in patients with bone metastases. In addition, all treatment options were compared against no treatment (placebo) to allow the active value of these treatments to be evaluated. You should decide if these are commonly used health technologies in your own setting.

**Validity of estimate of measure of effectiveness**

A systematic review was not undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. In many cases, data from the available studies were used selectively or the effectiveness estimates were arrived at through a narrative synthesis. Despite this, a weighting scheme to reflect differences in sample sizes was not adopted and further differences between the primary studies were not investigated. However, extensive sensitivity analyses were conducted on most model parameters to assess the robustness of the estimates used. The ranges used appear to have been appropriate and these analyses improved both the internal validity and the generalisability of the study.

**Validity of estimate of measure of benefit**

The authors used health utility (QALYs) and monetary benefits (derived using willingness-to-pay) in their economic analysis.

**Validity of estimate of costs**

The costs were analysed from the perspective of the NHS. It appears that all the relevant cost categories have been included in the analysis. Although summary costs were reported for inpatient cost categories, the costs and the quantities were reported separately for community health care costs. The detailed cost analysis means that the analysis could be easily reworked for other settings. The resource use and cost data were taken from published sources and sensitivity analyses were conducted to assess the robustness of the estimates used. Discounting was conducted appropriately.

**Other issues**

The authors compared their findings with those of other studies and found them, generally, to be in agreement. Any differences were attributed to differing study methodology and the lack of available data. The issue of the generalisability of the results to other settings was not directly addressed. The study results were not presented selectively and the results of the sensitivity analyses, in particular, were reported in detail. The study involved breast cancer patients with bone metastases and this was reflected in the authors’ conclusions. Limitations to the study were represented by the lack of robust health utility values that were based on empirical-driven estimates published in the literature. In addition, estimates of the relative efficacy of different bisphosphonates were not available, thus indirect comparisons were conducted.

**Implications of the study**

The authors did not make explicit recommendations for changes in policy or practice. Further research should be conducted to provide robust health utility estimates associated with bisphosphonate therapy. In addition, future research should concentrate on direct head-to-head comparisons in order to derive robust estimates of the relative efficacy of different bisphosphonates.

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Other publications of related interest
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