Cost-effectiveness of oral ibandronate versus IV zoledronic acid or IV pamidronate for bone metastases in patients receiving oral hormonal therapy for breast cancer in the United Kingdom


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 present study compared oral ibandronate, intravenous (IV) zoledronic acid, IV generic pamidronate and a placebo for the treatment of bone metastases in patients with breast cancer who were receiving oral hormonal therapy. Oral ibandronate was administered at a dose of 50 mg/day, IV pamidronate at 90 mg every 3 - 4 weeks, and IV zoledronic acid at 4 mg every 3 - 4 weeks.

Type of intervention
Palliative therapy.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population for the model was women with breast cancer and metastatic bone disease who were assumed to be receiving oral hormonal therapy. The population characteristics were aligned with those of Phase III trials of oral ibandronate in metastatic bone disease from breast cancer. The patients in these trials had a median age of 57 years (range: 27 - 92), and had received a diagnosis of bone metastases 6 months earlier. Most of the patients (84%) had a World Health Organization performance status of 0 or 1, and 70 to 80% had received oral hormonal therapy.

Setting
The setting was tertiary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness evidence was taken from 1986 to 2005. The resources used and costs were taken from 2001 to 2004. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from completed studies and expert opinion.

Modelling
A model was built to estimate the per-patient costs and benefits for expected mean survival. A decision model was used. A probabilistic sensitivity analysis was undertaken using a Monte Carlo simulation to evaluate the effect of uncertainty.
Outcomes assessed in the review
The outcomes included:

the relative risk reduction for skeletal-related events (SREs);
the expected number of SREs;
the months per patient with or without SRE;
the discontinuation rates due to adverse events and failed compliance; and
the risk of drug-related renal toxicity.

Study designs and other criteria for inclusion in the review
The study designs used were Phase III trials, placebo-controlled trials, and other published literature. No inclusion or exclusion criteria were reported.

Sources searched to identify primary studies
MEDLINE was searched for all years and all languages. To collect data for oral bisphosphonates, the search terms used were "cost" or "economic", and "oral", and "bisphosphonate" or "ibandronate" or "ibandronic" or "clodronate". For zoledronic acid in metastatic bone disease from breast cancer, the search terms used were "IV" or "intravenous", and "zoledronic" or "zoledronate", and "placebo", and "breast", and "metastatic" or "metastases".

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

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

Number of primary studies included
At least 45 primary studies were included in the review.

Methods of combining primary studies
A narrative method was used to combine the studies.

Investigation of differences between primary studies
Not reported.

Results of the review
The expected number of SREs was 3.23 for placebo, 2.00 for oral ibandronate and IV zoledronic acid, and 2.10 for IV pamidronate.

The SRE relative risk reduction was 38% for oral ibandronate and 35% for IV pamidronate.

The months per patients with SRE over 14.3 months' survival were 2.00 for oral ibandronate and IV zoledronic acid, and 2.10 for IV pamidronate. The months per patients without SRE were 12.30 for oral ibandronate and IV zoledronic acid, and 12.20 for IV pamidronate.
The probability of discontinuation and switching to oral ibandronate was 12.5% at 6 months.

The discontinuation rate due to adverse events at one month was 3.1% for oral ibandronate, 4% for IV zoledronic acid, and 2.0% for IV pamidronate.

The risk of renal impairment for patients receiving zoledronic acid was 5% and the probability of renal failure was 0.015%.

The authors adequately referenced the corresponding ranges for most of the parameters included in the model.

Methods used to derive estimates of effectiveness
This analysis was also based on authors’ assumptions and expert opinion.

Estimates of effectiveness and key assumptions
Due to the absence of direct comparative survival data, a mean survival of 14.3 months was assumed for patients with breast cancer and bone metastases who were receiving oral hormonal therapy. This mean survival was assumed to be equivalent for all of the bisphosphonates considered in the model. The model also incorporated several key assumptions that were based on review by two clinician experts in the UK and one in Belgium:

50% of patients starting hormonal therapy were positive for both oestrogen and progesterone receptors, and received hormonal therapy for about 65% of their metastatic life;

50% were assumed to be positive for only one type of receptor, and received hormonal therapy for 40% of their metastatic life;

typical patients were assumed to remain on hormonal therapy for 7.5 months (just over half of the mean survival time);

once hormonal therapy had failed, the patients would be switched to a 4-month chemotherapy cycle;

the patients could discontinue treatment for drug-related adverse events (assumed at 1 month) or for non-compliance (assumed at 6 months).

The SRE relative risk reduction for IV zoledronic acid was assumed to be similar to the SRE relative risk reduction for oral ibandronate (38%).

From expert opinion, the probability of discontinuation because of failed compliance was assumed to be 12.5% after 6 months for IV bisphosphonates.

No drug-related renal impairment was assumed for oral ibandronate and for IV pamidronate. This assumption was supported by expert clinician opinion.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs). The QALYs were estimated by summing years of survival, weighted by quality of life (QoL). The time with or without SREs was adjusted for QoL using utility estimates based on published data and on authors’ assumptions. The methods used to derive utilities in the references given were not stated.

In patients with metastatic bone disease, a 0.4 baseline utility was used for a month without an SRE, and one of 0.28 for a month with an SRE. A 0.4 utility for an SRE-free month when receiving IV pamidronate or IV zoledronic acid was also used. The authors assumed a 5% increase in baseline utility per month without an SRE when using ibandronate, owing to its effects on reducing bone pain.
Direct costs
Only the direct health care costs were considered, assuming a single funding source for all costs at the hospital level. The direct costs covered SRE management (including all medical services given to patients in fracture management with surgery and radiotherapy, elective and nonelective treatment), IV bisphosphonate administration (i.e. personnel time and supplies), laboratory tests, treatment for renal impairment or failure, treatment for pain, and drug acquisition.

The radiotherapy costs excluded transport to the radiotherapy department. No health care-professional costs would be specifically associated with the administration of an oral bisphosphonate, except patient monitoring costs. The costs of chemotherapy would be similar for patients receiving different bisphosphonates and were therefore excluded from the analysis.

Discounting was appropriately not carried out, as the costs were incurred during less than 2 years. The quantities and the costs were analysed separately. However, the quantities were not reported, only the unit costs and their sources. Staff time and supplies for bisphosphonate infusions were obtained from published literature and validated for the UK setting. For SRE management, the total cost was estimated from 2003 NHS costs. The resources used and unit costs were taken from 2001 to 2004. The price year was 2003.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were reported.

Currency
UK pounds sterling (()).

Sensitivity analysis
One-way sensitivity analyses were carried out using ranges taken from the medical literature. Variability in the data was explored for several areas of uncertainty. These included prolonged survival of 24 months, no QoL advantage for oral ibandronate, a 7% reduction in analgesics used, and a 2% adverse event discontinuation rate for all bisphosphonates and no renal toxicity for zoledronic acid. Other areas of uncertainty explored were 100% compliance/no discontinuation due to failed compliance, nursing cost as a function of infusion time, no SRE efficacy advantage for oral ibandronate over pamidronate, and a 50% decrease in SRE treatment cost.

A probabilistic sensitivity analysis with 5,000 Monte Carlo simulations of the cost-effectiveness was undertaken. The probability of each strategy being cost-effective was calculated for each threshold value of a QALY gained (0 to 100,000).

Estimated benefits used in the economic analysis
The differences in QALYs were driven by utility weights. Taking a fixed reduction in utility for the time with SREs into consideration, as well as a 5% increase in baseline utility with oral ibandronate per month with an SRE, the total QALYs were 0.477 with oral ibandronate, 0.459 with IV zoledronic acid and 0.458 with IV pamidronate QALYs.

Oral ibandronate led to a gain of 0.018 QALYs in comparison with IV zoledronic acid and 0.019 QALYs in comparison with IV pamidronate. These corresponded to an additional 6.7 and 7.1 quality-adjusted life-days, respectively.

Cost results
With an expected survival of 14.3 months for patients with breast cancer and bone metastases who were receiving oral hormonal therapy, the model projected that the total cost of treatment would be 7,700 for oral ibandronate, 8,008 for
IV zoledronic acid and 7,858 for IV generic pamidronate. The savings per patient were 307 with oral ibandronate in comparison with zoledronic acid, and 158 in comparison with IV generic pamidronate.

**Synthesis of costs and benefits**
The reduction in cost and increase in outcome resulted in oral ibandronate being the dominant treatment option.

All one-way sensitivity analyses showed that oral ibandronate consistently remained cost-effective versus both IV bisphosphonates, given a cost-effectiveness threshold of 30,000 per QALY. Oral ibandronate remained cost-saving in the absence of a utility benefit.

By means of pair-wise comparisons, the cost-effectiveness acceptability curves showed that at a cost per QALY of at least 30,000, oral ibandronate was the cost-effective strategy in at least 82% of simulations versus IV zoledronic acid and at least 79% of simulations versus IV pamidronate.

**Authors’ conclusions**
From the perspective of the UK National Health Service (NHS), this model analysis found that oral ibandronate was cost-effective in comparison with intravenous (IV) zoledronic acid and IV pamidronate for the treatment of bone metastases in breast cancer patients who were concurrently undergoing oral hormonal therapy.

**CRD COMMENTARY - Selection of comparators**
A justification was given for the comparators used. The authors considered oral ibandronate in addition to other drugs of the bisphosphonate family. You should decide if these represent widely used drugs and technologies in your own setting.

**Validity of estimate of measure of effectiveness**
The authors did not state that they performed a systematic review of the literature. Although they reported that MEDLINE was searched to collect some data, it would appear that the epidemiological parameters were selectively taken from the literature. The authors did not consider the impact of differences between the studies identified when estimating effectiveness. They derived estimates of effectiveness from published literature, supplemented with their own assumptions, and justified their choice of assumptions with reference to the medical literature and expert opinion.

The authors acknowledged, as a limitation, their reliance on data from non-comparative trials of different bisphosphonates, leading to subjectivity in the assessment of drug efficacy and safety, as well as in the choice of assumptions. To overcome this, they applied the risk reduction of SREs with each bisphosphonate to the same placebo rate of SREs in patients with bone metastases due to breast cancer, as reported in one randomised trial. This was supported by expert clinician opinion. The estimates were investigated using a sensitivity analysis, but only some of the ranges selected were justified by reference to published literature.

**Validity of estimate of measure of benefit**
The authors used QALYs as a measure of benefits, based on published literature. The baseline utility was derived from the medical literature, whereas the authors estimated some of the other utilities. The methods to estimate missing utilities were reported and partly justified through the literature. Sensitivity analyses on the utilities and time horizon were conducted, and the ranges were reported but not the selection criteria for all of them.

**Validity of estimate of costs**
The authors reported that the study had been conducted from the UK NHS perspective and the indirect costs were appropriately not included. The costs and the quantities were not reported separately, which would make it difficult to rework the analysis for other settings. The unit costs were taken from published sources. A sensitivity analysis of SRE treatment costs was conducted to assess the robustness of the estimates used. Discounting was appropriately not carried
out since the time horizon of the model was shorter than 2 years. The price year was reported, which will aid any future reflation exercise.

Other issues
The authors compared some of their results with those from other studies and found, in general, that their findings were concordant. The authors addressed the issue of generalisability of the results to other settings. They did not report any further limitations of their study, except for the reliance on data from non-comparative trials.

Implications of the study
Though oral ibandronate was cost-effective in comparison with IV zoledronic acid and IV pamidronate for the treatment of bone metastases in breast cancer patients, owing to the limitations surrounding the model assumptions, it would be valuable to perform additional analyses when efficacy and safety data become available from comparative, randomised trials of oral ibandronate versus other bisphosphonates.

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