Cost-effectiveness of zoledronic acid in the prevention of skeletal-related events in patients with bone metastases secondary to advanced renal cell carcinoma: application to France, Germany, and the United Kingdom

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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.

CRD summary
The objective was to assess the cost-effectiveness of zoledronic acid (bisphosphonate) versus placebo in advanced kidney cancer (renal cell carcinoma) patients with secondary bone cancers (metastases). The authors concluded that their analysis was exploratory and suggested that zoledronic acid saved costs and increased benefits compared with placebo. As the methods used to select the small subgroup of included patients and those for the effectiveness analysis were not reported, the authors' conclusions should be treated with caution.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective of the study was to assess the cost-effectiveness of zoledronic acid versus placebo in patients with advanced renal cell carcinoma and secondary bone metastases.

Interventions
The authors compared zoledronic acid (bisphosphonate) with placebo (no bisphosphonates), along with concomitant antineoplastic therapy. The dosing regime was 4mg or 8mg, given as a 15 minute infusion, every three weeks for nine months (core study) plus 12 months (study extension).

Location/setting
UK, France and Germany/In-patient secondary care.

Methods
Analytical approach:
An economic model was run to estimate the cost-effectiveness of zoledronic acid versus placebo in renal cell carcinoma patients with bone metastases. The time horizon of the study was 21 months (nine plus 12 months). The authors reported that the perspective adopted was that of the government payer.

Effectiveness data:
Clinical and effectiveness data came from a subset of renal cell carcinoma patients enrolled in a randomised controlled trial (RCT) in which patients were randomised to receive zoledronic acid or placebo (Lipton, et al. 2003, see 'Other Publications of Related Interest' for bibliographic details). This subset of patients included 27 in the zoledronic acid group and 19 in the placebo group. The main effectiveness estimate used in the model was the median overall survival and the number of skeletal-related events. These were obtained from a subset of patients included in the RCT by Lipton et al (2003).

Monetary benefit and utility valuations:
A search of the MEDLINE database only identified one study reporting utilities for patients with metastatic renal cell carcinoma (Cella, et al. 2008, see 'Other Publications of Related Interest' for bibliographic details). This was an RCT in which quality of life was measured using the EQ-5D (European Quality-of-life) questionnaire.

Measure of benefit:
The measure of benefit was the quality-adjusted life-years (QALYs) gained. As benefits could be generated over a period of more than one year, future benefits were discounted using an annual rate of 3.5% in the UK, and 5% in France and Germany.

Cost data:
The direct costs included: treatment of skeletal-related events including vertebral and non-vertebral fractures, radiation therapy to bone, surgery to bone, and spinal cord compression; drug administration including clinical time and consumables; and the price of drugs. The costs of treating skeletal-related events were from UK, French and German health/diagnostic related group information. The cost of drug administration came from a number of studies and reports. The prices of drugs were obtained from the pharmaceutical company (Novartis) for Germany and France, and from the British National Formulary for the UK. The price year was 2008. As costs could be incurred over a period of more than one year, future costs were discounted using an annual rate of 3.5% in the UK and 5% in France and Germany. All costs were reported in Euros (EUR), with UK £ converted using an exchange rate of £1 to EUR 1.1196.

Analysis of uncertainty:
The authors reported that a probabilistic sensitivity analysis was conducted to assess the uncertainty in all parameters on the model results. For this, all model parameters were fitted with probability distributions, with a series of 1,000 Monte Carlo simulations generated. The results of this analysis were presented using cost-effectiveness acceptability curves.

Results
For zoledronic acid, the average QALYs gained per person were 0.6638 in France, 0.6638 in Germany and 0.6661 in the UK; the average cost per patient was EUR 5,056 in France, EUR 5,125 in Germany and EUR 4,079 in the UK.

For placebo, the average QALYs gained per person were 0.5075 in France, 0.5075 in Germany and 0.5086 in the UK; the average cost per patient was EUR 6,414 in France, EUR 6,347 in Germany and EUR 4,798 in the UK.

In all three countries, zoledronic acid was dominant over placebo as it was more effective and less costly.

Results of the probabilistic sensitivity analysis showed that the probability that zoledronic acid was cost saving and increased QALYs than placebo ranged from 67% in the UK to 77% in France (Germany was within the range).

Authors' conclusions
The authors concluded that the analysis results suggested that zoledronic acid saved costs and increased benefits when compared with placebo, but further research may be needed to confirm these results.

CRD commentary
Interventions:
The interventions under study were reported adequately.

Effectiveness/benefits:
Clinical and effectiveness estimates came from a very small subset of patients included in an RCT. The authors did not report the methods used to select this subset of patients, the precise definition of the subgroup, or when the subgroup analysis was planned. So it is not clear whether main measure of effectiveness was internally valid.

Costs:
The authors explicitly reported that a governmental perspective was adopted. For this perspective, all major relevant costs appeared to be included. The sources for the costs were adequately reported, with further information provided in supplementary tables. The discount rate used, the time horizon, the details of currency conversions and the price year were all reported.

Analysis and results:
The authors stated that an economic model was used to synthesise cost and outcome information. However, scant details of the model were reported and no diagram was provided. Uncertainty in the model was adequately evaluated using a probabilistic sensitivity analysis. The authors acknowledged that the main limitation to their study was that the main measures of effectiveness came from a post-hoc retrospective analysis of a very small subgroup of patients, so their
study should be viewed as exploratory.

Concluding remarks:
Given that the methods used to select the small subgroup of included patients and undertake the effectiveness analysis were not reported, the authors’ conclusions should be treated with caution.

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Bibliographic details
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Other publications of related interest
Lipton A, Zheng M, Seaman J. Zolendronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. Cancer 2003;98(5):962-969.

Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, Chen I, Motzer RJ. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomised trial. Journal of Clinical Oncology 2008;26(22):3763-3769.

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