Pamidronate for the prevention of skeletal-related events in multiple myeloma: what does the public think it is worth?

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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 pamidronate, a bisphosphonate class agent used to prevent pathological fractures and reduce radiation therapy in patients with advanced multiple myeloma.

Type of intervention
Secondary prevention.

Economic study type
Cost-benefit analysis.

Study population
Patients with stage III multiple myeloma, and at least one lytic lesion who were also undergoing chemotherapy.

Setting
Hospital. The economic analysis was conducted in Toronto, Canada.

Dates to which data relate
Data on effectiveness were taken from a clinical trial conducted between August 1990 and March 1994. Resource data were taken from a teaching hospital's records between 1990 and 1995. 1998 price years were used.

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

Link between effectiveness and cost data
Cost data were not collected from the same patient sample as that used in the effectiveness analysis. Costing was undertaken retrospectively.

Study sample
392 patients were randomised between the intervention and the control groups on a one to one basis. Patients were stratified between those receiving first line (initial chemotherapy) and those receiving second line (for relapse) chemotherapy. 203 patients were randomised to the pamidronate group and 189 patients were in the placebo group. 15 patients (4%) were excluded from the analysis due to problems with blinding. Overall 181 patients were evaluable in the placebo arm of the trial compared with 196 in the intervention arm. 133 patients on first line therapy received the intervention compared with 114 in the placebo group. For second line therapy patients, 63 received the intervention and 67 the placebo comparator. Power calculations were not used to determine sample size.
Study design
This was a multi-centre (88 centres) international double-blind randomised placebo controlled clinical trial conducted in the United States, Canada, Australia and New Zealand. The duration of the efficacy study was 36 weeks, which represented 9 cycles of pamidronate or placebo infusion therapy. Patients were, however, followed up for 17 months in order to monitor survival rates. No loss to follow up was reported.

Analysis of effectiveness
The analysis of effectiveness was based on intention to treat. The primary health outcomes in the analysis were incidence of pathologic fractures and radiation treatment. Pain levels, performance status and quality of life measures, and survival rates were also considered. The clinical and demographic characteristics were shown to be similar in the intervention and control groups in the analysis.

Effectiveness results
34 of the 196 patients in the pamidronate group (17%) suffered at least one pathologic fracture compared with 54 of 181 (30%) in the placebo group, \(P=0.004\). The need for radiation treatment was significantly higher in the placebo group compared with the intervention group: 40 patients (22%) versus 28 patients (14%) respectively, \(P=0.05\). For the first line chemotherapy sub-group, bone fractures were significantly lower: 19 (14%) versus 31 (27%), \(P=0.01\). There was however no significant difference for radiation bone treatment: 17 patients (13%) versus 17 patients (15%), \(P=0.63\). For patients receiving second line chemotherapy, no significant differences were observed in terms of bone fractures: 15 patients (24%) versus 23 patient (34%), \(P=0.19\). A significant difference was observed for patients requiring bone radiation treatment however: 11 patients (13%) versus 23 patients (34%), \(P=0.03\). Overall survival rates were similar between intervention and placebo groups although patients reported better pain control, with no deterioration in quality of life, in the pamidronate group.

Clinical conclusions
The monthly use of pamidronate significantly reduced the incidence of skeletal complications and also improved quality of life for patients.

Measure of benefits used in the economic analysis
The measure of benefits was monetary benefits. Willingness to pay for pamidronate treatment to reduce risk of skeletal fractures and adverse events was estimated. A random sample of the general population, in 7 locations in Ontario, 5 within the Toronto Metropolis with the remaining two from the city of Hamilton in southern Ontario and the town of Owen Sound in northern Ontario, was used to identify 100 individuals to take part in the economic study. All individuals were over the age of 18 and were interviewed on a face to face basis by two investigators. Individuals were presented with information on advanced multiple myeloma and the risks of bone fractures and radiation treatment using pamidronate with chemotherapy or chemotherapy alone. Individuals ranked the relative importance of risk reduction in each scenario with which they were presented on a scale from 0 ("not important at all") to 10 ("very important") Elicitations were then made of the additional income tax individuals would be prepared to pay to make the new drug available to anyone within Canada. The "payment card" method reported by Mitchell and Carson was used to minimise starting point bias. Scenarios for radiation treatment and bone fractures were presented randomly to avoid order effects. The final estimate of willingness to pay was assumed to be the maximum reported by individuals for the two scenarios and this was multiplied by an estimate of life expectancy reported by Statistics Canada for Ontarians in 1995. Lifetime willingness to pay was discounted at a rate of 3% per annum.

Direct costs
Direct costs associated with nine cycles of pamidronate therapy (90mg 4 hour infusion every four weeks) were estimated. Specifically costs included patient admissions, ambulatory care unit costs, administration, supplies of pamidronate and other materials and patient monitoring. An estimate of hospital resources consumed as a result of pathological fractures and radiation treatment were based on a random selection of 25 cases occurring during a five
year period within a Toronto teaching hospital. Costs were adjusted for the absolute risk reduction of events as a result of pamidronate therapy. Acquisition costs for the drug were obtained from the manufacturer, physician fees were taken from 1992 Ontario Fee Schedule of Benefits. The daily cost of hospitalisation was taken from a study published in 1997. 1998 prices were used and costs were not discounted due to the short duration of the study (36 weeks). A societal perspective was adopted in the economic analysis.

**Statistical analysis of costs**
Not conducted.

**Indirect Costs**
Not included.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
A series of one way sensitivity analyses was conducted. In the sensitivity analyses the effect of using cumulative WTP values were considered, additionally the cost of bone fractures and radiation treatment were also varied, using an analysis of extremes based on 95% confidence intervals. Finally the discount rate for WTP was also varied from 3% to 5%.

**Estimated benefits used in the economic analysis**
179 individuals were invited to participate in the survey of whom 79 declined (44%). A median rank of 9 for both the bone fracture and radiation treatment scenarios was observed (range: 2 - 10). The median willingness to pay for the treatment to have absolute risk reductions of 13% and 8% for the two scenarios respectively was Can$32 (95% CI: 20 - 55) and Can$28 (95% CI: 20 - 55). Mean life expectancy adjusted willingness to pay for the two risk reductions discounted at a rate of 3% was estimated to be Can$3,265 (95% CI: Can$1,999 - Can$4,526) in respect of bone fractures and Can$3,043 (95% CI: Can$1,917 - Can$4,169) in respect of the radiation treatment, (p=0.47). Assuming that the highest of these amounts represented the maximum that the Canadian taxpayer would be willing to pay, the age-adjusted mean WTP would be Can$3,364 (95% CI: Can$2,096 - Can$4,632).

**Cost results**
The total cost for nine treatment cycles of pamidronate was estimated to be Can$5,373. The average total cost per patient for treatment of pathologic bone fractures was estimated to be Can$8,579 (95% CI: Can$4,392 - Can$12,766). Similarly the average total cost per patient for radiation treatment was estimated to be Can$1,311 (95% CI: Can$878 - Can$1,744). Savings due to treatment avoided as a result of the absolute risk reduction (13% for bone fractures and 8% for radiation treatment) when using pamidronate were estimated to be Can$1,220 in total comprising Can$1,115 in bone fractures avoided and Can$105 for radiation therapy avoided. Therefore net costs of pamidronate therapy per patient were estimated to be Can$4,153.

**Synthesis of costs and benefits**
An incremental cost to society of paying for pamidronate therapy would be Can$789 (95% CI: Can$ -479 to $2,057). In sensitivity analysis if cumulative WTP values had been adopted, then there would be a net benefit to society of Can$2,155. Results were also sensitive to the discount rate used: with a 5% discount rate the overall cost to society was increased to Can$1,620 (95% CI: Can$665 - Can$2,574).

**Authors’ conclusions**
The authors concluded that the introduction of pamidronate into the Canadian healthcare system may result in a cost-neutral situation as costs may equate with benefits to society given that negative or zero costs lay within the 95% confidence interval. Further studies would be required in order to identify sub groups of the population for whom overall societal benefits could be realised.

CRD COMMENTARY - Selection of comparators
clinical study was placebo controlled only. It is not clear whether alternative options to pamidronate are available to reduce the risk of bone fractures and radiation treatment.

Validity of estimate of measure of benefit
clinical benefits were determined from a randomised controlled trial which is likely to reduce the chance of bias. Economic benefits were measured in terms of willingness to pay. An adequate explanation of the method used to elicit willingness to pay values was provided and measures were taken to reduce any possible bias. However, the authors noted that the public participation rate in the study was only 56%, and that there were statistically significant differences between respondents and non respondents which may bias the values elicited by the groups. The sample size may also have been insufficiently large to detect significant differences in values given between the two treatment scenarios.

Validity of estimate of costs
icient details were provided of the methods and sources of cost information. As noted by the authors, the study would have been enhanced with the inclusion of additional costs such as those for physiotherapy, care and productivity losses.

Other issues
results of the study may not be generalisable outside Ontario given that WTP estimates were taken from an Ontario population only. Furthermore the authors conceded that, as the costs and resource use were taken from observations at one teaching hospital in Ontario only, these may not be relevant to other institutions and locations either within the rest of Canada or elsewhere.

Implications of the study
Further economic studies are required to evaluate the use of pamidronate by population sub-groups, with detailed analyses of both direct and indirect costs.

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None stated.

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Other publications of related interest

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