Cost-effectiveness of pentostatin compared with cladribine in the management of hairy cell leukemia in the United Kingdom
Guest JF, Smith H, Sladkevicius E, Jackson G

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 aim was to assess the cost-effectiveness of pentostatin, compared with cladribine, as initial treatment for patients with hairy cell leukaemia. The authors concluded that pentostatin was cost-effective, compared with cladribine, at a willingness to pay £20,000 for a quality-adjusted life-year. The methods appear to have been appropriate and were clearly and transparently reported. The authors' conclusions appear to be appropriate.

Type of economic evaluation
Cost-utility analysis

Study objective
The aim was to assess the cost-effectiveness of pentostatin compared with cladribine as initial treatment for patients with hairy cell leukaemia.

Interventions
Pentostatin was administered at 4mg per m$^2$ every two weeks until blood parameters normalised and a bone marrow biopsy revealed no evidence of residual disease, then one or two more treatments were given. Cladribine was administered at 0.14mg per kg subcutaneously or intravenously once every three days for five administrations or once a day for five consecutive days on an out-patient basis, or as a continuous intravenous infusion over seven days on an in-patient basis. A third of patients received a second course of cladribine three months later.

Location/setting
UK/secondary care.

Methods
Analytical approach:
A Markov model was used to synthesise the effectiveness and cost data from a variety of sources. Each cycle length was three months and the time horizon was five years. The authors stated that the perspective was that of the UK NHS.

Effectiveness data:
A systematic literature review was conducted in MEDLINE, EMBASE, Current Contents, NHS EED, and the Cochrane Library and citations in relevant published papers were reviewed. Some missing data were interpolated. The main clinical effectiveness estimates were the rates of remission and relapse. Weighted averages of patients with comparable disease severity were calculated for the probability of remission (complete, partial, and none) and the probability of relapse after complete or partial remission, at various time points. For the probability of remission, only studies where pentostatin was administered as an intravenous bolus every two weeks and where cladribine was administered as a continuous intravenous infusion or two-hour intravenous or subcutaneous infusion on a daily basis were used. There was no restriction on the mode of administration for relapse rates. A meta-analysis was conducted to estimate the risk of adverse events. Mortality was assumed to be similar to that of the general population and was from standard sources.

Monetary benefit and utility valuations:
The systematic literature review found no relevant publications for the utility values. These were evaluated by taking a sample of the UK general public (n=229) and using the standard gamble technique, for the base case, as well as the
time trade-off technique and visual analogue scale.

Measure of benefit:
The primary measure of benefit was quality-adjusted life-years (QALYs). Secondary measures were the probability of relapse-free complete remission at five years and the probability of complete remission at five years (including after repeat treatment following relapse or no response). Benefits were discounted at 3.5% per annum.

Cost data:
The cost categories were: diagnostic tests; drugs; treatment administration on an in-patient or out-patient basis; haematological tests; biochemical tests; bone marrow trephine biopsy; bone marrow aspirate; follow-up visits; treatment of adverse events; and second- and third-line treatment after no response or relapse. The systematic literature review found no relevant publications and 10 haematologists were surveyed, using a structured questionnaire, for the data on the diagnosis of hairy cell leukaemia, patient management, resource use, and time to remission or relapse. Fifteen haematologists were approached; the reasons for non-participation were given. The costs were from the Department of Health's NHS Reference Costs, The Drug Tariff, and the British National Formulary. They were reported in UK pounds sterling (£), at 2007 to 2008 prices, and they were discounted at 3.5% per annum.

Analysis of uncertainty:
The uncertainty was explored, using one-way sensitivity analysis for the treatment effectiveness (ranges provided) and scenario analysis for the health-state utilities. Probabilistic sensitivity analysis, using 5,000 iterations, was conducted and the distributions were reported. The probabilistic results were described and presented on a cost-effectiveness plane.

Results
The proportion of patients expected to be in relapse-free remission at five years was 64% for pentostatin compared with 49% with cladribine. The proportion of patients expected to be in remission (including after repeat treatment following relapse or no response) at five years was 92% with pentostatin compared with 90% with cladribine.

Patients were expected to experience 3.77 QALYs with pentostatin compared with 3.64 QALYs with cladribine. The total health care cost over five years was £21,609 with pentostatin compared with £21,325 with cladribine.

Using pentostatin instead of cladribine was expected to have a cost per QALY of £2,180. Probabilistic sensitivity analysis showed that pentostatin was the most cost-effective treatment option 85% of the time, using a threshold of £10,000 per QALY, 90% of the time using a threshold of £20,000 per QALY, and 93% of the time using a threshold of £30,000 per QALY.

One-way sensitivity analysis showed that the results were sensitive to changes in the probability of: complete remission after first-line treatment; relapse among patients in complete remission after first-line treatment; patients receiving cladribine as an in-patient; the number of doses of pentostatin per course of treatment; and patients receiving a second course of cladribine at three months. Furthermore the cost per QALY increased to £66,000 if the number of doses of pentostatin increased from nine to 17. Scenario analysis showed that the cost-effectiveness of pentostatin remained under £6,500 regardless of whether the utilities were estimated using time trade-off or the visual analogue scale, or from patients with cancer.

Authors’ conclusions
The authors concluded that pentostatin was a cost-effective treatment, compared with cladribine, in the management of hairy cell leukaemia, at a willingness to pay £20,000 for a QALY.

CRD commentary
Interventions:
Both interventions were well described and appropriately compared with each other. The interventions were likely to be relevant in other settings.

Effectiveness/benefits:
The systematic literature review was appropriate and well described. The sources were provided and the method of pooling the results was described. It seems that all best available evidence was used. The authors discussed the limitation of pooling observational data to estimate the effectiveness of the interventions. The method of estimating the utilities was well described and appropriate. QALYs were the most appropriate benefit measure, given the impact of leukaemia on quality of life.

Costs:
The perspective was stated and the costs appear to have been appropriate for this NHS perspective. The survey method for estimating the resource use was well described and appropriate, but 10 clinicians might be considered to be a small sample. A detailed breakdown of the cost categories was given and the costs were appropriately discounted and adjusted for inflation.

Analysis and results:
The Markov model used to synthesise the data was appropriate. It was well described and presented in a diagram. The incremental analysis was appropriate for determining the cost-effectiveness of the strategies. The results were well reported in tables and the uncertainty was explored, using a variety of methods. One-way sensitivity analysis was conducted on the effectiveness of the treatments, but not the costs and utilities. A cost-effectiveness acceptability curve might have been more appropriate than a cost-effectiveness plane for the results of the probabilistic sensitivity analysis. Some limitations of the analysis were discussed by the authors.

Concluding remarks:
The methods appear to have been appropriate and were clearly and transparently reported. The authors' conclusions appear to be appropriate.

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