Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: a cost-utility analysis
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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
This study evaluated the cost-effectiveness of bendamustine, as a first treatment, for patients with chronic lymphocytic leukaemia, who were unsuitable for chemotherapy regimens containing fludarabine. The authors concluded that bendamustine was likely to be cost-effective, compared with chlorambucil. The evaluation appeared to be of high methodological quality and the reporting was clear and thorough, but the clinical evidence was limited to one clinical study.

Type of economic evaluation
Cost-utility analysis

Study objective
This study evaluated the cost-effectiveness of bendamustine, as a first treatment, for patients with chronic lymphocytic leukaemia, who were considered unsuitable for chemotherapy regimens containing fludarabine.

Interventions
Bendamustine intravenous infusion was compared with oral chlorambucil, as initial chemotherapy. All patients received either drug for three 28-day treatment cycles. Those who remained progression free for 12 months, on chlorambucil, continued on chlorambucil, if they later progressed, ad infinitum. Half of all other patients who progressed received fludarabine plus cyclophosphamide, and the other half received best supportive care.

Location/setting
UK/out-patient care.

Methods
Analytical approach:
A semi-Markov cohort model was used to simulate the natural history and treatment of chronic lymphocytic leukaemia, over the lifetime of each patient. Disease progression was captured using the health states of partial response, stable disease, complete response, progressive disease, best supportive care, and death. The authors stated that the perspective was that of the UK NHS.

Effectiveness data:
The primary effectiveness data were from a 2009 open-label randomised controlled trial of bendamustine, compared with chlorambucil, as a first treatment for chronic lymphocytic leukaemia. This was the only trial of bendamustine for chronic lymphocytic leukaemia that was identified by a systematic review conducted for the National Institute for Health and Clinical Excellence (NICE) in 2011. The primary measures of effectiveness were the odds ratio of response, and progression-free survival. Time-to-event regressions were used to fit survival curves, to extrapolate the trial data. Regression results and their coefficients were presented in graphs and tables, with covariance measures.

Monetary benefit and utility valuations:
The utility values for patients initially and those with stable disease were mapped from European Organisation for Research and Treatment of Cancer (EORTC)-C30 questionnaire results, from the trial patients, to the EQ-5D, using a published algorithm. Utility increments and decrements, for state changes and adverse events, were from a published study of patients with chronic lymphocytic leukaemia.
Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary measure of benefit. Future benefits were discounted at a rate of 3.5% annually.

Cost data:
The resource use, for treatment in each of the health states and for adverse events, was elicited from an advisory board of five haematologists with experience in treating chronic lymphocytic leukaemia. The cost categories included health care use and medications. The unit costs were from the British National Formulary, NHS Reference Costs, or the NHS Blood and Transplant Annual Review. The price year was 2008 to 2009. Costs were reported in UK £. Future costs were discounted at a rate of 3.5% annually.

Analysis of uncertainty:
One-way sensitivity analyses were conducted on many parameters, including those for effectiveness, benefits, and costs. Subgroup analyses were undertaken for patients aged 65 years or older, with a World Health Organization (WHO) performance score of one or more, and aged 65 or older plus a WHO performance score of one or more. Probabilistic sensitivity analysis was conducted, varying all the parameters except the unit costs. These results were presented as a cost-effectiveness plane and cost-effectiveness acceptability curve.

Results
In the main analysis, bendamustine cost £15,179, and produced 1.27 QALYs, more than chlorambucil, resulting in an incremental cost-effectiveness ratio of £11,960 per QALY gained.

In the probabilistic sensitivity analysis, this ratio was £11,974 per QALY gained. The one-way sensitivity analyses did not increase the ratio by more than £2,000. Subgroup analyses did not increase it to more than £14,000 per QALY gained. At a willingness-to-pay threshold of £20,000 per QALY gained, bendamustine was cost-effective in 90% of simulations.

An expected value of perfect information analysis found that, based on a discounted 10-year stream of 1,079 incident patients each year, the value of reducing uncertainty was £3.7 million, or £403 per patient.

Authors' conclusions
The authors concluded that bendamustine was likely to be cost-effective, compared with chlorambucil, and further clinical trials were unlikely to be worthwhile.

CRD commentary
Interventions:
The interventions were well described and appear to have been valid first treatment options. It was not clear if any other options should have been assessed.

Effectiveness/benefits:
The effectiveness data were derived by appropriate methods, and assuming that no other valid treatment options exist, it seems that all the relevant data were identified and used. The reliance on one open-label randomised controlled trial has limitations. The model was constructed to inform a NICE single technology appraisal and, in addition to the main analysis, the paper addressed some criticisms of this model, from the NICE evidence review group. A wide range of probabilities was varied over time, which was appropriate and provided precise estimates of the effect, adequately addressing the criticisms of the utility estimates. Overall, the methods were appropriate, and the reporting was good.

Costs:
The authors clearly described how the resource use was gathered from experts, and they used appropriate UK unit cost sources. The expert opinions were varied appropriately in the probabilistic sensitivity analysis, reflecting the uncertainty in their elicitation. The reporting was clear, and the data were handled appropriately.

Analysis and results:
The evaluation appeared to be well conducted and reported. The conclusions reached were well supported by the analysis. Both the probabilistic sensitivity analysis and the expected value of perfect information analysis were well
conducted and clearly reported.

Concluding remarks:
The evaluation appeared to be of high methodological quality and the reporting was clear and thorough, but the clinical evidence was limited to one clinical study.

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