Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden
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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 aim was to determine the cost-effectiveness of maintenance rituximab treatment, after second-line therapy, for patients with follicular lymphoma. The authors concluded that the intervention was cost-effective compared with observation. The study was well conducted and, apart from being unable to assess the validity of the clinical trial, it was satisfactorily presented. Despite this limitation, the authors' conclusions appear to be valid.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
This study assessed the cost-effectiveness of a newly developed maintenance treatment for the management of patients, with relapsed or refractory follicular lymphoma, who were in remission after second-line therapy.

Interventions
The intervention was rituximab, a chimeric mouse and human anti-CD20 monoclonal antibody. It was given at a dose of 375mg per m$^2$ once every three months, until disease progression or relapse, and for a maximum of 24 months. No active treatment was used as the comparator (observation group).

Location/setting
Sweden/secondary care.

Methods
Analytical approach:
A Markov health state transition model was used to capture the long-term progression of the condition, over a 30-year time horizon. The model was based on one developed by Betro, et al. (2007, see ‘Other Publications of Related Interest’ below for bibliographic details). The authors reported that the perspective was that of the health care provider.

Effectiveness data:
The clinical data were derived mainly from a phase III randomised clinical trial, namely the EORTC20981 trial. Each treatment arm contained 167 patients with relapsed or refractory follicular lymphoma. The median duration of follow-up was two years. The two main outcomes were progression-free survival and overall survival. Other outcomes included the incidence of grade three and four adverse events. Progression-free survival and overall survival were extrapolated beyond the end of the trial, up to the 30-year horizon, by fitting a Weibull distribution to the data from the trial.

Monetary benefit and utility valuations:
The utility values were obtained from a previous study, conducted in the UK, using the European Quality of life (EQ-5D) questionnaire to evaluate the patients' utilities.

Measure of benefit:
Both quality-adjusted life-years (QALYs) and life-years gained (LYG) were the measures of benefit. These were discounted at an annual rate of 3%.

Cost data:
The economic analysis included the costs of rituximab treatment and administration, non-serious and serious adverse events during the maintenance phase (e.g. blood cell disorders, sepsicaemia, and nervous system disorders), treatment received upon relapse, and routine management during the progression-free phase. The resource use data were from the clinical trial. The unit costs were from a variety of sources including the National Corporation of Swedish Pharmacies (drug costs), hospital costs (out-patient visits and medical procedures), a national in-patient case-costing database, and expert opinion (in-patient costs and serious adverse events). The unit costs and resource quantities were presented separately. All costs were reported for the price year 2007 in Euros (EUR). Swedish kronor (SEK) were converted into Euros at an exchange rate of EUR 1 to SEK 9.25. Costs were discounted at an annual rate of 3%.

Analysis of uncertainty:
One-way sensitivity analysis was conducted on the following model parameters: time horizon, duration of treatment benefit, distribution used to extrapolate the survival data, unit costs of non-serious adverse events, exclusion of adverse events from the model, and unit cost per line of treatment upon relapse. Probabilistic sensitivity analysis was also conducted and the assigned distributions were reported. The results were presented in a cost-effectiveness acceptability curve.

Results
The total expected QALYs were 4.29 for rituximab and 3.38 in the observation group. Rituximab resulted in 5.96 LYG and observation resulted in 4.94 LYG. The total costs were EUR 39,617 with rituximab and EUR 28,156 with observation.

When rituximab was compared with observation, the incremental cost-effectiveness ratio was EUR 12,584 per QALY gained or EUR 11,187 per LYG.

Deterministic sensitivity analysis demonstrated that the results were most sensitive to variation in the duration of follow-up (time horizon) and the duration of the treatment benefit.

The cost-effectiveness acceptability curve showed that, when rituximab was compared with observation, there was a 100% probability of the cost per QALY gained being less than EUR 25,400. The incremental ratio did not, under any circumstances, exceed the maximum willingness-to-pay threshold in Sweden of EUR 54,000 per QALY.

Authors' conclusions
The authors concluded that rituximab maintenance treatment administered to patients with relapsed or refractory follicular lymphoma, who were in remission after second-line therapy, was cost-effective compared with observation.

CRD commentary
Interventions:
The interventions were clearly reported. No active agent was used as the comparator, allowing the additional value of the treatment to be evaluated. There was no discussion on other possible relevant comparators, such as other active agents, that might have been included in the analysis.

Effectiveness/benefits:
A randomised controlled trial was an appropriate source for the clinical data, given the strengths of this design. The details of the study, such as the randomisation methods and power calculations, were not reported, which makes it difficult to objectively assess the validity of the data. QALYs and LYG were appropriate benefit measures and they allow comparisons to be made with other economic evaluations for this and other diseases. The extrapolation of the survival data was conducted using established methods and the assumptions were testing in the sensitivity analysis.

Costs:
The categories of costs and their sources were consistent with the perspective stated. The resource use data were collected during the trial and the unit costs were derived from appropriate national sources. The reporting of the costing was very good. The unit costs, resource quantities, price year, and discounting were reported and, in general, appropriate methods appear to have been used.
Analysis and results:
The costs and benefits were appropriately combined, using an incremental approach. The issue of uncertainty was comprehensively addressed, using both a deterministic and a probabilistic approach. The findings of the base-case and the sensitivity analyses were well reported. The authors acknowledged and discussed some limitations to their study. In general, the economic evaluation appears to have been well conducted.

Concluding remarks:
The study was well conducted and, apart from the methods of the clinical trial, it was satisfactorily presented. Despite this lack of reporting, the authors’ conclusions appear to be valid.

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