Cost effectiveness of rituximab maintenance therapy in follicular lymphoma: long-term economic evaluation
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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 examined the long-term cost-effectiveness of rituximab maintenance therapy, compared with usual care (observation), after induction chemotherapy for patients with relapsed or refractory follicular lymphoma. The authors concluded that rituximab was cost-effective from the perspective of the French National Health Service. The methods were appropriate and the sources were valid and well described. The authors’ conclusions appear to be robust.

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

Study objective
This study examined the long-term cost-effectiveness of rituximab maintenance therapy, compared with usual care (observation), after induction chemotherapy, for patients with relapsed or refractory follicular lymphoma.

Interventions
Rituximab maintenance therapy consisted of 375mg per m$^2$ intravenously every three months and this followed salvage induction with six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone. The comparator was salvage induction alone followed by no rituximab (observation).

Location/setting
France/hospital.

Methods
Analytical approach:
The economic evaluation was based on a Markov model with a 30-year time horizon, which represented a patient's lifetime. The authors stated that the analysis was carried out from the perspective of the French National Health Service (NHS).

Effectiveness data:
The clinical evidence was from the European Organisation for Research and Treatment of Cancer (EORTC) 20981 trial, which was a open-label, multicentre, randomised controlled trial (RCT) with 465 patients, who received either rituximab or observation after induction chemotherapy. These two-year trial data were extended to long-term survival, using Kaplan-Meier curves, based on a Weibull distribution. The benefits of rituximab were conservatively assumed to last for five years. Overall survival and progression-free survival were the key clinical endpoints.

Monetary benefit and utility valuations:
The utility values were from a multicentre observational study of 215 patients, with follicular lymphoma in the UK. The values were elicited using the European Quality of life (EQ-5D) questionnaire.

Measure of benefit:
Quality-adjusted life-years (QALYs) and life-years (LYs) were the summary benefit measures.

Cost data:
The economic analysis included the costs of maintenance therapy (acquisition and the management of adverse events),
treatment of relapse (investigation, chemotherapy, radiotherapy, and stem-cell transplants), and routine management (follow-up and supportive care). These were from official French sources that provided the standard costs for services and procedures, including diagnosis-related group (DRG) data. The resource use data were from published sources, such as an observational study on prescription habits in France that included 79 physicians from both public and private hospitals, as well as 334 patients with follicular lymphoma, and from the opinion of three French experts, collected by questionnaire by mail. The price year was 2006 and the costs were in Euros (EUR). A 3% annual discount rate was applied.

Analysis of uncertainty:
Both a deterministic analysis and a probabilistic analysis were carried out to assess the uncertainty. The deterministic analysis considered variations in individual inputs and the probabilistic analysis used appropriate distributions for the clinical parameters, resource use inputs, costs, and other variables.

Results
The projected costs were EUR 71,314 with rituximab and EUR 62,251 with observation. The expected LYs were 6.5998 with rituximab and 5.4092 with observation. The expected QALYs were 4.7177 with rituximab and 3.6794 with observation. The incremental cost with rituximab was EUR 7,612 per LY gained and EUR 8,729 per QALY gained.

The most influential inputs of the model were the frequency and cost of treatments for relapse. The sensitivity analysis showed that the incremental cost-effectiveness ranged from rituximab being dominant to a cost of EUR 43,300 per LY gained or EUR 49,700 per QALY gained. Most of the ratios were within the range of EUR 7,000 to EUR 12,000. The probability of rituximab being cost-effective at a threshold of EUR 15,000 per QALY was 100%.

Authors' conclusions
The authors concluded that rituximab maintenance therapy was cost-effective from the perspective of the French NHS.

CRD commentary
Interventions:
The comparators were appropriately selected as the proposed strategy, which had been shown to be both effective and cost-effective in other countries, was compared against the usual care for this patient population.

Effectiveness/benefits:
The clinical data came from a published and well-conducted clinical trial. Its multicentre and randomised design should have ensured the validity of the clinical inputs. Further methods and the clinical results were reported in the primary publication of the trial (Van Oers, et al. 2006, see ‘Other Publications of Related Interest’ below for bibliographic details). Standard statistical methods were used to project the short-term data to the long-term. A conservative assumption was made to extend the effect of the treatment beyond the duration of the trial. This should bias the analysis against rituximab. The authors provided some key details on the derivation of utility values, which appear to have been appropriately estimated, using a validated instrument. Both the benefit measures were valid for capturing the impact of the interventions on disease progression.

Costs:
The cost categories were consistent with the viewpoint and a clear description of each cost item was given together with their sources. The observational study, used to assess French prescription habits, included a large number of clinicians and patients, which should have produced reliable data. Other data were from standard French sources, such as DRG data, and expert opinion, when needed. The costs were varied in the sensitivity analysis. In general, the economic analysis was transparent and was extensively described.

Analysis and results:
The costs and benefits were presented for all the alternatives, and an incremental analysis was conducted. Both deterministic and probabilistic sensitivity analyses were used to assess the uncertainty in most of the model parameters. The time horizon was appropriate for capturing the impact of the disease on a patient's health. An extensive description of the model was given. The discounting (3% for costs and zero for benefits) followed country-
specific guidelines. The authors compared their results with those of other published studies, which had consistent findings.

Concluding remarks:
The methods were appropriate and the sources were valid and well described. The authors’ conclusions appear to be robust.

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