Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma
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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 cost-effectiveness of rituximab (R) added to cyclophosphamide, vincristine, and prednisolone (CVP) as a first-line treatment for advanced follicular lymphoma (AFL), in adult patients with Ann Arbor Stage III or IV follicular non-Hodgkin lymphoma. The authors concluded that, in the USA, R-CVP was a cost-effective treatment for AFL in comparison with CVP alone. The study was based on valid methodology and was transparently presented. The authors’ conclusions appear to be robust.

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

Study objective
This study examined the cost-effectiveness of rituximab (R) added to cyclophosphamide, vincristine, and prednisolone (CVP) as first-line treatment of advanced follicular lymphoma in adult patients with Ann Arbor Stage III or IV follicular non-Hodgkin lymphoma.

Interventions
The R-CVP regimen was compared with CVP alone. The CVP regimen was cyclophosphamide at 750mg/m$^2$ intravenously (IV) on day one, vincristine between 1.4mg/m$^2$ and 2mg/m$^2$ IV on day one, and prednisolone at 40mg/m$^2$ orally on days one to five, for a 21-day cycle. The R-CVP consisted of CVP plus rituximab at 375mg/m$^2$ IV on day one of each cycle. Either cycle was repeated up to eight times.

Location/setting
USA/hospital.

Methods
Analytical approach:
This economic evaluation was based on a Markov model with a lifetime horizon (30 years). The authors stated that a societal perspective was adopted.

Effectiveness data:
The clinical inputs came from a selection of relevant studies, which were known to the authors. Progression-free survival with CVP or R-CVP was derived from a pivotal randomised controlled trial (RCT) with a four-year follow-up. Survival beyond the trial follow-up period was calculated using long-term observational studies and Kaplan-Meier survival curves. Experts’ opinions were also used where there was a lack of published data. Progression-free survival was the primary clinical outcome.

Monetary benefit and utility valuations:
The utility estimates were derived from published studies, the details of which were not given. Disutilities were applied to chemotherapy, stem-cell transplantation, and end-of-life care.

Measure of benefit:
Life-years (LYs) and quality-adjusted life-years (QALYs) were the summary benefit measures and were discounted at an annual rate of 3%.
Cost data:
The economic analysis included the following cost categories: study drugs (acquisition, administration, and treatment of severe side effects), other drugs (subsequent treatment for relapses), tests and visits, stem-cell transplantation, and costs of end-of-life care. The unit costs and quantities of resources used were presented separately. Drug costs were calculated using average wholesale prices, product inserts, RCT consumption patterns, and experts’ opinions. Other costs were based on Medicare reimbursement rates and published studies. Costs were in US dollars ($) and were discounted at an annual rate of 3%. The price year was not explicitly reported.

Analysis of uncertainty:
A deterministic one-way sensitivity analysis was undertaken on the model inputs using published and assumed ranges of values.

Results
The lifetime total costs per patient were $105,607 with R-CVP and $79,168 with CVP. The cost of rituximab accounted for 92% of the total cost difference between the regimens. All other cost categories had a negligible impact on the total costs.

The expected LYs were 13.68 with R-CVP and 12.17 with CVP and QALYs were 5.85 with R-CVP and 4.93 with CVP.

With R-CVP over CVP, the incremental cost per LY gained was $17,504 and the incremental cost per QALY gained was $28,565.

The sensitivity analysis identified the utility of follicular lymphoma and the cost of a course of rituximab as the most influential model inputs. However, even in unfavourable scenarios, the incremental cost per QALY gained with rituximab did not exceed the commonly accepted threshold of $50,000 per QALY.

Authors' conclusions
The authors concluded that R-CVP was a cost-effective treatment for advanced follicular lymphoma in the USA.

CRD commentary
Interventions:
The rationale for the selection of the comparators was clear in that the new agent was added and compared with a widely used combination regimen. The dosages and administration schedules were clearly reported.

Effectiveness/benefits:
The clinical estimates came from a small number of sources which were identified by the authors. The treatment effectiveness, which was the key clinical input, was based on data from a RCT, which, as the authors pointed out, is considered to be the most robust source of evidence due to the strengths of its design. Long-term data came from observational studies, which have some methodological limitations, but were the only available sources. In general, the authors used the best available evidence and judged the quality of their sources. Uncertainty underlying some clinical estimates was investigated in the sensitivity analysis. The use of two benefit measures was appropriate as both were relevant to the population. Quality-adjusted survival was appropriate given the impact of chemotherapy on patients' quality of life. Both LYs and QALYs also allow cross-disease comparisons to be made.

Costs:
The categories of costs did not reflect the perspective stated by the authors. From both the types of costs and their sources, it appears that the analysis was carried out from the viewpoint of the health care payer. The economic analysis was extensively described, especially with respect to drug consumption. This enhances the transparency of the economic analysis. Also, for cost items, the authors assessed the quality of their sources. The price year was not explicitly reported, but it appears, from the references, to have been 2006.

Analysis and results:
The costs and benefits were appropriately synthesised using an incremental analysis. The findings (both absolute and
incremental estimates) were clearly presented. The issue of uncertainty was investigated using a deterministic approach, which considered plausible ranges of values for the model inputs and identified the most influential factors. The use of a more comprehensive, probabilistic approach would have been interesting, but the findings were quite robust. The authors used two specific grading systems to judge the validity of the clinical and economic evidence. Both high- and low-quality sources of data were used, depending on the availability of data.

**Concluding remarks:**
The study was based on valid methodology and was transparently presented. The authors’ conclusions appear to be robust.

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