Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell 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.

Health technology
The use of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) was compared with rituximab plus CHOP (R-CHOP) for the treatment of elderly patients with diffuse large B-cell lymphoma (DLBCL). The recommended dosages on day 1 were 750 mg/m2 for cyclophosphamide, 50 mg/m2 for doxorubicin, and from 1.4 mg/m2 up to a dose of 2 mg for vincristine. The dosage for prednisone was 40 mg/m2 per day for 5 days. The dosage for rituximab was 375 mg/m2 on day 1 of each of the 6 cycles.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised patients aged more than 60 years with untreated DLBCL.

Setting
The setting was a hospital. The study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2004. The resource use data were obtained from studies published between 1991 and 2003 and a study published on the Internet in 2004. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a review of the literature.

Modelling
A Markov state transition model was built to evaluate the clinical and economic outcomes for patients receiving R-CHOP or CHOP. The patients involved in the model were characterised by ages of 60 - 80 years, with Ann Arbor Stage 2, 3 and 4 disease and a performance status of 0 - 2. The five health states in the model were event-free, salvage, transplantation, end-of-life care and death. The authors assumed that the time horizon was 5 years and 6 cycles were given in the model. The authors also assumed that the transition rates were identical between treatments.
Outcomes assessed in the review
The review assessed the response rate, the event-free survival rate, the overall survival rate, and the probabilities of salvage and of transplantation.

Study designs and other criteria for inclusion in the review
The clinical evidence in the study came from a well-designed, randomised clinical trial, the LNH 98-5 (399 patients), that was linked to other long-term data on patients with DLBCL. The authors stated that findings of a non-Hodgkin lymphoma project were used as an alternative information source of transition rates, as they found no registry for the target population of this study when searching for information. It was unclear whether a systematic review of the literature had been undertaken.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The effectiveness evidence was derived from approximately three primary studies.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The outcomes of the review were the same for both groups.

Responses were seen in 76% of the patients treated with R-CHOP and 63% of patients treated with CHOP alone.

Event-free survival rates at 3 years were 53% with R-CHOP and 35% with CHOP alone. The overall survival rates at 3 years were 62% with R-CHOP and 51% with CHOP alone.

The probability of salvage was 1 and of transplantation (if receiving salvage) 0.1.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated using a modelling approach and were discounted at an annual rate of 3%. The utility estimates came from the review of the literature.

Direct costs
A societal perspective was adopted in the economic evaluation. The categories of costs considered in the analysis were those of the chemotherapeutic agent, post-treatment, salvage treatment and end-of-life care. The unit costs were not presented separately from the quantities of resources used. The costs were estimated from the review of the literature. The price year was not reported. Discounting was relevant because of the long time horizon of the study, and an annual rate of 3% was applied.

**Statistical analysis of costs**
It appears that a statistical analysis of the costs has been conducted in the economic study, although the authors did not explicitly report this.

**Indirect Costs**
The indirect costs were not included in the economic analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were conducted to determine the impacts of uncertainty in model parameters on the base-case results. The variables assessed included costs (CHOP, surveillance, salvage and transplantation, end-of-life care), the probability of salvage therapy, quality of life, time horizon and the time discount rate. The ranges of variable were derived from the review of the literature. A probabilistic analysis of selected variables was conducted to simulate random error. Sub-group analyses were also carried out.

**Estimated benefits used in the economic analysis**
R-CHOP increased the mean event-free survival by 0.90 years, from 2.19 years with CHOP to 3.10 years. It also increased overall survival by 1.04 years, from 3.11 years with CHOP to 4.15 years. The mean duration for quality-adjusted survival increased with R-CHOP by 0.66 years.

**Cost results**
The mean cost of CHOP (6 cycles) was $3,358 and the mean cost of rituximab (6 cycles) was $17,225, resulting in a net increase of $13,867.

The cost of post-treatment cancer surveillance was $3,950 for CHOP and $5,202 for R-CHOP, resulting in a net increase of $1,252.

The cost of salvage care was $4,507 for CHOP and $3,267 for R-CHOP, resulting in a net decrease of $1,240.

The cost of end-of-life care was $18,228 for CHOP and $13,725 for R-CHOP, resulting in a net decrease of $4,503.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs (to primary care) and benefits of the intervention relative to the comparator. The incremental costs with R-CHOP over CHOP alone were $12,304 per life-year and $19,297 per QALY.

The results of the sensitivity analyses indicated that R-CHOP remained cost-effective over wide ranges of the variables assessed. Detailed results of the sensitivity analyses were presented in the original paper.
Authors’ conclusions
Compared with the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), rituximab plus CHOP (R-CHOP) was cost-effective in elderly patients with diffuse large B-cell lymphoma (DLBCL).

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. CHOP alone was prescribed commonly in the USA. You should verify whether these health technologies are relevant to your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis was based on a well-conducted review of published studies. However, this study does not appear to have been a systematic review. The authors stated implicitly that the source used to obtain the transition rate did not match with the target population of the study. Hence, the internal validity of the effectiveness estimates does not appear to have been fully assessed given the limited information on the review of the literature.

Validity of estimate of measure of benefit
QALYs were used appropriately as the summary benefit measure. The estimate of benefit was derived from a Markov model, which was appropriate because it captured the transition of health states and time horizon for patients with DLBCL. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated explicitly the perspective adopted in the study. Detail items of cost were reported. It appears that all the relevant categories of costs have been included in the analysis. The costs and the quantity of resources used were not reported separately and the price year was not reported, thus limiting the reproducibility of the study in other setting. Details of the statistical analysis were not reported, but sensitivity analyses were conducted to assess the robustness of the estimates used. Discounting was relevant and was performed appropriately.

Other issues
The authors compared their findings with those from other studies. The issue of the generalisability of the results to other settings was not addressed, but sensitivity analyses were conducted and details of the costs were provided. Thus, the external validity of the economic analysis was relatively high. The authors noted that the assumption used in the model favoured CHOP over R-CHOP.

Implications of the study
The study results suggested that the use of R-CHOP should be appropriate in the treatment of elderly patients with DLBCL. However, further research is necessary to evaluate the combination of rituximab with various regimens and to investigate how cost-effective it will be.

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