Rituximab (MabThera®) for aggressive non-Hodgkin’s lymphoma: systematic review and economic evaluation

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Executive summary

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Description of proposed service

Rituximab, a novel immunotherapeutic agent, is proposed for first-line use, in its currently licensed indication for stage II–IV diffuse large B-cell lymphoma, in conjunction with the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy regime.

Epidemiology and background

Non-Hodgkin’s lymphoma (NHL) is a cancer of the lymphatic tissue, causing enlargement of lymph nodes and generalised symptoms. It is a heterogeneous condition. Diffuse large B-cell lymphoma (DLBCL), a clinical subtype of NHL, behaves in an aggressive fashion, with a short natural history but a long-term survival rate of about 30% with current therapies. In an average pre-2003 health authority covering 500,000 individuals, 22–23 people will present each year with DLBCL. Most will be over 50 years old. The primary objective of current treatments for this condition is to induce cure. First-line therapy is usually CHOP chemotherapy with or without radiotherapy. Second-line treatment is usually high-dose chemotherapy supported by bone marrow or peripheral blood stem cell transplant in fitter patients. For others, palliative chemotherapy is indicated.

Objectives

A systematic review of the literature was commissioned to determine the clinical and cost-effectiveness of adding rituximab to CHOP in people aged ≥18 years with DLBCL. The primary outcome was survival free of progression, relapse or death. Secondary outcomes were overall survival, response rates and toxic effects.

Data sources

Fifteen electronic bibliographic databases were searched to identify all literature relating to the clinical and cost-effectiveness of rituximab for the treatment of aggressive NHL.

Review methods

Comparative studies were selected for review if they addressed the clinical or cost-effectiveness of adding rituximab to CHOP in people aged ≥18 years with DLBCL. The internal validity of the study was assessed through the use of the validated Jadad scoring system. Data were abstracted into standardised data extraction forms.

Number and quality of studies and direction of evidence

In the systematic review of effectiveness, one randomised controlled trial (RCT) was identified. No other comparative studies of any design were identified. Although there were minor inadequacies in trial design and reporting, the study was, in most respects, methodologically rigorous and well conducted. The statistical evidence favoured the addition of rituximab to CHOP.

Summary of benefits

In the short term, the addition of rituximab to the CHOP regimen increased the likelihood of a complete-response by 20% ($p = 0.009$), without a significant rise in the risk of a serious adverse event (8%; $p = 0.19$), in people aged ≥60 years. Over a 2-year follow-up period, the intervention reduced the risk of death, progression or relapse by 45% ($p < 0.001$) and reduced the risk of death by 47% ($p = 0.007$) in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting. Arguments are presented that clinical effectiveness can be derived for a younger population on the grounds that disease biology is consistent by age and prognosis is inversely correlated with age.

Costs

Costs were estimated through resource use data taken from the published trial and the unpublished sponsor submission. Unit costs...
were taken from published sources, where available. The total cost of rituximab with CHOP (R-CHOP) and CHOP alone estimated from the model developed by ScHARR was £14,456 and £5773, respectively, for patients aged ≥60 years and £15,181 and £7311 for patients aged <60 years over a 15-year time horizon. The manufacturer’s (Roche) model estimated the total cost of rituximab with CHOP (R-CHOP) and CHOP alone as £11,807 and £2892, respectively, for patients aged ≥60 years and £14,643 and £5920 for patients aged <60 years over a 15-year time horizon.

**Cost per quality-adjusted life-year (QALY)**

An economic evaluation was undertaken to evaluate the cost-effectiveness of R-CHOP compared with CHOP alone for patients with DLBCL. Although the data sources and methodology employed were similar to the Roche company submission, the interpretation and results were numerically different. However, the overall conclusions regarding the overall cost-effectiveness were the same. The model employed by Roche estimated that treatment with R-CHOP generated 1.45 more QALY at an extra cost of £8915 compared with CHOP treatment over a 15-year time period, a cost/QALY ratio of £6143 for patients aged ≥60 years. For patients aged <60 years, 1.29 QALY were generated at an additional cost of £8723, a cost/QALY ratio of £6770. The ScHARR model estimated that the addition of rituximab to CHOP generated an additional 0.82 QALY at an extra cost of £8683 compared with CHOP alone therapy over a 15-year time horizon, a cost/QALY ratio of £10,596 for patients aged ≥60 years. For patients aged <60 years, 1.05 QALY were generated at an additional cost of £7870, a cost/QALY ratio of £7533. If we were to assume that the societal value of a QALY (the amount that one is prepared to pay to gain 1 QALY) was £30,000 then R-CHOP would be considered cost-effective compared with CHOP in the treatment of DLBCL. Extensive sensitivity analysis including both probabilistic and one-way sensitivity analysis undertaken in both models shows the overall results to be particularly robust.

### Cost-effectiveness

The cost-effectiveness modelling presented here has shown that rituximab when used in combination with the CHOP chemotherapy regimen is likely to be considered a cost-effective treatment for DLBCL when compared with the current standard treatment, CHOP chemotherapy only. Although both the ScHARR and the Roche models are based on the same data and use the same methodology, different interpretations of the clinical outcomes and costs have produced different results. However, the difference in the cost/QALY outcome does not lead to a difference in the overall result that the addition of rituximab to the CHOP regimen is likely to be considered cost-effective. Extensive sensitivity analysis undertaken in both models has shown the results to be particularly robust.

### Need for further research

As rituximab is a relatively recent anticancer drug developed for the treatment of malignancies arising from B-lymphocytes, there data are currently available from only one RCT comparing R-CHOP and CHOP treatments in DLBCL. However, as stated by Roche in their submission, there are other relevant trials ongoing.

Analysis of quality of life (QoL) in the area of NHL is limited and only one cost–utility analysis for the treatment of CHOP in NHL was identified. Both the ScHARR and ROCHE models utilised QoL utility scores from an unpublished data source. Further research within this area would help to improve the robustness of QoL utility analysis within DLBCL and also NHL as a whole. One way of achieving this
would be for the National Institute for Clinical Excellence to commission certain cancer networks to record stage, International Prognostic Index IPI score, outcome and QoL data for a cohort of patients receiving R-CHOP for DLBCL.

Further clinical trials might also establish whether R-CHOP may replace peripheral blood stem cell transplant in high-risk patients and whether the doses of chemotherapy in the elderly may be reduced if rituximab is added to less intensive regimens.

**Publication**

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