Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin’s lymphoma

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin’s lymphoma (FNHL) based upon the manufacturer’s submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The manufacturer’s scope restricts the intervention to rituximab in combination with CVP (cyclophosphamide, vincristine and prednisolone) (R-CVP); the only comparator used was CVP alone. The evidence from the one included randomised controlled trial (RCT) suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on the outcomes of time to treatment failure, disease progression, overall tumour response, duration of response and time to new lymphoma treatment in patients with stage III/IV FNHL compared with CVP alone. Adverse events were comparable between the two arms. This study was confirmed as the only relevant RCT. The economic analyses provided by the manufacturer were modelled using a three-state Markov model with with the health states being defined as progression-free survival (PFS), progressed (in which patients have relapsed) and death (which is an absorbing state). The model generated results for a cohort of patients with an initial age of 53 and makes no distinction between men and women. The model is basic in design, with several serious design flaws and key parameter values that are probably incompatible. Attempting
to rectify the identified errors and limitations of
the model did not increase the incremental cost-
effectiveness ratio (ICER) above £30,000. Although
the cost-effectiveness results obtained appear to
be compelling in support of R-CVP compared
with CVP for the trial population the results may
not be so convincing for a more representative
population. The results of the ERG analysis on the
impact of age suggest that ICERs increase steadily
with age, as the proportion of PFS that can be
converted to overall survival (OS) is diminished by
rising mortality rates in the general population.
For the most extreme scenario (no OS gain)
the ICER appears to remain below £30,000 per
QALY gained. On balance the evidence indicates
that R-CVP is more cost-effective than CVP. The
guidance issued by NICE in July 2006 as a result
of the STA states that rituximab within its licensed
indication (in combination with cyclophosphamide,
vincristine and prednisolone) is recommended
as an option for the treatment of symptomatic
stage III/IV follicular non-Hodgkin’s lymphoma in
previously untreated patients.

Description of the
underlying health problem

In the UK non-Hodgkin’s lymphoma (NHL)
represents about 3% of all diagnosed cancers. In
2002 the incidence of NHL was 16 per 100,000
population and 15.6 per 100,000 population in
England and Wales respectively. The overall rate
of NHL is increasing by 3–4% annually. This
is greater than expected when considering the
ageing population and improvements in diagnosis.
Follicular lymphoma (FL) is the second most
common form of NHL in the UK with an incidence
of approximately 4 per 100,000 population. It is
considered incurable and the aim of treatment
is to induce periods of remission, to lengthen
remission and to improve survival and quality of
life. There is no single accepted therapy for first-
line treatment of stage III/IV FNHL, with current
treatment options falling into four main categories:
alkylator-, anthracycline-, fludarabine- and R-CVP-
(rituximab plus cyclophosphamide, vincristine and
prednisolone)-based therapies. Guidelines from the
British Committee for Standards in Haematology
(BCSH) recommend CHOP (cyclophosphamide,
doxorubicin, vincristine and prednisolone), an
anthracycline-based therapy, for treatment of
grade III FNHL, although no guidance for the
treatment of grade IV FNHL is given. There is
currently no consensus as to whether combination
therapy provides additional treatment benefits
over monotherapy. However, recent published
clinical guidelines suggest that trials have shown
advantages for combination therapy or extended
chemotherapy with more frequent and longer
lasting remissions and improvements to quality of
life.

Scope of the ERG report

The ERG report presented the results of the
assessment of the manufacturer’s report regarding
the use of rituximab (within the context of the
licensed indication) in combination with CVP for
the first-line treatment of stage III/IV FNHL. The
scope of the appraisal is presented in Table 1. The
report included an assessment of both the clinical
and cost-effectiveness evidence submitted by the
manufacturer (Roche) of rituximab (MabThera®),
indicated for the treatment of previously untreated
patients with stage III/IV FNHL in combination
with CVP chemotherapy.
TABLE I  Scope of the appraisal

<table>
<thead>
<tr>
<th>Clinical effectiveness</th>
<th>Cost-effectiveness</th>
</tr>
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<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Adults with stage III/IV non-Hodgkin’s lymphoma who have not received any previous treatment</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>Rituximab in combination with CVP (cyclophosphamide, vincristine and prednisolone)</td>
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<tr>
<td><strong>Comparators</strong></td>
<td>CVP(CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone))</td>
</tr>
<tr>
<td></td>
<td>CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisolone)</td>
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<tr>
<td></td>
<td>MCP (mitoxantrone, chlorambucil and prednisolone)</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>Time to treatment failure</td>
</tr>
<tr>
<td></td>
<td>Tumour response (complete response, unconfirmed complete response, partial response, progressive disease)</td>
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<tr>
<td></td>
<td>Duration of response</td>
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<tr>
<td></td>
<td>Overall survival</td>
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<tr>
<td></td>
<td>Disease-free survival</td>
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<td></td>
<td>Adverse effects of treatment</td>
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<tr>
<td></td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Main focus of follicular lymphoma</td>
</tr>
<tr>
<td></td>
<td>Clinical trial data publications</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Clinical trials in previously treated patients</td>
</tr>
<tr>
<td></td>
<td>Reviews</td>
</tr>
<tr>
<td></td>
<td>Animal studies or in vitro research work</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>From the draft scope: Details of the time horizon for the economic evaluation based on the time period over which costs and benefits can reasonably be expected given the progression of the disease</td>
</tr>
</tbody>
</table>

Methods

The ERG report comprised a critical review of the evidence for the clinical and cost-effectiveness of the technology based upon the manufacturer’s/sponsor’s submission to NICE as part of the STA process.

As part of their critical review the ERG repeated the searches for studies of clinical and cost-effectiveness. An accepted tool relating to rigour of the review process and clarity of reporting was used to assess the methodological quality of the manufacturer’s literature review. The ERG assessed whether each paper reported in the manufacturer’s submission met the inclusion criteria according to: publication date; language; type of study (whether a full economic evaluation was included); intervention; and subjects. They conducted a detailed critique of the single efficacy trial included in the manufacturer’s submission. They critiqued the manufacturer’s economic model and the model was rerun after correcting for errors relating to costs and life-years gained; a Weibull survival curve was used to estimate survival.

In addition, because the submitted model is based on a cohort of patients with an unrealistically low average age (53 years), the ERG explored this further. It was observed that it was possible that at higher ages the apparently promising cost-effectiveness ratios may not be so attractive and could become unacceptable. It proved to be impossible to modify the model to allow accurate adjustment of age because of inherent structural problems and inherent inconsistencies in the model structures and, therefore, the ERG attempted a supplementary analysis. These results are necessarily imprecise approximations and should not be viewed as more than a general indication of the types of variations that may be expected if the ERG’s assumptions prove to be valid.
Results

Summary of submitted clinical evidence

The submitted clinical evidence includes one randomised controlled trial (RCT), M30921, comparing CVP chemotherapy alone with CVP in combination with rituximab and involving a total study population of 322 patients with stage III or IV FNHL. The evidence from this trial suggests that the addition of rituximab to a CVP chemotherapy regimen has a positive effect on the primary outcome of time to treatment failure; it is reported to increase from 6.6 months in patients receiving CVP to 27 months in patients in the R-CVP arm with a risk reduction of 66% (95% CI 55%–74%). Other positive outcomes were measured for disease progression, overall tumour response, duration of response and time to new lymphoma treatment. Overall survival (OS) was not estimable at 42 months and the 38% risk reduction had not reached statistical significance. Adverse events were comparable between the two arms for the proportion of patients experiencing at least one adverse event, although the proportion experiencing an adverse event in the first 24 hours was greater for the R-CVP arm (71% versus 51%). These are primarily represented by infusion-related events. Similar proportions of patients in each arm experienced grade 3–4 haematological toxicity and infection except for neutropenia (14.5% CVP versus 24.1% R-CVP).

Summary of submitted cost-effectiveness evidence

The submitted review of economic studies included 15 studies, only eight of which actually met the inclusion criteria established for the review. None of these studies, however, compared R-CVP with CVP. The data extraction of the economic literature undertaken by the manufacturer was lacking in depth and no quality assessment of the included studies was provided. However, given the fact that these studies do not compare the same health-care technologies as the manufacturer’s own economic evaluation, this is of limited importance.

The economic model included in the manufacturer’s submission is a three-state Markov model, with the health states being defined as:

- progression-free survival (PFS)
- progressed (in which patients have relapsed)
- death (which is an absorbing state).

Patients begin in the PFS state and at the end of each cycle (cycle length 1 month) can either stay within this health state or move to the progressed health state or death state. Once in the progressed health state patients either move to the death state or continue in the progressed health state; once in the progressed health state they cannot return to PFS (Figure 1). However, the progressed state has been adjusted (in terms of utility) to account for periods of PFS. Movement between health states is governed by transition probabilities. The probabilities applied to the PFS health state vary over time but are generally similar between the two arms. The probabilities applied to the progressed health state are constant and do not differ between the two arms. The submitted model generates results for a cohort of patients with an initial age of 53 and makes no distinction between men and women.

Commentary on the robustness of submitted evidence

The single study included in the manufacturer’s submission was confirmed as the only relevant RCT. In the manufacturer’s submission the only comparator used was CVP alone. A wide range of treatment options are used in the UK for the treatment of FNHL, but currently there is no consensus on the most effective treatment. These include alkylator-based regimens (e.g. CVP, chlorambucil) or anthracycline-based regimens.

![Figure 1: Structure of the Markov model (adapted from the manufacturer's submission). PFS, progression-free survival.](image-url)
(e.g. CHOP, CNOP, MCP) used either alone or in combination with rituximab. Clinical guidelines, however, note a lack of data directly comparing outcomes with alternative therapeutic strategies. There is mention in the manufacturer’s submission of other studies using a variety of treatments; however, no analyses were carried out comparing the results with R-CVP. Preliminary findings of a meta-analysis, available only as a conference abstract, are discussed descriptively.

There is an issue relating to the rationale for the outcomes used, including an explanation of the reasons for using time to treatment failure as the primary outcome instead of OS as is usual for oncology clinical trials. However, although OS is a preferred outcome measure, in the case of FNHL the submission presents a persuasive rationale for the use of time to treatment failure.

The model submitted in support of the manufacturer’s submission is basic in design. It suffers from several serious design flaws and key parameter values are probably incompatible. The ERG attempted to rectify the identified errors and limitations of the model, none of which increased the incremental cost-effectiveness ratio (ICER) above the conventional threshold of £30,000. However, because of design flaws within the model as outlined in the report it was impossible for the ERG to simultaneously correct all of the errors and limitations within it. Although the

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Results of analysis on impact of age on cost-effectiveness indices. Illustrative age-related model results, based on simple assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>All 10%</td>
</tr>
<tr>
<td>Proportion PFS gain is OS gain</td>
<td>0%</td>
</tr>
<tr>
<td>Incremental cost</td>
<td>£5944</td>
</tr>
<tr>
<td>Incremental life-years</td>
<td>0.000</td>
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<tr>
<td>Incremental QALYs</td>
<td>0.215</td>
</tr>
<tr>
<td>Incremental cost per life-year</td>
<td>N/A</td>
</tr>
<tr>
<td>Incremental cost per QALY</td>
<td>£27,619</td>
</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival; QALY(s), quality-adjusted life-year(s).

(b)

<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th>50</th>
<th>53</th>
<th>60</th>
<th>70</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max proportion of PFS gain is OS gain</td>
<td>67.0%</td>
<td>65.5%</td>
<td>59.4%</td>
<td>36.8%</td>
<td>12.5%</td>
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<tr>
<td>Incremental cost</td>
<td>£9401</td>
<td>£9322</td>
<td>£9007</td>
<td>£7843</td>
<td>£6588</td>
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<tr>
<td>Incremental life-years</td>
<td>1.277</td>
<td>1.248</td>
<td>1.131</td>
<td>0.701</td>
<td>0.238</td>
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<tr>
<td>Incremental QALYs</td>
<td>1.099</td>
<td>1.079</td>
<td>0.998</td>
<td>0.700</td>
<td>0.380</td>
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<tr>
<td>Incremental cost per life-year</td>
<td>£7364</td>
<td>£7472</td>
<td>£7962</td>
<td>£11,185</td>
<td>£27,686</td>
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<tr>
<td>Incremental cost per QALY</td>
<td>£8577</td>
<td>£8643</td>
<td>£9025</td>
<td>£11,197</td>
<td>£17,343</td>
</tr>
</tbody>
</table>

OS, overall survival; PFS, progression-free survival; QALY(s), quality-adjusted life-year(s).
cost-effectiveness results obtained appear to be compelling in support of R-CVP compared with CVP for the trial population, it could be argued that the results would not be so convincing for a more representative population.

The results of the ERG analysis on the impact of age (Table 2) suggest that ICERs increase steadily with age, as the proportion of PFS that can be converted to OS is diminished by rising mortality rates in the general population. For the most extreme scenario (no OS gain) the ICER appears to remain below £30,000 per quality-adjusted life-year gained.

**Conclusions**

On balance the evidence indicates that R-CVP is more cost-effective than CVP.

**Summary of NICE guidance issued as a result of the STA**

The guidance issued by NICE in July 2006 states that:

Rituximab within its licensed indication (that is in combination with cyclophosphamide, vincristine and prednisolone) is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.

**Key references**


5. The University of Sheffield School of Health and Related Research. Critical appraisal of secondary research. MScHealth Informatics, Unit Five. 2006. URL: www.shef.ac.uk/scharr/ir/mschi/unit5/3appraising.htm#casr.