Rituximab for the first-line treatment of stage III–IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic tissue, causing enlargement of lymph nodes and generalised symptoms. Follicular lymphoma (FL), a clinical subtype of NHL, develops slowly and often without symptoms for many years. FL takes a relapsing and remitting course, and median survival is 8–10 years, although more recent evidence suggest it could be as high as 15–20 years. In 2008, the incidence of FL in England and Wales was 3.4 per 100,000 persons. Over 70% of FLs are diagnosed in persons aged > 60 years, and 85–90% present with advanced disease, which is defined as lymph nodes on both sides of the diaphragm being involved (stage III) or disease is disseminated with one or more extralymphatic organ involved (stage IV).

Advanced FL is not curable, thus the aim of disease management is to both increase patient life expectancy and to increase patient health-related quality of life. For the majority of patients (90%), first-line therapy in stage III–IV FL is rituximab (R) (MabThera®, Roche Products) plus chemotherapy (R-chemotherapy), with around two-thirds receiving the cyclophosphamide, vincristine and prednisolone (CVP) regimen as the chemotherapy component of treatment. The next most frequent chemotherapy regimen is cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), which accounts for 16% of other chemotherapy regimens. Patients who are less fit and/or elderly may receive chlorambucil (Leukeran®, Aspen) as single-agent chemotherapy. The National Institute for Health and Clinical Excellence reviewed the use of rituximab in Technology Appraisal (TA) no. 110 in 2006, subsequently recommending the use of R-CVP as first-line treatment for symptomatic stage III–IV FL. Since TA110, the licence for rituximab has been extended so that rituximab can be administered in combination with any chemotherapy for first-line treatment of symptomatic stage III–IV FL. Rituximab monotherapy as a maintenance treatment may follow for patients who have responded to first-line treatment with R-chemotherapy, which aims to delay relapse by stabilising response to initial therapy, eradicating any residual disease and maintaining remission after successful remission induction therapy.

Objectives

The aim of this assessment is to systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of rituximab (in its licensed indication) in combination with chemotherapy compared with non-rituximab-containing chemotherapy, for the first-line treatment of symptomatic stage III–IV FL.

Methods

Eleven electronic databases were searched from inception to September/October 2010: MEDLINE, including MEDLINE In-Process & Other Non-Indexed Citations; Cumulative Index to Nursing and Allied Health Literature (CINAHL); EMBASE; The Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases; Science Citation

Index (SCI); and BIOSIS. Ongoing research was searched using clinical trials databases and registers. Relevant conference proceedings were searched and the reference lists of relevant articles and sponsor submissions were handsearched.

Comparative studies were selected for review if they addressed the clinical effectiveness or cost-effectiveness of adding rituximab to chemotherapy. In addition, comparative studies that involved either an intervention or comparator defined in the decision problem (i.e. R-chemotherapy or chemotherapy alone) were selected for potential use in a network meta-analysis. The studies had to include patients with symptomatic III–IV FL and to be of randomised controlled trial (RCT) design. Outcomes had to include one or more of the following: response rates, response duration, overall survival (OS), progression-free survival (PFS) or duration of disease remission. The quality of the studies was assessed using criteria based on those proposed by the NHS Centre for Reviews and Dissemination. Data were abstracted into standardised data extraction forms. Findings were tabulated and discussed in a narrative synthesis.

A systematic review of economic evaluations addressing the cost-effectiveness of the addition of rituximab to chemotherapy compared with chemotherapy alone was conducted. There was also one manufacturer submission (Roche) for this assessment, which included an economic model. In addition, a systematic review of the quality of life in FL was performed.

A probabilistic model was developed by the Assessment Group (AG) to assess the cost-effectiveness of the addition of rituximab to CVP, CHOP and MCP (mitoxantrone, chlorambucil and prednisolone) from a NHS perspective. The model has four health states: PFS after first line (PFS1), PFS after second line (PFS2), progressive disease and death. Patients start in PFS1 and receive first-line induction with chemotherapy with or without rituximab. Patients who relapse move on to PFS2 and are assumed to receive second-line treatment with or without maintenance rituximab. After progression, patients enter a progressive state and remain in that state until death. The model uses a 25 years time horizon and costs and benefits are discounted at 3.5%. A scenario analysis is presented incorporating first-line maintenance in responder to first-line induction with R-chemotherapy.

Results

Summary of benefits and risks

Four RCTs comparing R-chemotherapy with chemotherapy alone in untreated, symptomatic patients with stage III–IV FL were identified.

R-chemotherapy compared with chemotherapy alone increased the likelihood of a response to treatment in all four trials, with no additional toxicity of clinical relevance. Overall response rates (ORRs) were significantly improved in all four trials, with a difference between the R-chemotherapy and chemotherapy arms of between 5% and 24%, respectively. Complete response (CR) rates were also improved, with a difference between the R-chemotherapy and chemotherapy arms of between 2% and 25%. Exploratory meta-analyses were conducted to explore the results of synthesising the ORR, CR and partial response from the four trials. The level of statistical heterogeneity was very high and the AG therefore believes the response rates from the individual trials to be a more robust estimator of the efficacy of the specific R-chemotherapy regimens. These are subsequently used in the decision model.

Over a follow-up period of 4–5 years, R-chemotherapy significantly increased the OS rate compared with chemotherapy alone in three trials. The trials presented evidence that

R-chemotherapy prolonged other clinical outcomes, such as response duration, time to treatment failure, time to progression, time to next antilymphoma treatment, event-free survival and disease-free survival, compared with chemotherapy alone.

Summary of cost-effectiveness

The incremental cost-effectiveness ratio (ICER) for the addition of rituximab to CVP, CHOP and MCP was £7720, £10,834 and £9316 per quality-adjusted life-year (QALY) gained, respectively, when it was assumed that first-line rituximab maintenance was not used.

When it was assumed that patients responding to first-line induction with R-chemotherapy receive first-line maintenance rituximab for up to 2 years, the ICERs increased to £14,959, £21,687 and £20,493 per QALY gained, respectively. Sensitivity analyses (SAs) indicated that the ICER was mostly sensitive to the assumptions about the time horizon, the choice of parametric distribution to model the effectiveness in first-line induction, the maximum time a patient can remain progression free, assumptions regarding resistance to rituximab and the modelled treatment pathway. Results are not directly comparable across chemotherapies, as they are selected in clinical practice with regard to factors including age, performance status and disease aggressiveness.

Discussion

The results from four randomised trials (of good quality) comparing R-chemotherapy with chemotherapy alone showed an improvement in a number of clinical effectiveness outcomes. These benefits are achieved with minimal clinically relevant additional adverse events or toxicity. It is noted that data for outcomes such as OS are compromised in three of the studies owing to the use of additional treatments. Longer OS data follow-up would strengthen the findings, as the median OS has not yet been reached in any of the trials.

This assessment provides an indication of the cost-effectiveness of the addition of rituximab to CVP, CHOP and MCP in a UK setting. The model developed by the AG extends the analysis undertaken in previous economic models in terms of a greater level of detail in the modelled treatment pathway. A wide range of assumptions have also been examined in SAs. However, there are some limitations relating to the sources of data used in the AG model for the effectiveness in first and second line and the assumed utility values. There is little evidence available regarding the effectiveness of R-CHOP and R-MCP in first-line induction. There is also uncertainty about the effect of salvage treatment in patients previously treated with an anthracycline regimen. Finally, there is uncertainty whether or not rituximab is as effective in second line when patients have been previously treated with rituximab. The context for care and the mode of delivery is identical with the comparator therapies; thus, there are no implications that do not also apply to chemotherapies alone.

Generalisability

It is noted that patients included in the trials were generally younger than those seen in clinical practice in the UK. This assessment is based on data involving the following chemotherapeutic agents: CVP, CHOP, MCP and CHVPi (cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha). It is not certain that the results can be generalised to other R-chemotherapy regimens.

Conclusions

The addition of rituximab to CVP, CHOP and MCP is likely to be clinically effective in the first-line treatment of stage III–IV FL. The cost per QALY gained is estimated to be < £25,000 for all three comparisons under our base-case assumption and is considerably lower if first-line rituximab maintenance is not assumed. The main uncertainties in terms of influencing the ICER relate to the effectiveness of rituximab retreatment (i.e. resistance) and the effect of salvage treatment in patients previously treated with anthracycline regimens. Assumptions were made and the best evidence identified was used when appropriate and available. Therefore, results have to be interpreted in line with the assumptions made and the quality of the evidence available.

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Publication

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NIHR Health Technology Assessment programme

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