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

Papaioannou D, Rafia R, Rathbone J, Stevenson M, Buckley Woods H, Stevens J

CRD summary
This review found that addition of rituximab to chemotherapy regimens for stage III-IV follicular lymphoma showed an improvement in clinical outcomes with minimal clinically relevant extra adverse events or toxicity. This was a generally well-conducted review. The authors' conclusions reflect the evidence presented and appear reliable.

Authors' objectives
To evaluate the effectiveness of rituximab, in combination with chemotherapy, compared with chemotherapy alone, for the first-line treatment of symptomatic stage III-IV follicular lymphoma.

Searching
Eleven electronic databases, including MEDLINE, CINAHL, EMBASE, The Cochrane library and Database of Abstracts of Reviews of Effects (DARE), were searched from inception to October 2010. Search terms were reported. There were no language restrictions. Relevant conference proceedings and the reference lists of relevant articles and the manufacturer's submission were searched and experts in the field contacted to identify additional studies. Ongoing research was identified from clinical trial registers and databases.

Study selection
Randomised controlled trials (RCTs) that compared rituximab in combination with any of ten specified chemotherapy regimens with the same chemotherapy alone were eligible. Trials had to enrol patients with symptomatic stage III-IV follicular lymphoma who had not received any previous treatment. The primary outcome of interest was overall survival; secondary outcomes and response rates were listed in the report.

The included trials all involved different chemotherapy regimens. Median age ranged from 52 to 61 years and the proportion of men ranged from 37 to 55%. Co-interventions were given to both treatment groups in three of the trials.

Titles and abstracts were assessed by one reviewer. A sample of citations (10%) were checked by a second reviewer and any discrepancies resolved by discussion. Full texts of relevant items were selected for inclusion by one reviewer.

Assessment of study quality
Study quality was assessed using criteria based on those proposed by the Centre for Reviews and Dissemination for RCTs. Assessments were done by one reviewer and checked by a second.

Data extraction
Data were extracted by one reviewer and checked by a second. Discrepancies were resolved by discussion. For exploratory meta-analyses, data on numbers of patients and events in each group were used to derive relative risks and associated 95% confidence intervals.

Methods of synthesis
Data were tabulated and discussed in a narrative synthesis. Exploratory meta-analyses were performed for response rate outcomes using random-effects models. Heterogeneity in these analyses was explored qualitatively and using the Χ² test and I² statistic.

Results of the review
Four RCTs with 1,688 randomised participants were included in the review. Trials compared cyclophosphamide, vincristine and prednisolone (CVP), cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone (CHOP), mitoxantrone, chlorambucil and prednisolone (MCP) and cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-alpha (CHVPi) chemotherapies (details in the report) with the same regimen plus rituximab. Median follow-up ranged from 47 to 60 months. All four trials were rated adequate for randomisation, allocation concealment, power
calculation and intention-to-treat analysis but none reported blinded outcome assessment. Follow-up was at least 80% in all trials.

Overall survival ranged from 83% to 90% in the rituximab-chemotherapy groups and from 77% to 84% in the chemotherapy-alone groups. The difference between groups was statistically significant in three trials. Results from two trials were confounded by the effects of subsequent therapy provided to all responders to first-line treatment.

Overall response rates were significantly improved by rituximab in all four trials. A significant improvement in complete response rates was reported in two trials. Exploratory meta-analyses (details in the report) showed a significant difference for most response outcomes but heterogeneity was high ($\text{I}^2$=56 to 88%). There was no additional toxicity of clinical relevance with chemotherapy plus rituximab versus chemotherapy alone.

**Cost information**
Economic modelling indicated that the incremental cost-effectiveness ratio (ICER) for the addition of rituximab to chemotherapy ranged from £7,720 to £10,834 per quality-adjusted life-year (QALY) gained, assuming that first-line rituximab maintenance was not used. When it was assumed that patients who responded to first-line induction with rituximab plus chemotherapy receive first-line maintenance rituximab for up to two years, the ICERs ranged from £14,959 to £21,687 per QALY gained.

**Authors' conclusions**
Addition of rituximab to chemotherapy regimens showed an improvement in clinical outcomes with minimal clinically relevant extra adverse events or toxicity.

**CRD commentary**
The review question and inclusion criteria were clear. The search was thorough and included attempts to locate unpublished and ongoing trials. Some efforts were made to reduce risk of errors or bias affecting the review process. Study quality was assessed using standard criteria and full details of included trials were presented. The authors' decision to conduct a mainly narrative synthesis was reasonable in view of the differences between the trials. Results of exploratory meta-analyses were presented with appropriate caveats.

This was a generally well-conducted review. The authors' conclusions reflect the evidence presented and appear reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the addition of rituximab to CVP, CHOP and MCP chemotherapy regimens was likely to be clinically effective in the first-line treatment of stage III-IV follicular lymphoma.

**Research:** The authors stated a number of research priorities including research on the effectiveness of rituximab retreatment and trials comparing different rituximab-containing chemotherapy regimens.

**Funding**
NIHR HTA Programme on behalf of NICE.

**Bibliographic details**

**PubMedID**
23021127

**DOI**
10.3310/hta16370

**Original Paper URL**
Database of Abstracts of Reviews of Effects (DARE)
Other URL
Link to record on HTA database: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=32011000783& UserID=0
Link to record on NHS EED: http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?AccessionNumber=22013006241& UserID=0

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal, Murine-Derived /economics /therapeutic use; Antineoplastic Agents /economics /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /administration & dosage /therapeutic use; Chlorambucil /administration & dosage; Cost-Benefit Analysis; Cyclophosphamide /administration & dosage; Doxorubicin /administration & dosage; England /epidemiology; Female; Humans; Lymphoma, Follicular /diagnosis /drug therapy /epidemiology /pathology; Male; Middle Aged; Mitoxantrone /administration & dosage; Models, Economic; Prednisolone /administration & dosage; Prednisone /administration & dosage; Randomized Controlled Trials as Topic; Rituximab; Vincristine /administration & dosage; Wales /epidemiology

AccessionNumber
12012049759

Date bibliographic record published
10/12/2012

Date abstract record published
03/04/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.