A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma


CRD summary
This review concluded that chemotherapy combined with rituximab was superior to chemotherapy alone in patients with B-cell non-Hodgkin's lymphoma. This was a well-conducted review and these conclusions are likely to be reliable.

Authors' objectives
To examine the efficacy of chemotherapy plus rituximab (anti-CD20 monoclonal antibody) compared with chemotherapy alone for B-cell non-Hodgkin's lymphoma.

Searching
PubMed, EMBASE, Chinese Biomedical database and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2008. Search terms were reported. Three relevant conference proceedings were searched from 1995 to 2008. Reference lists of included studies, relevant reviews and practice guidelines were screened. Pharmaceutical companies were contacted in an attempt to locate unpublished studies. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that compared chemotherapy plus rituximab with the same chemotherapy alone in adults (over 18 years old) with histologically proven B-cell non-Hodgkin's lymphoma (regardless of disease stage of previous therapy received) were eligible for inclusion. Trials with 10 or fewer patients per treatment arm or studies of patients with HIV or primary central nervous system lymphoma were excluded.

The primary outcome was overall survival. Secondary outcomes were progression-free survival, event-free survival, time to treatment failure, time to progression and adverse events.

Most trials included untreated patients with diffuse large B-cell lymphoma, follicular lymphoma, or mantle cell lymphoma. Two trials included patients with relapsed or refractory follicular or mantle cell lymphoma. Chemotherapy regimens varied across trials. All trials compared regimens alone to the same regimen combined with rituximab. Chemotherapy was administered every 14 to 21 days.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved through discussion with a third reviewer.

Assessment of study quality
Two reviewers independently assessed trial quality according to the Jadad scale, assigning studies a score out of 5 points based on randomisation, blinding and drop-outs. Concealment of treatment allocation and use of an intention-to-treat analysis were also assessed.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RR) or odds ratios (OR) together with 95% confidence intervals (CIs).

Methods of synthesis
Fixed-effect models were used to estimate summary relative risks and odds ratios together with 95% confidence intervals. If heterogeneity was detected, random-effects models were used. Heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics.

Heterogeneity was investigated by performing sensitivity analyses based on lymphoma subtype, previous treatment,
stage, study duration, study quality, source of data, and the effects of single large studies.

Publication bias was assessed using forest plots and the Egger test.

Results of the review
Twelve RCTs were included in the review (n=4,996 patients). One trial scored 2 on the Jadad scale; the rest scored 3. All trials were reported to be randomised, three trials did not report the method of allocation concealment, all but one trial reported using an intention-to-treat analysis, and few drop-outs were reported. It appeared that all trials were unblinded. The median duration of follow-up ranged from 18 to 42 months.

Chemotherapy plus rituximab was associated with significantly greater overall survival (RR 1.09, 95% CI 1.06 to 1.12; 11 RCTs), overall response (RR 1.17, 95% CI 1.10 to 1.25; 12 RCTs), and disease control (RR 1.36, 95% CI 1.26 to 1.46; 11 RCTs) compared with chemotherapy alone. There was no evidence of statistical heterogeneity for overall survival, but there was substantial heterogeneity for overall response rate (p<0.0001) and disease control (p<0.02). Subgroup analyses based on lymphoma subtype showed similar results.

Chemotherapy plus rituximab was also associated with significantly greater adverse events in the form of fever (OR 4.18, 95% CI 1.55 to 11.28; two RCTs) or leukocytopenia (OR 1.32, 95% CI 1.10 to 1.58; five RCTs). There was no difference between treatment groups for the risk of treatment-related deaths.

Authors’ conclusions
Chemotherapy plus rituximab was superior to chemotherapy alone in patients with B-cell non-Hodgkin’s lymphoma, especially for diffuse large B-cell lymphoma and follicular lymphoma.

CRD commentary
The review addressed a focused question, supported by clearly defined inclusion criteria. The literature search was adequate; no language or publication restrictions were applied. The authors stated that publication bias was assessed, but the results were not reported in the review. Appropriate methods were used to minimise bias and errors at all stages of the review.

Trial quality was formally assessed using appropriate criteria and the results were clearly presented for most criteria. Relevant trial details were summarised in tables and in the text. Methods used to pool data were appropriate and the results were clearly presented.

The authors’ conclusions were supported by the results and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that concomitant treatment with rituximab and standard chemotherapy regimens should be considered the standard of care for patients with B-cell lymphomas, especially for diffuse large B-cell lymphoma and follicular lymphoma.

Research: The authors did not state any implications for further research.

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