A network meta-analysis of therapies for previously untreated chronic lymphocytic leukemia

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CRD summary
This review concluded that fludarabine, combined with cyclophosphamide and rituximab, was more likely than the other therapies, to prevent disease progression in younger, healthier, treatment-naive patients with chronic lymphocytic leukemia. The below optimal quality of the included trials, the indirect treatment comparison, and the small amount of evidence, limit the reliability of the authors' conclusions.

Authors' objectives
To compare medical therapies for previously untreated chronic lymphocytic leukaemia.

Searching
The Cochrane Library and MEDLINE were searched to November 2011 for articles published in English. Search terms were reported. The reference lists of retrieved articles were screened for other relevant articles.

Study selection
Randomised controlled trials (RCTs) of therapy for symptomatic, previously untreated, chronic lymphocytic leukaemia, were eligible for inclusion. Trials had to measure a survival outcome, provide survival curves, and report the number of patients at risk at set follow-up times. Data for the entire trial had to be available for the review. Trials that the authors decided were clinically different from the others, in their treatment patterns or included patients, were excluded.

The included trials were of various dosages of fludarabine, with cyclophosphamide and rituximab; fludarabine, with cyclophosphamide; alemtuzumab; chlorambucil; or fludarabine. The mean age of patients ranged from 58.5 to 65 years. The percentage of patients with advanced-stage disease ranged from 30 to 40. Where reported, the percentage of patients with Eastern Cooperative Oncology Group zero or one performance status, ranged from 57 to 97.

The authors did not state how many reviewers selected trials.

Assessment of study quality
Quality was assessed, using the Jadad criteria for randomisation, blinding and study withdrawals, to give a score out of 5. The authors did not state how many reviewers assessed trial quality.

Data extraction
Data were extracted using published survival curves, to determine progression-free survival, and calculate hazard ratios, with 95% credible intervals. The authors did not state how many reviewers extracted the data.

Methods of synthesis
Fixed-effect and random-effects network meta-analyses were used to calculate the pooled hazard ratios, with 95% credible intervals, assuming either Weibull or log-logistic survival distributions. A Bayesian approach was used, with Markov Chain Monte Carlo methods and non-informative prior distributions, for the model parameters. The goodness-of-fit was assessed, using the deviance information criteria. Sensitivity analysis was conducted by varying the initial parameter values.

Results of the review
Five RCTs were included in the review, with 2,625 patients (range 297 to 817). One trial scored 1, three scored 2, and one scored 3, on the Jadad scale.

The combination of fludarabine with cyclophosphamide and rituximab had the longest mean progression-free survival of 76 months (95% CrI 60 to 91), followed by fludarabine plus cyclophosphamide, at 60 months (95% CrI 46 to 73), fludarabine, at 38 months (95% CrI 27 to 49), alemtuzumab, at 24 months (95% CrI 15 to 32), and chlorambucil, at 23 months (95% CrI 15 to 32).
Authors' conclusions
Fludarabine combined with cyclophosphamide and rituximab was more likely to prevent disease progression in young, healthy, treatment-naive patients with chronic lymphocytic leukaemia, compared with the other therapies.

CRD commentary
The inclusion criteria for the review were clearly defined. Only two relevant data sources were searched and only studies published in English were included, so relevant studies might have been missed. Publication bias was not assessed and cannot be ruled out. It was not clear if any attempts were made to reduce reviewer error and bias during data extraction, quality assessment, and trial selection. Quality was assessed using a standard checklist, which indicated that the evidence was below optimal.

The treatments could not be compared directly as there was insufficient evidence, so an indirect, network meta-analysis was performed. The authors noted that combination therapies were often associated with greater toxicity, which should be considered alongside any improvements in progression-free survival.

The below optimal quality of the included trials, the indirect comparisons, and the small amount of evidence, limit the reliability of the authors' conclusions. The authors appropriately noted that network meta-analysis and extrapolation have limitations, and they recommended further research.

Implications of the review for practice and research
Practice: The authors stated that the combination of fludarabine with cyclophosphamide and rituximab should be considered as the optimal initial treatment.

Research: The authors stated that additional studies of fludarabine with cyclophosphamide and rituximab were necessary.

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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.