Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: a multiple-treatment meta-analysis
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CRD summary
This review concluded that the published evidence was insufficient to recommend any particular first treatment to improve overall survival for adults with untreated advanced chronic lymphocytic leukaemia. Given the poor evidence, this conclusion appears to be appropriate and reliable.

Authors’ objectives
To compare the benefits and harms of first treatments for untreated advanced chronic lymphocytic leukaemia.

Searching
PubMed, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched in June, 2011. No language and date restrictions were imposed. Search strategies were reported in an appendix. Conference abstracts (between 2004 and 2010) of randomised controlled trials (RCTs) were handsearched, as were reference lists of eligible trials and relevant systematic reviews and meta-analyses.

Study selection
Eligible were randomised controlled trials of first-line therapy, comparing at least two chemotherapy or chemo-immunotherapy regimens from 11 specified categories (presented in the review). Participants had to be adults with intermediate-to-high risk (Rai classification), or Stage B to C (Binet staging) B-cell chronic lymphocytic leukaemia. At least 80% of participants had to be previously untreated. The primary outcome of interest was overall survival; secondary outcomes included progression-free survival and treatment-related mortality.

The patients in the included trials were enrolled between 1978 and 2008. Where reported, the median age of participants ranged from 54 to 70 years. Between zero and 100% of patients had been diagnosed as in Rai classes III or IV. Most comparisons for overall survival were between chlorambucil alone, conventional combinations, fludarabine alone, or fludarabine-based combinations.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Trial quality was assessed, using published criteria, for randomisation, allocation concealment, blinding, intention-to-treat analysis, completeness of follow-up, salvage strategies at progression, and similarity in clinical characteristics between treatment arms.

Two reviewers independently assessed quality.

Data extraction
Comparisons had to be between different treatment categories. Hazard ratios and 95% confidence intervals (preferably unadjusted) were extracted or calculated, for overall- and progression-free survival. The numbers of deaths were extracted for treatment-related mortality.

Two reviewers independently extracted the data. Any discrepancies were resolved by consensus or with a third reviewer.

Methods of synthesis
Where there were two or more head-to-head trials reporting direct evidence, the hazard ratios and their 95% confidence intervals were pooled in random-effects meta-analyses. Peto’s method was used for the meta-analysis of treatment-related mortality. In all meta-analyses, statistical heterogeneity was assessed using Cochran’s Q and I², with I² of more than 50% indicating intermediate heterogeneity, and more than 75% indicating high heterogeneity.
Network meta-analysis was performed for overall- and progression-free survival, according to the Bayesian framework, to estimate effect sizes and 95% credible intervals. The main analysis assumed consistency between the treatments; the sensitivity analysis relaxed this assumption. The probability that each treatment would be ranked first, second, etc., among the alternative regimens was calculated. Further details of the synthesis were reported in the review and the appendix.

**Results of the review**

Twenty-five randomised controlled trials were included (7,926 patients). None of the trials reported double blinding, and none reported complete follow-up for more than 80% of patients. For the remaining quality domains, the results were mixed. Where reported, the median follow-up ranged from 22 to 180 months.

**Overall survival**: Of the 13 direct treatment comparisons, only one statistically significant difference was found, favouring combination immunochemotherapy based on fludarabine-rituximab over that based on fludarabine; this was based on data from only one trial.

**Progression-free survival**: Seven of the nine direct treatment comparisons showed statistically significant differences; all but two of these were based on data from one trial. The remaining two comparisons showed that fludarabine alone was superior to chlorambucil (HR 0.80, 95% CI 0.69 to 0.94; three trials; $I^2=40\%$), and fludarabine-based combinations were superior to fludarabine alone (HR 0.50, 95% CI 0.42 to 0.60; three trials; $I^2=0$).

**Treatment-related mortality**: Two of the eight direct treatment comparisons showed significant differences. One was based on one trial (chlorambucil versus a fludarabine-based combination); the other was based on two trials, and found that chlorambucil had a significantly lower rate of treatment-related deaths than fludarabine alone (OR 6.30, 95% CI 1.95 to 20.36; $I^2=0$).

**Multiple treatment analyses**: The results with and without inconsistency factors were nearly identical (fully reported in the paper and the appendix) for overall and progression-free survival. The analyses for treatment-related mortality were inconsistent and self-contradictory, and were not reported by the review authors. Similar results were shown in the sensitivity analyses, which used alternative models for inconsistency between direct and indirect data. The removal of one trial that enrolled some previously treated patients did not substantially change the results.

**Authors' conclusions**

The published evidence was insufficient to recommend any particular first treatment to improve overall survival for adults with chronic lymphocytic leukaemia.

**CRD commentary**

The review question was clear and supported by replicable inclusion criteria. Relevant data sources were searched for published and unpublished trials. No language restrictions were applied, reducing the risk of relevant trials being missed. All the review processes were duplicated, minimising the potential for reviewer error and bias.

Suitable quality assessment criteria were used; the results showed that the quality of the included trials varied. The authors acknowledged that there were clinical differences between the trials. Many of the direct treatment comparisons were based on single trials, particularly for the two survival outcomes.

Given the poor evidence, the authors' conclusion of no recommendation appears to be appropriate and reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for clinical practice.

**Research**: The authors stated that more trials were needed to establish reliable conclusions on the clinical outcomes of the treatment regimens available for chronic lymphocytic leukaemia. Trials should focus on head-to-head comparisons of newer treatments, with each other and with older treatments, and evaluate overall survival as the main outcome. Research was needed to investigate the effects of treatment regimens on frail elderly patients with chronic lymphocytic leukaemia, and to provide more useful data on the relative effects, harms, and costs.

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