Authors' objectives
To review the available literature on the use of fludarabine as a first-line treatment for B-cell chronic lymphocytic leukaemia (B-CLL).

Searching
MEDLINE (1966 to September 2001), EMBASE (1980 to September 2001), the Science Citation Index (1981 to September 2001) and the Cochrane Library (Issue 3, 2001) were searched. In addition, the reference lists of identified studies and reviews were checked for further relevant articles, experts in the field were contacted, and internet search engines were used.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies of fludarabine (administered either intravenously or orally) in isolation as a first-line therapy at the recommended doses were included in the review. The recommended doses were 25 mg/m2 daily for 5 consecutive days in every 28 days intravenously for approximately six cycles (intravenously), or 40 mg fludarabine phosphate per m2 body surface given daily for 5 consecutive days every 28 days (orally). Fludarabine was compared with chlorambucil alone at the standard dosage; chlorambucil (intermediate dosage) plus prednisone; high-dose chlorambucil; cyclophosphamide, doxorubicin, prednisolone (CAP); or cyclophosphamide, doxorubicin, vincristine, prednisolone (ChOP).

Participants included in the review
Adults presenting with Binet stages B and C for B-CLL or Rai stages 3-4 B-CLL, who had not been previously treated for B-CLL, were included in the review.

Outcomes assessed in the review
The outcomes included in the review were: attainment of clinical response (partial and complete response); time to achieve partial or complete response; adverse effects associated with attaining that response during the course of treatment; length of progression-free survival or time to disease progression, or initiation of second-line therapy; and quality of life. Only outcomes measured objectively or using validated measurement tools were included in the analysis.

How were decisions on the relevance of primary studies made?
Two reviewers selected studies for the review. Decisions were made independently of the data extraction and before scrutiny of the results.

Assessment of study quality
Quality was assessed using the Jadad checklist, which assesses randomisation, blinding and withdrawals. In addition, the authors of RCTs were contacted for additional information. Two reviewers carried out the quality assessment using predefined assessment forms. Any disagreements were resolved by consensus.

Data extraction
Two independent reviewers extracted the data using predefined assessment forms. Any disagreements were resolved by consensus. If studies included both untreated and previously treated patients, only data for untreated patients were extracted for the analysis. If there was no stratification of the results, data for both treated and untreated patients were
Methods of synthesis
How were the studies combined?
The studies were grouped according to whether fludarabine was compared with standard regimens of chlorambucil, or compared with either non-standard chlorambucil or combination chemotherapy, and combined in a narrative.

How were differences between studies investigated?
Differences between the studies could be seen in the tables and were discussed in the text.

Results of the review
Five RCTs (n=1,919) were included in the review.

Fludarabine compared with standard chlorambucil regimen.

Based on one generally well-conducted trial, fludarabine showed a significantly higher response rate than chlorambucil (60% versus 35%, P<0.001) and induced a longer median duration of progression-free survival (20 months versus 14 months, P<0.001). There was a trend towards longer overall median survival with fludarabine than with chlorambucil, but it was not statistically significant. There were more adverse events in the fludarabine group than the chlorambucil group, particularly infections, with 16% of fludarabine patients experiencing major infections compared with 9% of the chlorambucil patients.

Fludarabine compared with non-standard chlorambucil regimen, or combined chemotherapy.

One incomplete study found little difference in the overall response rate between fludarabine and chlorambucil plus prednisone (70% versus 66%). One small study reported a benefit of high-dose continuous chlorambucil over fludarabine. However, the study was underpowered and the review authors stated that the results should be interpreted with caution.

One RCT reported no statistically significant difference in the complete response rate, or overall survival, between fludarabine and CAP. Median time to progression had not been reached at time of evaluation for the patients in the fludarabine group, and was 208 days in the CAP group. The difference between groups was statistically significant (P<0.001). There were significantly lower rates of nausea (P=0.003) and alopecia (P<0.001) with fludarabine than with CAP. Another RCT comparing fludarabine with both CAP and ChOP showed a significantly higher complete response rate with fludarabine than with either CAP (40% versus 15%, P<0.0001) or ChOP (40% versus 27%, P=0.004). There was no statistically significant difference between treatment groups for time to disease progression or overall survival. However, time to second-line therapy was better with fludarabine (45.4 months) than with CAP (25.7 months) or ChOP (32.2 months). There were significantly lower rates of nausea (P=0.003) and alopecia (P<0.001) with fludarabine than with either CAP or ChOP, but significantly higher rates of haematological side-effects.

Cost information
A cost analysis found the costs for oral fludarabine to be approximately £5,000 to £6,000. A cost-utility analysis (where the base-case scenario was set at 3 years) provided an estimate of £48,000 for the cost per quality-adjusted life-year. However, sensitivity analyses suggested that this estimate was very sensitive to changes in effectiveness and treatment costs, making it inconclusive.

Authors’ conclusions
There is early evidence of the effectiveness of fludarabine as a first-line treatment for CLL, based on a single relatively small RCT. Results regarding improved response rates and longer durations of median time to progression appear promising. The extent to which the results for intravenous fludarabine apply to oral fludarabine use, the impact of fludarabine on overall survival, the incidence, severity and duration of adverse events, and the impact of fludarabine on quality of life remain uncertain.
CRD commentary
The authors set out a clear objective at the beginning of the review, and the inclusion criteria were clearly defined in terms of the participants, intervention, outcomes and study design. Several appropriate sources were searched for relevant literature, although the authors did not state whether any language restrictions were applied to the search. Both the data extraction and quality assessment were carried out in duplicate, which helps to reduce the risk of bias. Quality was assessed using appropriate criteria. Details of the individual studies were clearly tabulated and, given the clinical differences between the studies, the narrative synthesis of the studies was appropriate. This was generally a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the priority for clinicians and patients should be to support attempts to investigate the effectiveness of fludarabine through recruitment to the Medical Research Council (MRC) CLL4 study and other new studies.

Research: The authors stated that a major trial (MRC CLL4) investigating the use of fludarabine as first-line therapy compared with chlorambucil and fludarabine plus cyclophosphamide is currently underway. This trial will provide further information about quality of life, and will be powered to detect a difference in overall survival. However, the extent to which results for intravenous fludarabine are applicable to oral fludarabine remains uncertain, and further research on the effectiveness of oral fludarabine is urgently required.

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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.