FLUDARABINE AS FIRST LINE THERAPY FOR CHRONIC LYMPHOCYTIC LEUKAEMIA

A West Midlands Health Technology Assessment Collaboration report

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Fludarabine as first line therapy for CLL

West Midlands Health Technology Assessment Collaboration (WMHTAC)

The WMHTAC produces rapid systematic reviews about the effectiveness of health care interventions and technologies, in response to requests from West Midlands Primary Care Trusts. Reviews take approximately 6 months and aim to give a timely and accurate analysis of the available evidence, with an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

Contributions of authors

Conflicts of interest

Acknowledgements

Fludarabine as first line therapy for CLL

West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the use of Fludarabine as first line therapy for chronic lymphocytic leukaemia was:

Borderline – because of the relatively high cost per QALY

Clinicians and purchasers should be encouraged to support the MRC trial.

**Anticipated expiry date: 2005
(or until such time as the MRC trial reports)**

- This report was completed in September 2002

- The searches were completed in January 2002

Fludarabine as first line therapy for CLL

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Fludarabine as first line therapy for CLL

1.   Executive summary

Description of proposed service

Fludarabine is a relatively recently developed chemotherapeutic agent, for which an oral formulation has recently become available. It is currently licensed for use in patients with B-cell chronic lymphocytic leukaemia patients with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen i.e. as a second line of treatment. In 2001, NICE issued guidance for England and Wales advising the use of oral fludarabine in these patients. This report considers the effectiveness and cost-utility of fludarabine (iv and oral) used as first-line treatment of B-cell CLL as an alternative to oral chlorambucil.

Background and epidemiology

B-Cell Chronic Lymphocytic Leukaemia (B-CLL) is a cancer of the B-lymphocytes, a type of white blood cell. It is slowly progressive, characterised by a gradual accumulation of malignant cells in blood, bone marrow and lymphatic tissues. Despite responses to treatment both first and second line, and that median overall survival is 10 years, B-CLL is widely acknowledged to be incurable. The disease most commonly occurs in older persons and the overall incidence rate in the West Midlands in 1999 was 5.10 and 2.74 per 100 000 of the European standard population for men and women respectively. The prevalence is considerably in excess of incidence due to the long median survival times of patients – overall approximately 10 years (more than 10 years in $^2/_3$ patients). The ten-year prevalence rate of cases diagnosed in the West Midlands between 1990-1999 (still alive on 01/01/2000, as at October 2001) is 46%. Specific treatment for B-CLL is generally unjustified until patients become symptomatic. On presentation of symptomatic disease progression, a hierarchy of treatments is invoked. First line treatment has traditionally involved the use of an oral alkylating agent such as chlorambucil with or without corticosteroids. However there is growing interest in the use of fludarabine as a first-line therapy.

Effectiveness - method

A systematic review of RCTs comparing fludarabine with any other agent used as first line therapy in CLL was conducted. MEDLINE, EMBASE and the Cochrane Library were searched to October 2001. The searches were supplemented by contact with experts, citation checking and Internet searches. Quality assessment using the Jadad score and data abstraction were performed in duplicate, and analysis was qualitative only with no meta-analysis

Effectiveness - results

Five trials were identified comparing the use of fludarabine to other first line therapies. One trial provided a comparison between fludarabine and the currently licensed first-line therapy, chlorambucil which was the main comparator of interest. In this trial, fludarabine was found to elicit a higher response rate compared with chlorambucil (60% vs 35%, p<0.001), and induce a longer median duration of progression-free survival (20 months vs 14 months, p<0.001). Although there was a trend towards longer median overall survival with fludarabine (66 months vs 56 months) this difference was not statistically significant. Offsetting these benefits were finding of significantly higher incidences of adverse events with fludarabine treatment compared to chlorambucil, especially with the incidence of

infections where 16% of fludarabine patients experienced major infections compared with 9% of the chlorambucil-treated patients.

Economic evaluation - methods

The economic evaluation comprised a systematic review of previous economic evaluations of fludarabine used at any stage of treatment of patients with CLL, an analysis of cost data and the development of a decision analytic model of the cost utility of fludarabine used first-line, given the appearance of a tension between potential improvements in effectiveness and increased cost of fludarabine compared to chlorambucil.

Economic Evaluation - results

There were no previously conducted evaluations of the cost-effectiveness of fludarabine as a first-line treatment for CLL. The cost analysis undertaken found that the costs for oral fludarabine were approximately £5000 to £6000, and the majority of the cost incurred by the costs of drug acquisition. The cost estimate provided is subject to some debate and uncertainty, particularly about the incidence, severity and duration of adverse events and the costs attributable to them. In previous evaluations of iv fludarabine used in second-line treatment, there was uncertainty surrounding the cost estimates; the uncertainty surrounding the cost estimate is substantially greater for oral fludarabine as the adverse events are stated to be minimal. The cost-utility analysis (where the base case scenario was set at three years) provided costs per QALY estimate of £48 000, a figure which is at the limits of what would normally be considered to be an effective use of resources by the NHS. Sensitivity analyses conducted around this estimate by manipulating the measures of effectiveness of treatment and the costs associated with treatment reveal that the base case estimate is highly sensitive to these parameters, and show that fludarabine as first-line treatment can vary from being clearly inefficient to justifiable in terms of cost utility.

Conclusions

There is early evidence of 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 evidence concerning cost utility is inconclusive. The major areas of continuing uncertainty are the extent to which the results of iv fludarabine apply to oral fludarabine use, the impact of fludarabine on overall survival, the incidence, severity and duration of adverse events as a result of oral fludarabine treatment (especially in patients given prophylaxis against adverse events), the impact of fludarabine treatment on overall quality of life, and the costs of fludarabine treatment.

Implications for research

A major trial is in progress (the MRC CLL4 trial) on the use of fludarabine used as first line therapy, compared with chlorambucil and fludarabine plus cyclophosphamide. One of the objectives of this trial is to measure quality of life directly, which should better inform future estimates of clinical effectiveness. This trial is also powered to detect a significant difference in overall survival. However it remains uncertain to what extent the results for iv fludarabine are applicable to oral fludarabine and this trial is using both regimens but not distinguishing between the two formulations. In addition, other important issues surrounding the cost of fludarabine treatment will be addressed in this report. Further research on the effectiveness and costs of oral fludarabine are urgently required

Implications for practice

The priority for clinicians and patients should be to support attempts to reduce uncertainty about the effectiveness and cost effectiveness of fludarabine through recruitment to the MRC CLL4 study, and other new studies to address issues of effectiveness and cost.

Abbreviations

As used by the authors in the specific context of this report.

AML	Acute myeloid leukaemia
BM	Bone marrow
BNF	British National Formulary
CAP	Cyclophosphamide, doxorubicin, prednisolone
CCST	Corticosteroids
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CLL	Chronic lymphocytic leukaemia
CR	Complete response/remission
CVP	Cyclophosphamide, vincristine, prednisolone
EORTC	European Organisation for Research on the Treatment of Cancer
HA	Health Authority
ICER	Incremental cost-effectiveness ratio
Iv	Intravenous
MRC	Medical Research Council
NCI	National Cancer Institute
NEED	NHS Economic Evaluations Database
PR	Partial response/remission
PS	Performance status
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Response/remission rate (overall – including partial and complete responses)
TLS	Tumour Lysis syndrome
WHO	World Health Organisation

Definitions of terms

As used by the authors in the specific context of this report.

Chemoresistant	Generally synonymous with refractory – see below
First line	Treatment options applied when patient first becomes symptomatic, often after a period of 'watchful waiting'
High risk disease	Generally synonymous with Rai stages III-IV and Binet stage C
Intermediate risk disease	Generally synonymous with Rai stages I-II and Binet stage B
Low risk disease	Generally synonymous with Rai stage 0 and Binet stage A
Recurrence	Resurgence of CLL *following a response to treatment*, usually marked by onset of new symptoms or return of previously experienced symptoms.
Refractory	Where treatment fails to bring about any response – see below
Relapse	Synonymous with recurrence – see above
Remission	Improvement in disease, including clinical factors and symptoms.
Response	Improvement brought about by treatment following a recurrence. There is no standard definition for the terms partial and complete response and therefore these should be described in studies. Complete response *is not* synonymous with cure.
Response - nodular	Defined as only evidence of disease was lymphoid nodules in bone marrow without evidence of diffuse or infiltrative pattern.
Second line	Treatment options applied when patients have relapsed/recurred following, or proved refractory/chemoresistant to, first line treatment options – see above
Stage	Used to predict prognosis and stratify patients. No standard system exists but most commonly used are Rai and Binet systems based on factors such as lymphocytosis, anaemia, thrombocytopenia and areas of lymphoid involvement.
Third line	Treatment options applied when patients have relapsed/recurred following, or proved refractory/chemoresistant to, both first and then second line treatment options – see above

2.   Aim of the review

2.1 The technology

Fludarabine (Fludara®) is a synthetic adenine nucleoside analogue, which is currently indicated for the treatment of patients with B-CLL who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent containing regimen. It can be administered either intravenously or in a tablet form, the latter of which was licensed for use in January 2001.

2.2 The condition

B-Cell Chronic Lymphocytic Leukaemia (B-CLL) is a cancer of the B-lymphocytes, a type of white blood cell. It is slowly progressive, characterised by a gradual accumulation of malignant cells in blood, bone marrow and lymphatic tissues.

2.3 Objective of the report

The aim of this report is to review the available literature on the use of fludarabine as a first-line treatment for B-CLL.   Fludarabine as second-line therapy has recently been the subject of NICE guidance[1]. This guidance highlighted that fludarabine as first-line therapy would be a topic whose research would need to be reviewed. The review process will incorporate a systematic review on the evidence on effects and effectiveness and an assessment of cost-effectiveness based on a decision analytic model.

3.   Background

3.1 Chronic lymphocytic leukaemia (CLL) - Description

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in adults. The disease is a malignant disorder of the lymphocytes. Lymphocytes are of two main types – B-lymphocytes and T-lymphocytes. CLL most commonly arises from a malignant clone of immune-incompetent B-lymphocytes with a characteristic phenotype. Thus, the vast majority of CLL is B-CLL, which is the condition of interest.

The disease is far from uniform in presentation and clinical course. Approximately one third of patients never require treatment for CLL and die from causes unrelated to CLL, another third present with initial indolent disease which is followed by progression to requiring treatment (on presentation of symptoms) and another third require immediate treatment for aggressive disease. Disease progression is characterised by a gradual accumulation of malignant cells in blood, bone marrow and lymphatic tissues. This results in impairment in the production and function of normal blood cells, particularly the red blood cells, platelets and white blood cells. These impairments become manifest as anaemia, thrombocytopenia, and immunosuppression respectively. The disease can also cause enlargement of lymph nodes.

The patient's doctor often diagnoses CLL when a routine blood test reveals lymphocytosis (very high levels of lymphocytes in the blood). Although patients may initially respond to first-line therapy, all patients will ultimately relapse and will receive second-line or salvage

chemotherapy with another regimen or combination of regimens. Despite good responses to second-line treatment, many patients will die of progressive disease.[2] Although median overall survival is 10 years, CLL is widely acknowledged to be incurable, because the malignant cells are never completely eliminated from the body with currently available treatments.

Chemotherapy is generally reserved for patients with intermediate (Binet Stage B; Rai Stage I or II; see Tables 1 and 2) or advanced (Binet Stage C; Rai Stages III or IV; see Tables 1 and 2) disease. Patients with indolent disease classified as Rai Stage 0 or Binet Stage A are monitored using a policy of "watchful waiting" and receive therapy when there is evidence of disease progression causing symptoms. There appears to be no overall survival benefit for early initiation of treatment in this group with chlorambucil, which is the standard first-line treatment for B-CLL, confirmed by a meta-analysis.[3] Patients with intermediate stage disease can also be monitored without treatment until signs of disease progression are evident, but Binet Stage B patients usually begin treatment. Low risk (indolent) disease, corresponding to Rai stage 0 and Binet stage A, has an expected survival of 10 years; intermediate risk disease (Rai I and II, Binet B) has median survival of between 7 and 9 years; and high risk disease (Rai III and IV, Binet C) has a median survival of 5 years. More than 25% patients with low risk disease die of unrelated causes, while in 40% of all patients, disease progresses to a more advanced stage. Ultimately, 50% patients require treatment at some time for symptomatic disease.

The main objectives of treatment are to prolong and maximise quality of life by inducing long-term remission, to successfully treat symptoms arising from disease progression and to accomplish this with minimum treatment side effects. Specific anti-cancer treatment does not commence until the disease becomes symptomatic. Established first-line therapies (i.e. when the patient first presents with symptoms of the disease which require specific anti-cancer treatment) include chlorambucil, cyclophosphamide, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and CAP (cyclophosphamide, doxorubicin and prednisolone). Chlorambucil is regarded in the literature and by clinicians as the standard first-line therapeutic regimen for B-CLL. Fludarabine is also increasingly being considered as a first-line therapy, and it appears that this agent may induce a higher response rate, and patients may remain asymptomatic for longer periods of time, which may lead to an improved quality of life during that time.

3.2 Chronic lymphocytic leukaemia (CLL) - Epidemiology

CLL is the most common leukaemia in adults. In 1999, (according to the West Midlands Cancer Intelligence Unit) there were 82 deaths from CLL in the West Midlands (55 men and 27 women). There were 261 new cases (151 men, 110 women) of B-CLL diagnosed in the West Midlands in 1999 and it is most common in older persons, with the average age of diagnosis being 64 years. It appears to be nearly twice as common in men than women. The overall incidence rate in the West Midlands Region in 1999 was 5.10 and 2.74 per 100,000 of the European Standard population for men and women respectively (information supplied by the West Midlands Cancer Intelligence Unit). This suggests that in an average health authority (HA) with a population of 500,000 persons there will be approximately 18 new cases each year.

The prevalence is considerably in excess of incidence due to the long median survival times of patients – overall approximately 10 years (more than 10 years in $^2/_3$ patients). The ten-year prevalence rate of cases diagnosed in the West Midlands between 1990-1999 (still alive on

01/01/2000, as at October 2001) is 46%. Of a total of 1949 patients, 1057 patients had died and 892 were still alive (information supplied by the West Midlands Cancer Intelligence Unit).

3.3 Chronic lymphocytic leukaemia (CLL) - Aetiology

The causes of CLL are largely unknown. Risk factors may include genetic abnormalities e.g. amplification leading to Trisomy 12, which may be present in one third of CLL patients and exposure to carcinogens such as benzene and cigarette smoke.

Prognostic assessment of B-CLL patients is generally based on either the Binet or Rai clinical staging systems. [4,5] These two different staging systems (outlined in Tables 1 and 2) typically enables the division of patients with CLL into three prognostic groups on the basis of severity of disease by the number of main effects present, and has improved clinician's ability to identify patients who need immediate treatment.

Table 1 - Binet staging system for CLL

Stage A	No anaemia; no thrombocytopenia; fewer than 3 lymphoid areas enlarged
Stage B	No anaemia; no thrombocytopenia; 3 or more lymphoid areas enlarged
Stage C	Anaemia (Hb <10g/dl) and or platelets $<100 \times 10^9$/L

Table 2 - Rai staging system for CLL

Low risk	Stage 0	Lymphocytosis in blood ($>5 \times 10^9$/L) and marrow (>30%)
Intermediate risk	Stage I	Lymphocytosis in blood & marrow with enlarged lymph nodes
	Stage II	Lymphocytosis in blood & bone marrow with enlarged spleen and/or liver (with or without enlargement of nodes)
High risk	Stage III	Lymphocytosis in blood and bone marrow with anaemia
	Stage IV	Lymphocytosis in blood & bone marrow with thrombocytopenia (platelets $<100 \times 10^9$/L)

The International Workshop on CLL (IWCLL) has recommended integrating the Rai and Binet systems based on the following equivalence; Binet stage A = Rai stages 0-II, Binet B = Rai I-II and Binet stage C = Rai stages III-IV.

Although clinical staging is the most important prognostic factor, with over 90% of Binet stage A patients surviving for five years,[6] other biological parameters which reflect the clinical heterogeneity of disease have been under investigation. These include the pattern of bone marrow infiltration by malignant cells, tumour cell proliferation, immunophenotype, and higher levels of particular biological markers in blood serum.

It appears that even though the prognostic assessment of patients with CLL is generally based on clinical staging systems, there is the possibility that newer markers may improve assessment of prognosis, which may in turn aid clinicians in establishing treatment regimens for patients. Some of these markers include soluble CD44, the antigen CD14 and beta2-

microglobulin and soluble CD23.[7,8] The use of these biological markers may be incorporated into clinical-prognostic models and may result in further stratification of Rai Stage 0-II patients and Binet Stage A patients, who are typically monitored by "watchful waiting" until the presentation of symptoms of disease progression, such as anaemia and bleeding. A subsequent possibility is the revision of treatment strategies for these patients who have been diagnosed with indolent CLL, who are currently not being treated for CLL but whose prognosis (due to the presence of increased levels of the markers outlined above) is worse than for those who do not present with increased levels of these markers.

3.4 Treatment - Established first-line treatments

It has been widely acknowledged that specific treatment for B-CLL is generally unjustified until patients become symptomatic.[3] Patients are thereby monitored using a strategy of "watchful waiting", and this may in some cases extend over a period of years.   When symptomatic disease progression occurs (requiring specific treatment for B-CLL), first-line treatment is initiated.

On presentation of symptomatic disease progression, a hierarchy of treatments is invoked. The order of which treatments are given in the hierarchy reflects a balance between the chance of reversing progression and the level of side-effects likely to be suffered by the patient in achieving the desired clinical response.

First line treatment has traditionally involved the use of an oral alkylating agent such as chlorambucil with or without corticosteroids. Occasionally cyclophosphamide may be used as an alternative. However there is growing interest in the use of fludarabine as a first-line therapy.

3.5 Treatment - Chlorambucil as first-line treatment

The CLL Trialists Group[3] conducted a meta-analysis on the effects on survival of single-agent chlorambucil compared with combination regimens of cyclophosphamide/vincristine/prednisone (COP) and cyclophospahmide/vincristine/prednisone/doxorubicin (ChOP). Ten trials in which data was available for 2022 patients were included. There was no difference between chlorambucil compared with the combination regimens for five-year survival (both 48%, difference 0%, 95% CI -6%, 5%). In addition, the early inclusion of an anthracycline with chlorambucil was also shown not to improve survival compared with treatment with chlorambucil alone.[3] Also of note was that in the trials included, the combination regimens did not produce high response rates.

In a randomised controlled trial, Jaksic et al[9] examined the use of high-dose chlorambucil in 228 previously untreated patients and compared this treatment to ChOP treatment. An overall response of 89% was attained for the high-dose chlorambucil patients compared with 75% for the patients receiving ChOP (p<0.001). At a median follow-up time of 37 months, median overall survival for the high dose chlorambucil patients was 68 months compared with 47 months for the ChOP patients (p<0.005). Low incidences of toxic side effects were also reported for both treatment arms of the trial.[9] This is in contrast to the experience of clinicians who have voiced concerns about toxicity levels of this regimen and have indeed reported high levels of toxicity with the use of the standard dosage of chlorambucil.[10]

From this analysis it appears that chlorambucil is the standard first-line treatment of choice to induce a remission by successfully treating the symptoms arising from progression of B-CLL from an indolent disease (where the patient is monitored by a watchful waiting strategy) to a disease state where treatment for symptomatic disease is required. However, there is no evidence that the use of chlorambucil prolongs length of overall survival compared to other first-line treatments.

3.6 Current service cost

The chronic and slowly progressive nature of B-CLL and the long duration of the disease suggest that both at an individual and a population level it is responsible for a considerable amount of morbidity and mortality associated both with the disease and the side effects of chemotherapeutic treatment.

Because treatment of CLL is part of general haematological or oncology services, the cost of caring for this group of patients is very difficult to derive from routine financial information available in the NHS. However, consideration of the long duration of disease and the variety of treatments to which an individual might be exposed to over the course of their illness, suggests that the costs of caring for CLL are likely to be considerable.

3.7 Fludarabine – Description of new intervention

Fludarabine (Fludara®) is manufactured by Schering Health Care Limited. It is a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. It is an antimetabolite preventing normal cellular division.

3.7.1 Intravenously administered fludarabine

The use of intravenous fludarabine was licensed for use in the UK in August 1994 for the 'treatment of patients with B-cell CLL with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen' i.e. as second line therapy. It had been previously licensed in the US, by the Food and Drug Administration in April 1991 from Berlex Laboratories Inc. under the trade name Fludara® for 'patients with B-cell CLL who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen'.

In addition to general guidance for use of cytotoxic drugs (see Appendix 1), the British National Formulary (BNF)[11] states the following specifically for fludarabine:

> "Fludarabine is recommended for patients with B-cell chronic lymphocytic leukaemia (CLL) after initial treatment with an alkylating agent has failed; it is given intravenously daily for 5 days every 28 days. Fludarabine is generally well tolerated but does, however, cause myelosuppression which may be cumulative. CNS and pulmonary toxicity, visual disturbances, heart failure, and autoimmune haemolytic anaemia have been reported rarely."

3.7.2 Orally administered fludarabine

Oral fludarabine has been licensed for use in Britain since January 2001, but to be used in the same way as intravenous fludarabine. The recommended dose for of Fludara tablets is 40mg

fludarabine phosphate /m^2 body surface given daily for five consecutive days every 28 days. Studies providing evidence on the bioavailability of oral fludarabine and the equivalence of the oral preparation with the intravenous preparation shows that oral fludarabine are likely to elicit a similar clinical response to the intravenously administered preparation of fludarabine[12].

Guidance on the use of fludarabine from the National Institute of Clinical Excellence released in September 2001 recommends the use of oral fludarabine for patients either failing or intolerant of first-line chemotherapy who would have otherwise have received combination chemotherapeutic regimens of ChOP, CAP or CVP.[1] The oral preparation of fludarabine has a more favourable cost-effectiveness profile compared to intravenously administered fludarabine and is therefore preferred to the intravenous preparation of fludarabine on this basis.

Although fludarabine has been licensed only for use as a second-line therapy, many clinicians consider fludarabine to be particularly useful as a first-line agent. Communication with some clinicians indicates that the drug is commonly used in first-line therapy. In addition, there is one major on-going trial[13] in the UK that is evaluating the use of fludarabine as a first-line therapy in which many of these clinicians are involved.

3.8 Fludarabine - Effectiveness evidence of as second line treatment

A recent systematic review by Hyde et al[14] investigated whether the use of fludarabine (in its licensed indication as second-line therapy) should be supported and further encouraged, by comparing the effectiveness of fludarabine to other second-line therapies for B-CLL. As stated previously, second-line treatment usually consists of an anthracycline containing chemotherapy regimen such as CHOP or fludarabine.

The searches in this apparently well-conducted, comprehensive systematic review identified two RCTs but only one of these contributed data to the analysis.[15] Though the reviewers concluded that this RCT was well conducted, it was small, comparing disease progression, survival and adverse events in 48 previously treated patients given fludarabine with 48 treated with CAP (a combination therapy regimen comprising cyclophosphamide, prednisone and doxorubicin). Overall response rates were 48% for the fludarabine treated patients compared to 27% of the patients treated with the CAP regimen.[15] The 95% confidence interval for the 21% difference in response observed ranged from +2% to +40%.[15]

The time to progression in responders was increased from a median of 179 days for the patients treated with CAP to 324 days for the fludarabine-treated patients. However this difference was not statistically significant (p=0.22). There were no differences observed in overall survival. The incidence of non-haematological side-effects, especially alopecia, was statistically significantly less.

Although the results from the RCT included in this review show benefit of fludarabine compared to CAP, the reviewers acknowledged that it was necessary to interpret the findings with caution given the small size of the only RCT identified and the large confidence intervals around the difference in response rate.[14] Greater numbers of fatal adverse events during treatment with fludarabine which were not statistically significant and variability in the results of case-series considered in the review were also noted. However, qualitatively it appeared that the balance between beneficial effects and adverse events favoured fludarabine over CAP for second-line treatment. Clinical experience, particularly regarding adverse event profiles,

supported this and suggested that the benefit for fludarabine in comparison with CAP, also applied to the more commonly used anthracycline-containing regimen, CHOP.

3.9 Fludarabine - Side effects of treatment

Although the immediate side effects (nausea, vomiting and alopecia) of fludarabine treatment in second-line treatment of B-CLL have been shown to be less troublesome than CAP[15] adverse haematological events have been reported in the literature.

Myelosuppression is the major dose-limiting effect associated with fludarabine treatment. The most frequent infectious complications associated with fludarabine treatment are respiratory tract infections and fever.[16] There have also been a number of reports of opportunistic infections including *Pneumocystits carinii* pneumonia and *Listeria monocytogenes* infection. In saying that, many of these opportunistic infections developed in patients who were treated with a combination of fludarabine with prednisolone. The results of some studies indicate that a sustained reduction in T lymphocyte count (especially CD4+ cells) may contribute to the increased incidence of infectious episodes associated with fludarabine therapy.[17]

Given that the most important long-term adverse effect is immunosuppression, prophylactic antibiotic treatment is recommended against *pneumocytis carinii* pneumonia. The British Committee for Standards in Haematology has also recommended that fludarabine treated patients should receive irradiated blood products to avoid transfusion-related graft-versus-host disease. Due to the additional lymphocytic activity, the use of concurrent corticosteroids increases this risk and therefore should be avoided unless otherwise indicated.

Autoimmune haemolytic anaemia (AIHA) is also relatively common in patients with B-CLL which is often severe, difficult to treat and potentially lethal. Myint et al[18] reported the development of AIHA in 12 of 52 patients with CLL who were treated with fludarabine. Of these 12 patients, only three had a previous history of haemolytic anaemia and six of eight patients experienced an exacerbation of AIHA when re-treated with fludarabine subsequent to attaining control of their haemolysis.[18]

Isolated cases of tumour lysis syndrome (TLS) have been reported in the literature.[19] In most cases TLS was successfully treated and did not recur when subsequent fludarabine treatment was preceded by prophylactic measures comprising hydration and allopurinol.[19] For mild renal impairment (associated with TLS), dose reduction is suggested; and avoidance is suggested if creatinine clearance is <30ml/min.

4. Clinical effectiveness

4.1 Clinical Effectiveness - Methods

This review was designed to build on the NHS HTA report and adheres to guidance on undertaking systematic reviews and health technology assessments (CRD report No.4). Further details on the WMHTAG approach are available (DES Handbook)

4.1.1 Search Strategy

A broad comprehensive search for studies assessing the effectiveness of fludarabine was undertaken involving:

- Electronic bibliographic database searches ; MEDLINE (Ovid) 1966-September 2001; Embase (Ovid) 1980-September 2001; Science Citation Index (Web of Science) 1981-September 2001; Cochrane Library 2001 Issue 3
- Citation checking of studies and reviews obtained
- Contact with experts in the field
- Internet search engines

4.1.2 Inclusion and exclusion criteria

Types of studies: RCTs only. In the event of no RCT being identified, we would have expanded our search and included other study designs in our assessment of effectiveness.

Intervention: Fludarabine (administered either intravenously or orally) in isolation as a first line therapy at the recommended dosages given on the product information sheet i.e. 25 mg/m^2 daily for five consecutive days in every 28 days intravenously for approximately six cycles (intravenously) or 40mg fludarabine phosphate /m^2 body surface given daily for five consecutive days every 28 days (orally).

Comparator: The agent chlorambucil, at a recommended dosage of 40mg/m^2 once every 28 days. Other dosage regimes including differing dosages of chlorambucil in isolation or in combination with other agents were considered for the purposes of this review as a different comparator to chlorambucil at the above recommended dosage. This is because the side effects elicited by these combinations may be different from chlorambucil at the licensed and recommended dosage. Comparison with other agents used as first-line were also considered, but were not the main focus of the review. The studies assessing the comparisons of fludarabine with non-standard chlorambucil regimes and other drug combinations used first line are described in Appendices 7-9.

Population: Adults presenting with Binet stages B and C for B-CLL or Rai stages 3 -4 B-CLL, who have not been previously treated for B-CLL.

Outcomes: Attainment or otherwise of a clinical response (partial and complete response), time to achieve partial or complete response, any adverse effects associated with attaining that response during the course of treatment, length of progression-free survival/ time to disease progression or initiation of second-line therapy, and any quality of life measurements.

Two reviewers applied the inclusion and exclusion criteria to the trials (SH & BW). Decisions were made independently of the data extraction and prior to the scrutiny of results.

4.1.3 Quality assessment strategy

The quality of the RCTs was assessed using the Jadad checklist.{Jadad} In addition we attempted to contact the authors of the RCTs for further information, but only two authors responded

Data abstraction and quality checking will be conducted using pre-determined assessment forms. Quality checking will be conducted with another reviewer and any differences will be resolved by discussion. Data will only be included in the final analysis for outcomes measured objectively or use validated measurement tools.

4.1.4 Data extraction strategy

Data concerning study characteristics, study quality and results were extracted independently by two reviewers (SH and BW) using a series of pre-determined assessment forms. Any differences were resolved by consensus.

4.1.5 Analysis

As fludarabine was to be compared to a variety of differing first-line treatments for B-CLL, the method of analysis was qualitative, and meta-analysis was not employed.

4.2 Clinical Effectiveness - Results

4.2.1 Quality and quantity of data available

The searches identified 177 studies. By applying the inclusion criteria documented above, 43 studies were selected as potentially relevant on the strength of their title and their full text obtained.   Studies clearly identifiable by their abstract as reviews, biochemical/pharmacological based laboratory tests and case series were excluded at this stage.

There were five RCTs included.[15,20-23] Reasons for exclusion of the remaining 15 were that the studies were not randomised controlled trials or that the trials did not include an assessment of the effectiveness of fludarabine or that the patients had been previously treated. If a trial included both untreated patients and previously treated patients, the data for the untreated patients was extracted for analysis. In the event where there was no stratification of results (i.e. adverse events) the data of both treated and untreated patients was extracted *in toto*. Where full results were not available, as much data relating to results and quality of the study was extracted.

Of the five included RCTs, three trials[15,20,23] had been fully reported in peer-reviewed journals while the remaining two studies were abstracts from conference proceedings of the IWCLL meeting in 1999.[21,22] We have additional information on the Jaksic et al[21] trial from published protocols. [24] In Figure 1, A flow diagram outlining the identification of the RCTs included in the review is given below in Figure 1:

Figure 1 - Identification of RCTs included in systematic review of effectiveness

Medline   198 hits
Cochrane   57 hits
Embase   75 hits
Cinhahl   2 hits
Drug company/authors   2 hits
Conference Abstracts   2 hits

Total 336

310 rejected on the basis of title/abstract

20 obtained

5 Included RCTs   **15 excluded**

13 case series
3 letters discussions
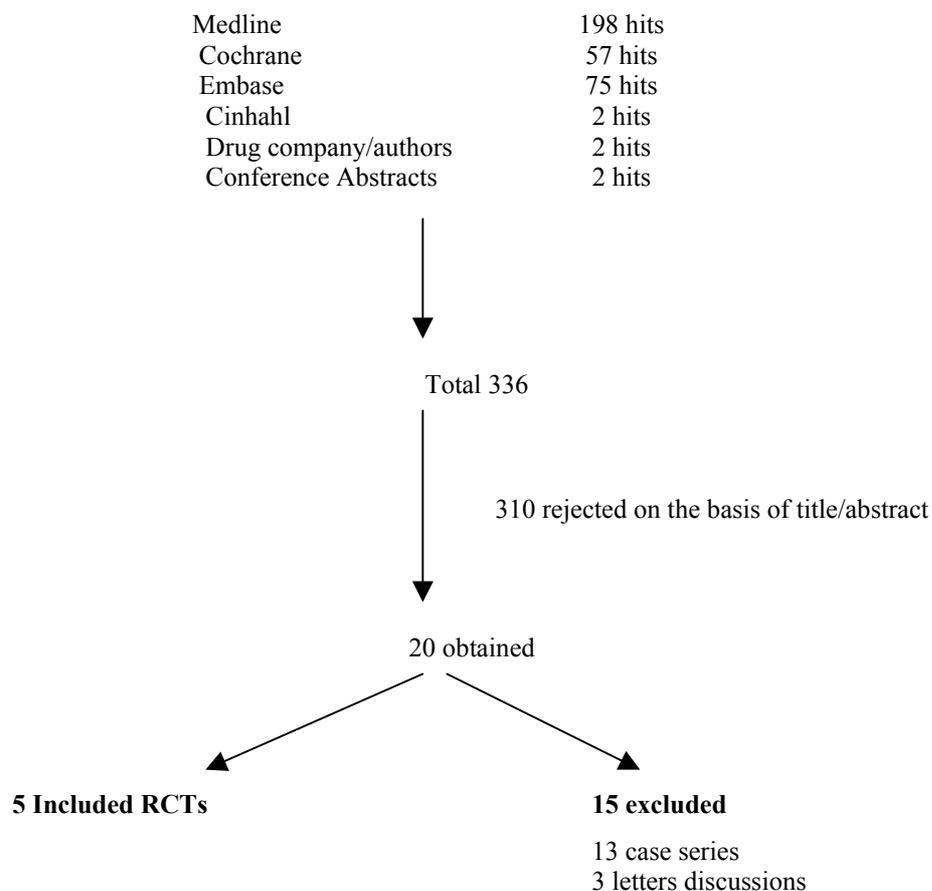
Of the 5 included RCTs, one by Rai et al[20] was of particular relevance, comparing fludarabine with chlorambucil. For this reason the report concentrates on this study which is described in full in the following section. The other four trials of less direct relevance, which examined the effectiveness of fludarabine used first line, but in comparison with either non-standard chlorambucil regimens or combination chemotherapy, are in contrast briefly summarised in the main text with full details being provided as appendices.

4.2.2 Effectiveness of fludarabine compared with chlorambucil alone at standard dosage

Included study characteristics

The trial conducted by Rai et al[20] compared fludarabine using a standard dosage regime with chlorambucil in patients who had received no prior therapy for B-CLL, for whom their disease was classified as Rai stages I-II (provided participants were symptomatic or had specific risk factors) or III-IV. This comparison was part of a three-arm trial, which also compared the effectiveness of a combined regimen of fludarabine, plus chlorambucil to the fludarabine and chlorambucil in isolation. Recruitment to the combined arm was however stopped early. A total of 195 were allocated to fludarabine, which was given in standard dosage ($25mg/m^2/d$ for 5 days repeated every 28 days) for a maximum of 12 cycles. 200 were allocated to chlorambucil, also given at standard dosage ($40mg/m^2$ once every 28 days) for a maximum of 12 cycles. In both cases the drug was stopped if there was disease progression, complete

remission or a response that reached a plateau over two months of treatment. The only specified prophylaxis for each treatment arm was allopurinol. Switching from fludarabine to chlorambucil or chlorambucil to fludarabine was allowed if there was no partial response, if disease progression occurred, or if the patient relapsed within 6 months of stopping the initially allocated drug. Specified outcomes were disease response, progression-free survival, overall survival, toxicity and quality of life. The latter consisted of assessment of need for transfusion, incidence of infection and performance status. The primary outcome was progression-free survival. A power calculation was conducted; the target number of patients for the trial as a whole (544) including an additional combined fludarabine plus chlorambucil arm was exceeded. The characteristics of this trial are outlined in Table 3.

Quality Assessment

The study was generally well conducted. Allocation was likely to have been concealed and there was minimal loss to follow-up for the outcomes reported. The study was open to detection bias through lack of blinding. However, this was offset somewhat by centralised review being required for specimens from patients who had a complete remission. Some outcomes are missing for the group randomised initially to receive the combination regimen of fludarabine plus chlorambucil. The quality assessment for this study is shown in Table 4.

Disease response rates

The rates of complete response and partial response were significantly higher in both groups treated with fludarabine(60% for fludarabine, 55% for fludarabine plus chlorambucil) than chlorambucil (35%) (p<0.001 for both). However there was no significant advantage to treatment with a combination regimen of fludarabine and chlorambucil compared to fludarabine with respect to response rates.

Table 3 - Characteristics of RCT comparing fludarabine to chlorambucil alone at standard dosage

First author, year	Rai, 2000[20]		
Aim	Two arm comparison of Fludarabine with chlorambucil, and a combination regimen of fludarabine plus chlorambucil.		
Number randomised	544		
Inclusion criteria	>18 yrs old, no previous treatment for B-CLL, stage 3 or 4 B-CLL. Rai stage 1-2 if had 1 of: weight loss, night sweats, extreme fatigue, lymphadenopathy, splenomegaly, hepatomegaly, >50% increase lymphocytes over 2 months EOGPS of 0,1 or 2. Baseline liver/kidney function >1.5x normal Requiring treatment Negative Coombs test		
Exclusion criteria	Any previous treatment		
Demographics	**Flu**	**Chl**	**Flu + Chl**
	179	183	137
	64 (33-88)	62 (36-89)	63 (32-83)
	71%m	67%m	66%m
	88% white	87% white	91% white
	61% Rai 1-2	59% Rai 1-2	61% Rai 1-2
Follow-up: Adequate (target <10% unreported) Length	35/409 Adequate Median duration of follow-up: 62 months		
Intervention	Flu (25mg/m^2 total body surface area, IVD, d 1-5, p/28 days, max.12 cycles		
Comparator	Chlorambucil (40mg/m^2 po, 1x p/28days), max. 12 cycles Fludarabine (20mg/m^2 total body surface area, IV, days 1-5, p/28days) with Chlorambucil (20mg/m^2 po, 1x p/28days), max. 12 cycles		
Concomitant Rx:	All patients: 300mg oral allopurinol p/day for 9 days commencing 1 day before treatment through to day 8 during each treatment cycle for first three cycles		
Pre-treatment tests:	Blood smears, bone marrow aspirates, biopsy for central pathological review		
Outcome measures	Response rates*, overall survival, response according to stage, side effects		
Response definitions CR = Complete remission PR = Partial remission PD = Progressive disease SD = Stable disease	CR: Absence of lymphadenopathy, splenomegaly, hepatomegaly and constitutional symptoms on examination; absolute neutrophil count >1500 p/cm^3, platelets>100 000cm^3, haemoglobin>11g p/dcl (without transfusion), absolute lymphocyte count<4000p/cm^3; bone marrow of normal cellularity, with <30% lymphocytes and no lymphoid nodules. PR: decrease>50% in lymph node, spleen and liver size (if enlarged before therapy); decrease> 50% peripheral blood lymphocytes from pre-treatment value; absolute neutrophil count >1500 p/cm^3 or increase>50% over pre-treatment value, platelets>100 000cm^3 or increase>50% over pre-treatment value, haemoglobin>11g p/dcl or 50% increase over pre-treatment value (without transfusion). PD: increase>50% lymph node, spleen and liver size (if enlarged before therapy or detection of enlarged if not enlarged pre-treatment); or both SD: None of the above criteria being met		
NOTE: * Denotes primary outcome			

Table 4 - Quality assessment of RCT comparing fludarabine to chlorambucil alone at standard dosage

Elements of Jadad score	Rai et al[20]
A. Generation of allocation schedule	
A1 *Was the trial described as randomised?*	Yes
A2 *Was allocation truly random? or*	Yes
Was allocation quasi-random? or	No
Was allocation systematic? or	No
Was the method of randomisation not stated or unclear?	No
B. Concealment of treatment allocation	
B1 *Was concealment adequate? or*	Yes
Was concealment inadequate? or	No
Was concealment unclear?	No
C. Implementation of masking	
C1 *Was the trial described as "double-blind"?*	No
C2 *Was the treatment allocation masked from the participants?*	No
	No
C3 *Was the treatment allocation masked from the investigators?*	Unclear
C4 *Was treatment allocation masked at the outcome assessments?*	
D. Completeness of the trial	
D1 *Were the number of withdrawals in each group stated?*	Yes
D2 *Was an intention-to-treat analysis performed?*	Yes
D3 *What were the drop-out rates in each group of the trial for each of the main outcomes?*	Generally: Fludarabine 7/179 Chlorambucil 10/193 Progression-free survival restricted to responders
D4 *Are there substantial differences in completeness between the groups?*	No
Total Jadad score (maximum 5)	3

Duration of progression free survival and time to progression

There was a significantly longer duration of response for the 107 patients (who achieved a complete or partial remission) who received fludarabine as a first-line treatment by itself than with the 67 patients (who achieved a complete or partial remission) who were treated with chlorambucil alone (25 months for fludarabine, 14 months for chlorambucil, p<0.001). In addition, there was a significantly longer time to progression for patients who achieved a complete or partial response to fludarabine compared with chlorambucil (20 months vs. 14 months p<0.001), and these differences were also evident on examination of responses by stage.

Table 5 - Results of RCT comparing fludarabine to chlorambucil alone at standard dosage

	Fludarabine	Chlorambucil	Fludarabine plus Chlorambucil	Comments
Number entered into study	195	200	149	Accrual into the fludarabine + chlorambucil was halted when interim analysis found unacceptably high levels of toxic side effects. No differences between fludarabine and chlorambucil groups at baseline.
Drop-outs/exclusions before assessment	15 ineligible, 1 dropped out before assessment	7 ineligible, 0 drop outs before assessment	10 ineligible, 2 dropped out before assessment	
Losses to follow-up	9	7	13	
Number randomised	179	193	137	
Number of patients evaluated for response	170 (173 for progression-free survival)	181 (183 for progression-free survival)	123	
Evaluated as intention-to-treat	Yes			
Clinical response rates (CR + PR)	107/179 = 60%	67/193 = 35%	75/137 = 55%	Difference between fludarabine and chlorambucil = 25%, (95% CI 15%, 35%) (p<0.001 for both comparisons)
Follow-up period	Median duration of follow-up was 62 months.			
Median duration of response$^\xi$	25 months	14 months	Not given	P (log rank) <0.001, Significantly favours fludarabine
Median time to progression	20 months	14 months	Not given	P (log rank)<0.001, Significantly favours fludarabine
Median overall survival	66 months	56 months	55 months	P [log rank] =0.1 Not statistically significant, but shows trend towards longer overall survival with fludarabine
Patients evaluated for adverse events$^\xi$	170	178	129	No statistically significant difference in overall survival among the three groups.
Overall survival one year after treatment	155	172	117	
Overall survival two years after treatment	140	147	106	
Overall survival three years after treatment	124	132	94	
Overall survival four years after treatment	95	101	70	
Overall survival five years after treatment	60	52	44	
Deaths during Rx	1	0	0	No difference
Thrombocytopenia**	22/170 = 13%	25/178 =14%	55/149 = 43%	1% (95%CI -8% to 7%)
Neutropenia**	46/170 = 27%	34/178 = 19%	64/149 = 43%	8% (95% CI -1% to 17%)
Infection**	27/170 = 16%	16/178 = 9%	48/129 = 28%	7%(95% CI 0% to 14%)
Differences in side effects	Differences in side effects favours chlorambucil.			

*   Denotes statistical significance

** Proportion of patients with severe (grade 3) or life threatening (grade 4) side effects

$^\xi$ Results available only for those who gained a complete or partial remission

Overall survival

There were no differences in overall survival amongst the three groups (p = 0.21) or between the chlorambucil group and the fludarabine group. The median survival times for the groups receiving fludarabine, chlorambucil and fludarabine plus chlorambucil were 66, 56 and 55 months respectively, not statistically significant, but showing a trend favouring fludarabine.

Toxicity and side effects

All side effects of treatment were graded on a six point scale with 0 defined as none, 1 as mild, 2 as moderate, 3 as severe, 4 as life-threatening and 5 as lethal. Most of the recorded side effects were classified as being of grade 1 or 2. The two single-drug regimens used in two arms of this three-arm trial were said to be "well tolerated" by the authors of the trial. The criteria used in the assessment of the occurrence of infection was hospitalization for treatment of infection or need for parenteral antibiotics. This was assessed on retrospective review of case-notes, and 16% of 170 patients evaluated for adverse effects in the fludarabine group had major infections, compared to 9% of 178 patients in the chlorambucil group (difference 8%). Therefore it is possible that the incidence of infection may have been higher for the fludarabine group, especially in those who were lost to follow-up. Indeed, the rates of incidence of grade 3 and 4 neutropenias were higher in the fludarabine group than the chlorambucil group.

Quality of life

This was claimed to be assessed, and included need for transfusion, incidence of infection and performance status. Data on incidence of infection was as given above. No data was reported concerning need for transfusion and performance data, despite further enquiry of the lead author. Data on performance and transfusion data would have been helpful in informing cost estimates and the degree to which beneficial effects such as improved response times and longer duration of progression-free survival are offset by adverse side effects.

Discussion of results

This study by Rai et al[20] is crucial to the examination of the effectiveness of fludarabine as a first-line therapy. It was the only fully reported randomized controlled trial to make a comparison between fludarabine and chlorambucil, the currently best accepted first-line therapy, in the population of interest.

The key points were:
- This was a relatively small trial.
- The study was generally well conducted. The study was open to detection bias through lack of blinding, but this was offset somewhat by central review being required for specimens from patients who had a complete remission.
- Accrual was stopped into the fludarabine plus chlorambucil group when an interim analysis showed unacceptably high levels of life-threatening toxic side effects associated with fludarabine plus chlorambucil treatment.
- For both groups using fludarabine (60% for fludarabine alone, 55% for fludarabine plus chlorambucil), the rates of complete remission and response rates (complete remission plus partial remission) were significantly higher than those for chlorambucil (35%) alone (p<0.001 for both comparisons).

- This benefit appears to be offset somewhat by the increased incidence of adverse side effects, the profile of which favours chlorambucil (especially infections where there was a higher incidence of major infections associated with fludarabine treatment (29% vs 17%; diff +12%; 95% CI +4%, +20%). In addition, there was a higher incidence of haematological side effects e.g, grade III or IV infections (16% vs 9%; diff +7%; 95%CI 0 to +14%)
- The data for the progression-free survival (20 months vs 14 months; p<0.001) also favours fludarabine alone over chlorambucil alone. However, this data by definition only applies to patients who responded to treatment.
- Although there was a trend towards longer overall survival with a median overall survival of fludarabine of 66 months compared to chlorambucil (median overall survival; 55 months) this difference was not statistically significant (p=0.1).
- Although nett benefit for those who respond to fludarabine is clear, there is limited information about the balance of benefit and harm in the non-responders.
- There was limited information on impact on quality of life.

4.2.3 Effectiveness of fludarabine compared with other first line therapies

Four trials were identified that compared fludarabine to other chemotherapeutic regimes used in CLL.[15,21-23] For full results and discussions of each trial see Appendices 7-9.

Two of these trials compared the use of fludarabine as first line therapy to high-dose chlorambucil[24] and chlorambucil plus prednisolone.[22] Although the comparisons included chlorambucil, the variation in dosage schedule and amount means that it elicits varied effects and cannot be considered in the main part of the review with the comparison of chlorambucil at the recommended dosage of $40mg/m^2$ once every 28 days. In the Jaksic et al study, a higher response rate was observed with high dose chlorambucil compared with fludarabine, but this was offset by a higher rate of adverse events for the high-dose chlorambucil arm of this trial.[21] This study was underpowered, small and little further information was available on which to further assess the quality and results of this trial. In the Spriano et al trial evaluating the comparison between fludarabine with chlorambucil plus prednisolone as first-line therapy, there appeared to be little difference in response rates.[22] Given that the data available from this study was a conference presentation abstract, little more can be said about this trial with regard to the quality and results obtained.

The remaining two trials evaluated the use of fludarabine as first-line therapy compared to CAP (a combination of cyclophosphamide, prednisolone and doxorubicin).[15] One of these contained a further comparison of fludarabine and CAP with ChOP (a combination of vincristine, cyclophosphamide, prednisolone and doxorubicin).[23] In the latter, most recent trial, the rate of remission induced by fludarabine was significantly higher than that elicited by CAP and ChOP.[23] The duration of response was significantly longer for fludarabine compared to CAP in both trials. There was a trend for an advantage for patients treated with fludarabine over those treated with ChOP, however, the difference in duration of response was not statistically significant. Significantly lower rates of nausea and alopecia were also observed in the fludarabine group compared with both CAP[15] and ChOP, although the incidences of haematological side effects was significantly greater for the fludarabine and ChOP groups compared with CAP.

4.2.4 Ongoing Trials of Fludarabine in Chronic Lymphocytic Leukaemia

There are high quality randomised controlled trials that have been recently completed and are ongoing in this area. The most prominent and directly relevant in the consideration of first-line treatment of chronic lymphocytic leukaemia is the Leukaemia Research Fund sponsored MRC-CLL4 trial.[13] The comparison between fludarabine, chlorambucil and fludarabine plus cyclophosphamide is being investigated and will be completed in June 2004.[13] This is particularly important because it makes a comparison that is directly relevant to current practice, and it is one of the few trials to directly measure the outcome of impact on quality of life. A particular point to note is that this trial could possibly provide a more accurate estimate of the incidence and severity of adverse side effects in fludarabine-treated patients who are receiving prophylaxis (routinely given in practice) against adverse side effects.

In addition, 500 patients will be enrolled over a period of five years and the study will have more than 90% power to detect an absolute difference of 15% from 40-55% in survival at five years post-first line therapy using a 2-sided p-value. There will be approximately 65% power to detect a difference in survival of 10%. This means that there should be a good chance to detect any differences (should any be observed) between the effects on survival of fludarabine and chlorambucil.[13]

4.3 Clinical Effectiveness - Discussion

- A systematic review of RCTs examining the effectiveness of fludarabine used first-line for B-CLL was undertaken. The comparator of greatest interest was chlorambucil at standard dosage, but comparisons with other agents were also reviewed
- The comprehensive search for studies assessing the effectiveness of fludarabine was based around interrogation of four large bibliographic databases (MEDLINE, EMBASE, Science Citation Index and the Cochrane Library).
- Five randomised controlled trials were found, only one of which compared fludarabine (n=195) with chlorambucil at standard dosage (n=200).
- Other comparators were:
  - Fludarabine plus chlorambucil
  - Chlorambucil plus prednisone
  - High dose chlorambucil
  - CAP
  - ChOP
- No placebo controlled trials were identified
- None of the trials employed the oral formulation of fludarabine
- For the comparison of main interest, fludarabine with chlorambucil,[20] there were:
  - Higher rates of response (60% vs 35%; diff +25%; 95%CI +15%, +35%)
  - Longer median progression-free survival times (20 months vs 14 months; p<0.001)
  - Longer median overall survival times (66 months vs. 56 months; p=0.1)
  - Higher incidence of haematological side effects e.g. grade III or IV infections (16% vs 9%; diff +7%; 95%CI 0 to +14%)
  - Higher incidence of major infections (29% vs 17%; diff +12%; 95% CI +4%, +20%)
- Other information on impact on quality of life, claimed to have been collected, on need for transfusion and performance status was not reported

- On this basis there is early evidence that fludarabine is more effective than chlorambucil first-line
- This finding needs to be amplified with further research including
  - Replication of findings in another trial, particularly one using the oral version of fludarabine
  - Clarifying the effect on survival
  - Better estimation of the degree to which increased incidence of adverse events with fludarabine, off-sets the benefits associated with increased response, particularly taking into account that large numbers of patients are affected by side-effects, but have minimal clinical response
  - Direct measurement of impact on quality of life i.e. using SF-36 or disease specific equivalents
- Ongoing trials, particularly MRC CLL-4[13] should answer many of these questions, and recruitment into them should be encouraged

Concerning other comparators examined
  - Recruitment into the fludarabine plus chlorambucil arm of Rai et al (2000) was stopped early because of increased incidence of serious side-effects
  - The trial comparing fludarabine with chlorambucil with prednisone has not yet been fully reported
  - The trial comparing fludarabine with high dose chlorambucil is too small and too poorly reported to offer firm conclusions
  - Fludarabine appears to be more effective than CAP[15], and at least as effective as ChOP,[23] although the value this information is limited by the frequency with which these regimes are used first line.

5.   Economic evaluation

Objectives

The objectives of this section were to:
- Systematically review existing economic evaluations of fludarabine used in the treatment of CLL. Although this focused on the use of fludarabine first-line, evaluations concerning its use second-line were also considered, recognising that economic evaluations on the topic may be sparse.
- Collate available data on costs, particularly as they related to the additional and saved costs which might arise from greater use of fludarabine
- Relate these costs to effects identified in the systematic review of effectiveness and if feasible to undertake a simple model of the cost-utility of using fludarabine first line in the treatment of CLL as against using it second line, this being the indication for which it is currently licensed.

5.1   Systematic Review of Economic Evaluations – Methods

5.1.1   Search Strategy

A specific search strategy for information on costs, cost-effectiveness and quality of life was undertaken and involved searches of:
- Bibliographic databases – Medline (Ovid) 1966-October 2001 and the NHS Economic Evaluation Database (NEED)
- Internet sites of UK health economics units

5.1.2   Inclusion Criteria and Analysis

The inclusion criteria were not restrictive allowing all studies containing any information on costs or economic evaluations of fludarabine in the treatment of CLL to be included. Any study generally quantifying quality of life in CLL was also considered. The quality of all included studies was assessed. Where full economic evaluations were identified, the appraisal system used was based on the BMJ guidelines for economic appraisals.[25] Analysis was qualitative, with conclusions being drawn on the basis of the abstracted results from the included studies. The process was undertaken by one reviewer (SH) with additional scrutiny in areas of difficulty from a second reviewer (CH).

5.2   Systematic review of economic evaluations – results

5.2.1   Number of included studies

There were two included studies dealing with the use of fludarabine first line.[26,27] A further two assessments, which were linked, considered the costs and cost-effectiveness of fludarabine used second line.[1,14] Both referred to an unpublished economic evaluation by the manufacturer of fludarabine, which we were unable to consider directly in this review. Finally a study exploring measurement of quality of life in oncology, including CLL, was included to inform estimates of utility employed in the economic model. It is consequently not discussed in detail in this section, but in the section describing the model and the results from it.

5.2.2   Economic evaluations of fludarabine used first line

Best[26] attempted to assess the cost-utility of fludarabine used in two scenarios, the first of which compared the costs and effects of iv fludarabine used first line, with those of chlorambucil and prednisone (the second concerned the use of fludarabine second line). The only effect incorporated into the cost-utility estimate was an increase in time free of progressive disease after treatment (32 months vs 24 months, for fludarabine and chlorambucil + prednisone respectively). Using a rough estimate of the utility associated with remission as 0.96, and with disease as 0.81, and estimates of proportions achieving remission as 74% and 77% for fludarabine and chlorambucil + prednisone respectively, QALY gains of 0.29 and 0.23 were suggested, again for fludarabine and chlorambucil + prednisone respectively. On this basis the gain in QALYs associated with changing from use of chlorambucil + prednisone first line to fludarabine first line was 0.06. Costs, considering drug costs, out-patient appointments and costs associated with infections requiring in-patient treatment, were estimated as £7,043 for fludarabine and £589 for chlorambucil and prednisone, both over 6 months. The majority of the difference £6,454 was accounted for by differences in drug costs (£4,590 vs £286). There was also an attempt to estimate the costs the might be saved from having a longer period in remission with fludarabine, but the savings based on a reduction of one outpatient visit per six months in remission, were modest (£230

per patient responding and £180 per patient responding for fludarabine and chlorambucil + prednisone respectively). On this basis the central estimate for cost per QALY gained implied (although not formally stated) was approximately £110,000, which was presumably the basis of the overall conclusion, "Not proven that fludarabine is more cost-effective than current first-line treatment".

Unfortunately although the approach by Best[26] is explicit, incorporating the best evidence available at the time, the evidence on effectiveness in particular is inconsistent with that now available from the trial by Rai et al e.g. difference in overall response rates this suggests is 25% favouring fludarabine (95%CI 15% to 35%). This alone suggests that the estimate of cost-utility should be re-assessed. However, there are other issues suggesting that the cost-utility figure offered should not be accepted:

- The structure of the model does not seem to capture all the potential benefits and disbenefits of fludarabine
- The basis of the utility estimates is unclear
- The costs do not incorporate changed practice with respect to fludarabine, particularly the availability of an oral formulation and the fact that its use second-line is now established
- The estimates take little account of uncertainty, particularly with respect to the confidence intervals existing around estimates of effectiveness

The second economic evaluation of use of fludarabine first line is a study by Levy et al.[27] This attempted to compare quality adjusted survival in fludarabine, with CAP and ChOP used first-line. The source of the data was the patients included in study by Leporrier et al,[23] reported in the clinical effectiveness section of the systematic review. Unfortunately the nature of the comparison limits its value, as does the fact that costs are not considered and no attempts made to derive estimates of cost-effectiveness or cost-utility. However, directly measuring the impact on quality of life has been noted as a consistent omission in the conducting and reporting of the results of RCTs on the effectiveness of fludarabine. This study provided a method of estimating this, and in consequence a brief description of the approach employed follows.

Levy et al[27] used a "Q-TWiST" method in which four clinical states are defined - toxicity (time spent with toxicity due to chemotherapy) [TOX], treatment free of toxicity [CT], no treatment or symptoms [TWiST], and relapse [REL]. The average time spent in each state was then calculated – in the paper, because only the incidence of toxic adverse events was available from the trial, estimates of duration of these adverse events derived from a consensus of 32 experts were used. Each state is then weighted by utility coefficients that reflect relative value according to quality of life. The resulting quality adjusted time without symptoms or toxicity [Q-TWIST] is thus:

$$Q\text{-}TWIST = U_{TOX}\,TOX + U_{CT}CT + TWiST + U_{REL}\,REL^{27}$$

On the basis of the Leporrier et al[23] trial the mean TWiST was 27.05 months with CAP, 31.5 months with ChOP and 32.95 months with fludarabine[27]. The sensitivity analyses showed that whatever the utility weights, the mean Q-TWIST was always significantly greater with ChOP or fludarabine compared with CAP. These estimates help confirm the effectiveness of fludarabine over ChOP and CAP and help quantify the net benefit, which appears to be smaller than expected. A similar approach would certainly be of value applied to the RCT comparing fludarabine with chlorambucil, although ideally the estimates of duration in various toxic adverse event states should be measured directly.

5.2.3 Economic evaluations of fludarabine used second line

The main included study was NICE technology appraisal guidance issued in September 2001[1] and the documents supporting it. In the guidance oral fludarabine was recommended as treatment for patients with B-CLL who have either failed or are intolerant of first-line therapy and who would have otherwise received (as second-line therapy) either ChOP (comprising cyclophosphamide, doxorubicin, vincristine and prednisolone), CAP (comprising cyclophosphamide, doxorubicin and prednisolone) or CVP (comprising cyclophosphamide, vincristine and prednisolone). The use of the orally-administered fludarabine regimen was preferred to the intravenously administered regimen on the basis of more favourable cost effectiveness.

The basis for the conclusion that fludarabine used second line, particularly in its oral formulation, was likely to be cost-effective appears to have been:
- Guidance document itself and the supporting cost-effectiveness annexe[1,28]
- The Assessment report, subsequently published as an HTA monograph[14]
- Schering Health Care Ltd submission to NICE (unpublished)

The economic evaluation under-pinning the guidance document, appears to be a review of existing economic evidence, supplemented by some simple modelling of cost-effectiveness (cost-per year of remission) and to a lesser extent cost-utility. The cost-effectiveness estimates and the data on which they appear to be derived are summarised in the table below.

Table 6 - Summary of cost-effectiveness data given in NICE guidance, and the cost and effectiveness data on which based (additional information drawn from Cost-Effectiveness Annexe)

	Drug cost (low)	Other* (low)	Total (low)	Drug cost (high)	Other* (high)	Total (high)	Effect**	Cost per year of remission***
Oral fludarabine	£2,700 (4.1 cycles)	£1,000 ^	£3,700	£3,900 (6 cycles)	£3,900 ^^	£8,800	155 days	£9000 to 21 000
IV fludarabine	£2,700 (4.1 cycles)	£3,300 ^	£6,000	£3,900 (6 cycles)	£7,900	£11,800	155 days	£14 000 to 28 000
ChOP	£800 (3.6 cycles)	£2,100	£2,900	£960 (6 cycles)	£7,700	£8,700	48 days	£22 000 to 67 000
Notes: * Other – costs beyond drug acquisition including in particular: administration costs; costs of prophylaxis, costs associated with treating adverse events; costs associated with additional tests and monitoring ** Increase in days of progression free survival based on data from RCT by French Cooperative Group comparing fludarabine with CAP; thus assumes that effect of ChOP is same as CAP. Not clear how values derived – assumed that duration of response in trial is multiplied by proportion achieving response i.e. for fludarabine 324 * 0.48 = 155 *** Ranges derived by using low or high cost values. Low values derived from Schering Health Care Ltd submission to NICE; high values derived from Roche data ^ Figures given in §4.2.4 of guidance differ, as they refer to additional administration costs alone ^^ Unable to identify how figure was derived								

The NICE guidance[1] suggests the mean incremental cost-effectiveness ratios for oral fludarabine against ChOP is £2700 per year of remission (low cost of treating side effects) [increased cost, £800; gain in progression free survival 107 days] or £200 per year of remission (high costs of treating side effects) [increased cost, £54; gain in progression free survival 107 days]. The latter figure is smaller than the former because in the second scenario the costs of treating side effects induced by ChOP treatment are also higher. The Cost Effectiveness Annexe clearly indicates the poor quality of evidence and high level of uncertainty are enormous problems assessing cost-effectiveness. On balance, however, the final guidance felt able to state that, "it is probable that oral fludarabine is cost effective against ChOP". It is clear that this was thus a pragmatic decision based on the best available evidence at the time. However, it is unclear whether the full implications of uncertainty were

appreciated given that sensitivity of the cost-effectiveness estimates to variation in effectiveness estimates did not appear to have been undertaken. Two further issues of note are:

- Cost per year of remission is a potentially misleading cost-effectiveness measure. It needs to be emphasised that the effect being measured is a year in remission as opposed to having progressive disease or being in a health state other than remission. It does not mean an <u>additional</u> year of life in remission (there being no evidence that fludarabine used second line alters overall survival)
- It is debatable whether attempting to assess the cost-effectiveness of fludarabine used second line, in isolation from what might occur in subsequent lines of treatment is appropriate, given that use of fludarabine second line is unlikely to mean that ChOP will not be used at all; instead it is likely that in a proportion of patients ChOP will be used as a third line treatment, rather than a second line treatment. Alternatively stated, the incremental cost of using fludarabine second-line is highly unlikely to be the difference in cost of a cycle of treatment with fludarabine with the cost of a cycle of treatment with ChOP; further the incremental effect of using fludarabine is highly unlikely to be indicated by the difference in mean response duration between the two agents.

Like the NICE guidance document, the Assessment Report[14] is essentially a review of existing economic evaluations. Unlike the Cost Effectiveness Annexe to the NICE guidance, no additional evaluation or modelling of cost-effectiveness or cost-utility was attempted. The identified costs of treatment with iv fludarabine (oral fludarabine was not licensed when the report was compiled) were similar to those given in the NICE guidance document[1] and the Cost Effectiveness Annexe[28], as was concern about variation in the wider costs stemming from wide variation in estimates of costs associated with treating adverse events. The main conclusion of the report was that a very cautious interpretation of apparently favourable estimates of cost-effectiveness of fludarabine relative to ChOP was required. A key component of the report in this respect was the appraisal of the submission to NICE on fludarabine by Schering Health Care Ltd. discussed in greater detail below.

The last evaluation underpinning the NICE guidance was the manufacturer's submission to NICE. This is unpublished and the only record of the economic evaluation is the detail provided in the Assessment report.[14] This is reproduced in the table below.

Table 7 - Summary of key details of economic evaluation contained in the Schering Health Care Ltd submission to NICE identified in report by Hyde et al.

Feature of evaluation	Details in Schering Health Care Ltd submission to NICE
Intervention	Intravenously administered fludarabine *
Comparators	CHOP, CAP
Source(s) for effectiveness data	Phase III trial (French Cooperative Group on CLL, 1996) for intravenous fludarabine vs CAP, and "expert opinion" for CHOP
Perspective	Health sector
Type of economic evaluation	▪ Main analysis: cost-effectiveness analysis (i.e. incremental cost per year of remission gained)
Base-case effectiveness result	▪ Response rates: significantly more pre-treated patients responded to fludarabine than with CAP ▪ Response durations: fludarabine median duration: 324 days; CAP median duration: 179 (P=0.22) ▪ Expected disease-free days: iv fludarabine: 155 days; CHOP and CAP: 48 days
Price year	2000
Resource use data	Taken from retrospective audit of notes for 25 patients with CLL who received a second line therapy (n=17 for iv fludarabine, n=5 for CHOP; n=3 for fludarabine containing combination regimens)
Source(s) for cost data	Taken from a range of national and local sources, e.g. BNF, and local hospital trusts
Base-case cost result	(1) Intra-venous fludarabine: data commercially in confidence (2) CHOP: data commercially in confidence (3) CAP: data commercially in confidence
Base-case ICER	Intra-venous fludarabine vs CHOP: £10,588 per year of remission
Approach to sensitivity analysis	One-way sensitivity analysis only
Parameters	▪ Rate of response (ranges based on data reported in case series studies) ▪ Duration of response (ranges based on data reported in case series studies) ▪ Number of courses of therapy (consistency with trial data i.e. 6 courses of therapy) ▪ Costs per patient (+/- 1 SD)
Results	ICER ranges from dominance to £10,264 per year of remission

Notes:
ICER = Incremental cost-effectiveness ratio
* Oral fludarabine also considered in the Schering submission, but was not recorded in the HTA assessment report[14] as it was not licensed when this report was being compiled

The key weaknesses noted in the Assessment report[14], assessed in relation to standard criteria for appraising health economic evaluations, were:

- The clinical trial was not used as a source of data on resource use and costs.
- All data on resource use had been collected as part of a separate audit or observational study of patients receiving second line treatment of CLL.
- The lack of comparability of the resource use data from the patient groups. The data revealed that the three patient groups used for comparison were not similar, particularly in terms of their mean age, sex distributions, time between diagnosis and second line treatments and percentage of patients with serious co-morbidity.

- The comprehensiveness and the consistency of the resource use data reported in this analysis. The data collection was retrospective and therefore relied on routine data sources. There was also a concern about of data collection, as the resource use was not assessed during remission and failed to account for the long-term consequences of treating CLL, which implies there was not a fixed time interval over which data were collected.

These weaknesses explain why there was concern about interpreting the ICERs given at face-value.

5.3 Systematic review of economic evaluations - conclusions

Unfortunately, there are no usable evaluations of the cost effectiveness of fludarabine as a first-line therapy for B-CLL in comparison with chlorambucil. The value of an assessment using effectiveness data which pre-dates publication of a recent RCT comparing fludarabine with chlorambucil is debatable.

Up-to-date evaluations have been conducted on the use of intravenous and oral fludarabine as a second-line treatment for B-CLL. NICE have recently recommended the use of oral fludarabine as second-line therapy for B-CLL over the intravenous formulation on the basis of more favourable cost effectiveness[1]. However, there is considerable uncertainty around the estimates of cost-effectiveness. This and the fact that these assessments compare fludarabine with ChOP, as opposed to fludarabine with chlorambucil, greatly limits the value of these assessments in gauging cost-effectiveness of fludarabine used first-line. The assessment of attempts to evaluate cost-effectiveness of fludarabine used second-line, does however indicate some important issues needing to be considered in any new attempt to evaluate or model the cost-effectiveness/utility of fludarabine used first line.

5.4 Cost Analysis - Methods

The cost analysis focused on the comparison of the costs for first-line treatment with fludarabine with the cost of first-line treatment with chlorambucil. Summary costs per cycle of treatment have been estimated, and the strategies and resource requirements were identified through:
- Dialogue with clinicians
- The BNF[11]
- Unit Costs of Health and Social Care[29]
- The Cost Effectiveness Annexe, (a supporting document for the NICE guidance)[28]

5.5 Cost Analysis - Results

The resource requirements for the treatment strategies with fludarabine and chlorambucil are outlined in Table 10. The costs of the resources given in Table 8 are outlined in Table 9.

Table 8 - The resource requirements for the first-line treatment of B-CLL with fludarabine (oral formulation) and chlorambucil

	Treatment	
Type of Resource	**Fludarabine***	**Chlorambucil**
Pre-treatment tests	1x bone marrow trephine biopsy 1x full blood count 1x differential blood count 1x reticulocyte count 1x Coombs test 1x Chest X-ray 1x Abdominal ultrasound	1x bone marrow trephine biopsy 1x full blood count 1x differential blood count 1x reticulocyte count 1x Coombs test 1x Chest X-ray 1x Abdominal ultrasound
Drug	Fludarabine $40mg/m^2$ for 5 days every 28 days for 6 cycles {BNF} [20] E.g. 70kg 180cm dosage calculation: 7.5 tablets per day (Each tablet contains 10mg fludarabine phosphate (Dubois and Dubois Formula,[30] for five days (37.5 per week)	Chlorambucil $40mg/m^2$ for 1 day every 28 days up to 12 cycles[20] E.g. $1.75m^2$ patient dosage calculation: 3.5 tablets per day, for one day per month week) for 12 months (42 tablets total)
Prophylaxis during therapy	Septrin 2 tablets, 2x daily 2 days per week for 18 months.	Nil
Monitoring	On completion of each cycle of treatment (Day 28) for 6 cycles	On completion of each cycle of treatment for 12 cycles (Day 28):
Appointments	1x outpatient appointment with haematologist prior to commencement of therapy 6x Outpatient appointment Haematologist on completion of each cycle on Day 28 {Personal Communication}.	1x outpatient appointment with haematologist prior to commencement of therapy 6x Outpatient appointment Haematologist on completion of each cycle on Day 28 {Personal Communication}.

Table 9 - The cost estimates for the first-line treatment of B-CLL with fludarabine (oral formulation) and chlorambucil

Type of Resource	Treatment	
	Fludarabine*	Chlorambucil
Pre-treatment tests	1x bone marrow trephine biopsy 1x full blood count 1x differential blood count 1x reticulocyte count 1x Coombs test 1x Chest X-ray 1x Abdominal ultrasound Total Cost estimate = **£200**[28]	1x bone marrow trephine biopsy 1x full blood count 1x differential blood count 1x reticulocyte count 1x Coombs test 1x Chest X-ray 1x Abdominal ultrasound Total Cost estimate = **£200**[28]
Drug	Fludarabine $40mg/m^2$ for 5 days every 28 days for 6 cycles {BNF} E.g. 70kg 180cm dosage calculation: 7.5 tablets per day (Each tablet contains 10mg fludarabine phosphate (Dubois and Dubois Formula, {Schering}, for five days (37.5 per week) 2 x 20-tablet pack @ £372.00 (per cycle) for 6 cycles **=£4464.00**[11]	Chlorambucil $40mg/m^2$ for 1 day every 28 days up to 12 cycles[20] E.g. $1.75m^2$ patient dosage calculation: 3.5 tablets per day, for one day per month week) for 12 months (42 tablets total) 2x 25-tablet pack @£8.17 (0.2mg chlorambucil per tablet) **=£16.00**[11]
Prophylaxis during therapy	Septrin 2 tablets, 2x daily 2 days per week for 18 months. 32 x20-tablet packets @£3.34 **=£107.00**[11]	Nil
Monitoring	On completion of each cycle of treatment (Day 28) for 6 cycles: Total cost = **£560**[28]	On completion of each cycle of treatment for 12 cycles (Day 28): Total cost **= £1120** (estimate from Cost effectiveness Annexe)[28]
Adverse events	**£270**[28]	Nil
Appointments	1x outpatient appointment with haematologist prior to commencement of therapy 6x Outpatient appointment Haematologist on completion of each cycle on Day 28 {Personal Communication}. Medical Consultant: 15 minutes at £109 per patient-related hour £27.25 per appointment. £27.25 x 6 cycles = **£164**.[29]	1x outpatient appointment with haematologist prior to commencement of therapy 6x Outpatient appointment Haematologist on completion of each cycle on Day 28 {Personal Communication}. Medical Consultant: 15 minutes at £109 per patient-related hour £27.25 per appointment. £27.25 x 12 cycles = **£327.00**.[29]
Total Costs	**£5765**	**£1663**

Assumptions

A number of assumptions were made in assigning resources and their subsequent costs, and these are detailed below.

- Staff costs include components to reflect investment in pre- and post-registration education, overheads, and on-going training and were derived from the cost for patient-related activities and contact.
- The recommended dosage of fludarabine (oral formulation of $40mg/m^2$) of total body surface area for five consecutive days, every 28 days for a recommended maximum of 6 cycles.
- The recommended dosage of chlorambucil is $40mg/m^2$ for one day every 28 days up to 12 cycles, as used by Rai et al[20]
- The dosage schedules may vary depending on how soon the response may be attained by either treatment regime. It is entirely possible that patients who respond to chlorambucil treatment within six cycles of treatment would not receive twelve cycles of treatment. Conversely, it is also feasible that patients treated with fludarabine may receive more than six cycles of treatment.

- Summary costs have been rounded to the nearest £.
- The costs have not been adjusted to allow for any dose escalation on treatment initiation with chlorambucil.
- Any reductions in dosage (due to side effects) have not been incorporated in this analysis.

5.6 Cost Analysis - Discussion

A cost analysis has been taken using a number of different sources for information on resources used and subsequent costs of those resources. The main points of the analysis are discussed below.

It appears the main difference between the costs of first-line treatment of BCLL with fludarabine compared to that of chlorambucil is due to the substantially higher drug cost of fludarabine. In addition the use of prophylactic medication to prevent the occurrence of adverse side effects associated with fludarabine use also appears to increase the total cost associated with the treatment.

The variation in dosage schedules for the two treatment regimens appears to increase the cost of monitoring and appointments for chlorambucil appeared to fludarabine. As outlined in the assumptions above, the number of cycles patients may receive of each treatment can be dependent of time taken to elicit any response i.e. patients may receive fewer than 12 cycles of chlorambucil, and patients may also receive more than six cycles of fludarabine. The increase in monitoring costs for chlorambucil compared to fludarabine does not substantially alter the difference between the costs of treatment of the two regimens.

One of the assumptions made here and in modelling the costs is that very few patients will die before they receive second-line treatment for B-CLL, that is, most will survive long enough that they will require second-line treatment. It is reasonable to assume that the patients who received fludarabine as first-line treatment would then receive chlorambucil as a second-line treatment, and it is almost certain those patients who receive chlorambucil as first-line treatment will receive fludarabine (as it is currently licensed in the UK) as second-line treatment. Therefore it seems unlikely that the costs associated with treatment over the time course of the disease will differ, regardless of which medication is used as first-line treatment.

An important point to note is that this cost analysis did not consider costs arising from adverse events in chlorambucil treated patients, nor did it quantify the costs saved by treatment producing responses more frequently and of longer duration. The extent to which the incidence and subsequent cost of adverse events can be reduced by the use of prophylaxis is unclear at this time. The estimate of the cost of treating adverse events has been taken from the cost effectiveness annexe to the NICE guidance.[28]

From this analysis, it appears that the costs of fludarabine treatment for patients with B-CLL are substantially greater than the costs for chlorambucil treatment for these patients, and that the main cost differences arise from the difference in drug acquisition costs. In addition, the cost estimates are subject to some uncertainty, because of the as yet unknown costs of treating side effects in patients who have been given prophylaxis.

5.7 Modelling - methods

Given that there appeared to be a tension between potential improved effectiveness and increased cost of fludarabine relative chlorambucil, it was felt important that a simple model of cost-utility was attempted. It was clear that information on key aspects of effectiveness and costs was limited, so the intent was as much to indicate the impact of uncertainty as to provide definitive estimates of cost-utility. A decision analytic model was developed. The decision tree model is shown in Figure 2 below. It was chosen as the best compromise between providing a reasonable representation of the clinical scenario under examination and making best use of the available effectiveness data, particularly from the RCT by Rai et al.[20] It is acknowledged that impact of adverse events in particular is not directly modelled; the potential impact of these is not however ignored.

Figure 2 - Decision analytic model of fludarabine compared with chlorambucil
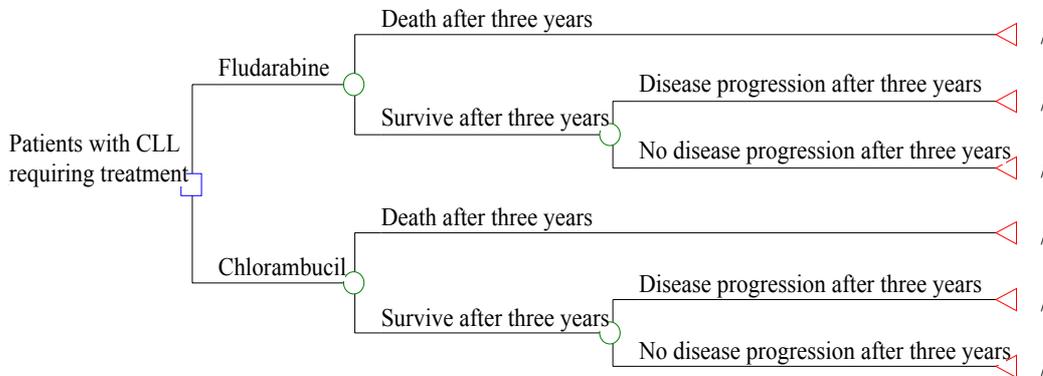
The tree indicates the main comparison is between treatment with fludarabine, and treatment with chlorambucil, with respect to three health states:
- Death
- Survival with disease progression
- Progression-free survival

The tree shown is for three years duration; others were constructed for one, two, four or five years. However, the three-year duration was chosen as the base-case as the best compromise between completely capturing the impact of fludarabine, apparently manifest over several years, and robustness of data. Effectiveness data in the Rai et al trial were based on limited numbers of patients beyond three years.

The data used to populate the model and their sources are shown in Table 10.

Table 10 - Values of the parameters, and their sources, used to populate model for base-case estimate of cost-utility

Parameter	Values		Source
Probability of death at 3 years	Fludarabine	0.26	Read from survival curves in study by Rai et al[20]
	Chlorambucil	0.30	
In survivors, probability of progression at 3 years	Fludarabine	0.68	Read from survival curves in study by Rai et al[20]
	Chlorambucil	0.84	
Utility for death *	0		Estimated by authors.
Utility for progression **	0.6		QoL estimates undertaken by Holzner et al[31] on 81 patients with CLL used to inform estimates
Utility for being progression-free	0.8		
Cost course of treatment with fludarabine	£5495		Cost analysis in preceding section of this report ***
Cost course of treatment with chlorambucil	£1663		
Notes:			
* Death assumed to occur mid-way through period, at 1.5 years. Health state prior to death assumed to be 50% progression-free and 50% in progression. ** Progression assumed to occur mid-way through period at 1.5 years. Health state prior to progression assumed to be progression-free. Likelihood that further responses and periods remission will occur in many patients after first episode of remission unable to be quantified *** Unable to consider costs arising from adverse events, particularly in chlorambucil treated patients, or to quantify and costs off-set by treatment producing responses more frequently and of longer duration			

The study by Rai et al[20] was the main source of effectiveness data. The quality of life (QoL) data for the modelling was estimated by the authors. Data from a study by Holzner[31] were used to inform this estimate, but values were not directly transcribed. In the study, Holzner et al measured QoL using the EORTC QLQ-C30 and FACT-G on 418 cancer patients, 81 of whom had CLL.[31] Although the main purpose of the research was to assess the correlation between the results of the two different scales, the data can be used to give a general indication of reasonable utility values for CLL. Mean global quality of life on EORTC QLQ-C30 was 64.9/100 (SD 21.9); mean total score on FACT-G was 84.6/120 (SD 15.1).[31] Baseline characteristics for CLL patients suggested considerable heterogeneity, particularly with respect to time since initial diagnosis (range 1.0 to 15.6 years). 44% had received prior chemotherapy.

In order to investigate the impact of uncertainty on the base-case estimate of cost-utility, one-way sensitivity analyses were conducted on a variety of parameters concerning effectiveness, utility and costs. The nature of these and the sources of the data are indicated in Table 11 below.

Table 11 - Values of the parameters, and their sources, used in sensitivity analyses

Parameter	Values		Source
Effectiveness			
Consider data after 1,2,4 & 5 years			From study by Rai et al[20]
Probability of death at 3 years	Fludarabine Chlorambucil	0.26 0.19 to 0.41	Difference implied by 95% CI for difference between fludarabine and chlorambucil
In survivors, probability of progression at 3 years	Fludarabine Chlorambucil	0.68 0.61 to 1.0	
Utility values			
Utility for death	0		Estimated by authors.
Utility for progression	0.5 to 0.7		QoL estimates undertaken by Holzner et al[31] on 81 patients with CLL used to inform estimates
Utility for being progression-free	0.7 to 0.9		
Include estimate of disutility of additional adverse events associated with fludarabine	0.1 reduction for 1 month		Estimated by authors Assumes adverse effects of chlorambucil would cause little or nor disutility
Costs			
Include estimate of cost of adverse events associated with fludarabine	£270		Cost-effectiveness annexe of NICE guidance[28]. Assumes minimal adverse events associated with chlorambucil
Include cost of follow-up treatment in case of progression, where chlorambucil used after fludarabine & vice versa	Cost difference - £1438		Modelled using base-case probabilities for survival and progression, and costs for fludarabine and chlorambucil
Include cost of follow-up treatment in case of progression, where initial treatment repeated	Cost difference - £5619		Modelled using base-case probabilities for survival and progression, and costs for fludarabine and chlorambucil

5.8 Modelling - results

The base-case result estimates that on average over three years:
- Fludarabine treatment results in 1.9 QALY
- Chlorambucil treatment results in 1.82 QALY
- Gain of 0.08 QALY is achieved at a cost of £3830
- Cost/QALY of £48,000

The results of the sensitivity analysis are summarised in the Table 12 below:

Table 12 - Results of the sensitivity analyses around the base-case cost per QALY estimate

Factor	Cost/QALY
Year 1 2 3 4 5	 Chlorambucil dominates fludarabine £96,000 £48,000 £52,000 £21,000
Probability death Fludarabine 0.26; chlorambucil 0.19 Fludarabine 0.26; chlorambucil 0.3 Fludarabine 0.26; chlorambucil 0.41	 Chlorambucil dominates fludarabine £48,000 £19,000
Probability progression Fludarabine 0.68; chlorambucil 0.61 Fludarabine 0.68; chlorambucil 0.84 Fludarabine 0.68; chlorambucil 1.0	 £123,000 £48,000 £34,000
Utility being in progression 0.5 0.6 0.7	 £40,000 £48,000 £60,000
Utility being progression-free 0.7 0.8 0.9	 £66,000 £48,000 £38,000
Include disutility for possible adverse effects of fludarabine	£54,000
Include costs of possible adverse effects of fludarabine	£52,000
Include costs of second-line treatment in those progressing; chlorambucil first-line receives fludarabine second-line and vice versa	£18,000
Include costs of second-line treatment in those progressing; first-line drug is repeated second-line	£71,000

5.9 Modelling – discussion

Modelling the cost data with the clinical effectiveness data was also undertaken in this review, felt to be important because of the observed tension between potential improved effectiveness and increased cost of fludarabine relative to chlorambucil.

The three-year duration was chosen as the base-case as it represented the best compromise between completely capturing the impact of fludarabine, apparently manifest over several years, and robustness of data provided by the Rai et al trial.[20] The average cost per QALY of £54 000 for the base-case (for three years) margin is at the limits of what would be typically considered by the NHS as an effective use of resources. Sensitivity analyses conducted around this estimate by manipulating the measures such as the effectiveness of treatment (utilities of experiencing adverse effects, disease progression and not experiencing disease progression, and varying the probabilities of disease progression and death) and the costs (including costs for adverse effects of fludarabine, second-line treatment in those progressing who are treated with the same therapy as first-line and second-line treatment in those progressing who are treated with the alternate therapy from first-line treatment) provides cost per QALY that vary widely. The estimates in the sensitivity analyses show that fludarabine treatment can vary from being clearly inefficient to justifiable in terms of cost utility.

In the current MRC CLL4 trial[13] (in which many clinicians in the UK are involved), quality of life data are being collected, which will be particularly useful for informing future estimates of cost-effectiveness. In addition, this trial is sufficiently powered to detect any statistically significant difference in overall survival, and prophylaxis is also being given for the

amelioration of, and possible reduction in incidence of adverse effects (which is more likely to occur in clinical practice). This trial is due for completion in June 2004. Although this trial is collecting data on mortality and adverse events it is unclear to what extent the trial will provide more accurate estimates on the cost of treatment.

6. Discussion

In this report investigating the use of first-line treatment of B-CLL with fludarabine a number of important findings have been made, and a number of issues surrounding first-line treatment of this disease have been outlined.

Fludarabine as second-line therapy has recently been the subject of NICE guidance.[1] This guidance highlighted that fludarabine as first-line therapy would be a topic where the research would need to be reviewed. This report is the first systematic review examining the use of fludarabine as a first-line treatment for B-CLL. In particular this is the first time the clinical effectiveness of fludarabine has been evaluated against other first-line therapies, particularly against chlorambucil, the most widely used and currently licensed first-line treatment for B-CLL. In addition, an analysis of cost effectiveness has been undertaken with an attempt to model the data for clinical effectiveness relative to the costs associated with treatment with fludarabine and chlorambucil. Therefore this review represents an important and timely piece of work.

A number of important clinical findings were made. For the comparison of fludarabine with chlorambucil, there was a significant advantage of fludarabine over chlorambucil in terms of response rate (60% vs 35%, p<0.001) and time to disease progression after first line therapy (20 months vs 14 months, p<0.001. For comparison between fludarabine and the combination regimens CAP and ChOP, the remission induced by fludarabine was significantly higher than that elicited by CAP and ChOP,{Leporrier} with response rates of 40%, 27% and 15% for fludarabine, ChOP and CAP respectively. The duration of response was significantly longer for fludarabine compared to CAP in both trials. There was a trend for an advantage for patients treated with fludarabine over those treated with ChOP, however, the difference in duration of response was not statistically significant.

There were no significant differences in overall survival between patients treated with fludarabine and the comparators Chlorambucil, CAP and ChOP observed in any of the trials analysed in full.[20]{Johnson} {Leporrier} There was a trend towards a longer median overall survival with fludarabine treatment, compared with chlorambucil (66 months vs 55 months) but the difference between fludarabine and chlorambucil for this outcome was not statistically significant. However the trial was inadequately powered to detect any statistically significant difference in survival between the two treatments. However, the study conducted by Leporrier et al {Leporrier} was powered to detect any statistically significant survival differences and none were found for the comparison between CAP and ChOP, where the overall survival was 69 months, 70 months, and 67 months for fludarabine CAP and ChOP respectively. The results regarding survival certainly require additional clarification, especially regarding the use of fludarabine compared with chlorambucil, where the trend towards improved survival with fludarabine was observed. Although the ongoing MRC CLL4 trial[13] is powered to detect any significant differences in survival (and is due for completion in June 2004), but until those results are published, it does not appear that there is any additional survival benefit offered by the use of fludarabine compared to other first-line therapies.

Potentially offsetting the beneficial finding of increased response rates and longer duration of progression-free survival are the findings that there were significantly greater incidences of adverse side effects with fludarabine treatment, particularly for infections and haematological side effects in the Rai et al{Rai} comparing fludarabine with chlorambucil. However for the comparisons of Fludarabine with ChOP and CAP, there were significantly less nausea/vomiting incidences for the fludarabine-treated patients compared to the CAP- and ChOP-treated patients and no incidences of alopecia for the patients treated with fludarabine. In all the trials there were significantly more serious haematological adverse events observed with fludarabine compared with chlorambucil, ChOP and CAP. The estimation of the extent of side effects is difficult as prophylaxis given during treatment with fludarabine has also been said to ameliorate and reduce the incidence of negative side effects. Questions remain regarding the extent to which the side effects offset the benefits of treatment, because there are no published estimates of quality of life during treatment, – so it is difficult to estimate the impact on patients of each treatment regime.

Although the early evidence suggests that fludarabine is more effective than chlorambucil as a first line treatment, these findings need to be amplified with further research using oral fludarabine. Along with replicating the findings of the Rai et al trial, an important aspect would be the clarification on the effects of survival because the Rai et al trial[20] was not sufficiently powered to detect any statistical difference in survival. Gaining a more accurate estimate of the extent to which the benefits of treatment are offset by the incidence of adverse side effects is also important. This would need to take into account that although patients present with haematological side effects with minimal clinical response. The role of prophylaxis for side effects such as infections and haematological side effects would also need to be examined. Direct measures of quality of life would also provide a realistic indication of the precise benefits of treatment, the impact of treatment on patients, and would inform and provide for a more accurate cost-effectiveness estimate.

For the cost analysis, a review of the available evidence of costs of fludarabine as a first-line treatment relative to the costs of other first-line treatments was conducted. There were no usable evaluations of cost-effectiveness and most of the work that was identified was used in the evaluation of second-line therapy. There was a high level of uncertainty around the estimates of cost of treatment with fludarabine and the fact they were made for second-line treatment somewhat limits the usefulness of these estimates as a guide for the costs of first-line therapy. An analysis was then conducted of the resources and costs involved in treatment of B-CLL with both fludarabine and chlorambucil. The main difference in cost between fludarabine and chlorambucil (where fludarabine was far more expensive) was incurred by the higher drug cost of fludarabine and the cost of prophylaxis against serious adverse side effects. Gaining an estimate of the exact resource involvement and cost of treating side effects was not conducted, nor was an estimate of the costs saved as a result of a longer duration without disease progression elicited by fludarabine. The cost of treating side effects is controversial, because it is unknown to what extent that adverse side effects are ameliorated and the incidence of side effects (particularly haematological) are reduced by the use of relatively inexpensive prophylaxis. Therefore there is some uncertainty surrounding the cost estimate in this report.

Modelling the cost data with the clinical effectiveness data was also undertaken in this review. The base-case (for three years) margins are at the limits of what would be typically considered by the NHS as an effective use of resources. Sensitivity analyses conducted around this

estimate by manipulating the measures such as the effectiveness of treatment (utilities of experiencing adverse effects, disease progression and not experiencing disease progression, and varying the probabilities of disease progression and death) and the costs (including costs for adverse effects of fludarabine, second-line treatment in those progressing who are treated with the same therapy as first-line and second-line treatment in those progressing who are treated with the alternate therapy from first-line treatment) provides cost per QALY that vary widely. The estimates in the sensitivity analyses show that fludarabine treatment can vary from being clearly inefficient to justifiable in terms of cost utility.

There is a clear need for accurate data regarding mortality and quality of life and the information from the MRC CLL4[13] trial may be valuable for this. Particularly important will be the acquisition of accurate quality of life estimates for patients in the states alive, alive with no progression and alive with progression. In addition, data on the adverse events profile when patients are treated with prophylaxis will be valuable to assess the impact that each treatment regimen has on each patient. However it is unclear the extent to which this will provide clearer information on the costs of treatment, especially when second-line and possibly third line treatment is incorporated into an economic analysis, as assumptions about these costs can have a major impact on the assessment on whether fludarabine used as first-line therapy represents an efficient use of resources or not.

In conclusion, 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 evidence concerning cost utility is inconclusive. The major areas of continuing uncertainty are the extent to which the results of iv fludarabine apply to oral fludarabine use, the impact of fludarabine on overall survival, the incidence, severity and duration of adverse events as a result of oral fludarabine treatment (especially in patients given prophylaxis against adverse events), the impact of fludarabine treatment on overall quality of life, and the costs of fludarabine treatment.

Implications for Practice

Given that there appears to be no enhancement of survival in B-CLL with the current available evidence, the focus remains on eliciting a response to treatment with the available treatment options, with a minimum trade-off between gaining a response that will provide the longest duration of disease-free progression. It would appear that for younger patients who are at little risk of experiencing adverse side effects of treatment, more aggressive treatment with fludarabine may represent the best treatment option. For older patients at risk of adverse side effects - particularly haematological side effects - the best treatment option may be palliation with chlorambucil. Therefore, the priority for clinicians and patients should be to support attempts to reduce uncertainty about the clinical and cost effectiveness of fludarabine through recruitment to the MRC CLL4[13] study and other new trials to investigate issues of effectiveness and costs associated with fludarabine and other treatment regimens.

Implications for Research

There is clearly a need for additional research in the use of fludarabine as first-line treatment for B-CLL to obtain some clarification of areas of continuing uncertainty. It is important to obtain some clarification of survival data especially given that there is a trend towards improved survival in fludarabine-treated patients compared to the survival of patients treated with chlorambucil in the one trial comparing first-line treatment with fludarabine compared with chlorambucil. The collection of data relating to QoL and the incidence, severity and duration of adverse events is also highly important, especially when prophylaxis is given. In this way, more accurate estimates can be made pertaining to the clinical and cost effectiveness of fludarabine compared to chlorambucil and other first-line treatment regimens.

Appendix 1 - BNF general guidance on use of cytotoxic drugs[11]

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti-cancer activity and the potential for damage to normal tissue. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neoadjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of sub-clinical metastatic disease is known to be high). All chemotherapy drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

CRM guidelines on handling cytotoxic drugs:

1. Trained personnel should reconstitute cytotoxics;
2. Reconstitution should be carried out in designated areas;
3. Protective clothing (including gloves) should be worn;
4. The eyes should be protected and means of first aid should be specified;
5. Pregnant staff should not handle cytotoxics;
6. Adequate care should be taken in the disposal of waste material, including syringes, containers, and absorbent material.

Cytotoxic drugs may be used either singly, or in combination. In the latter case, the initial letters of the approved or proprietary names of the drugs, identify the regimen used. Drug combinations are frequently more toxic than single drugs but may have the advantage in certain tumours of enhanced response, reduced development of drug resistance and increased survival. However for some tumours, single-agent chemotherapy remains the treatment of choice.

Most cytotoxic drugs are teratogenic, and all may cause life-threatening toxicity; administration should, where possible, be confined to those experienced in their use.

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from some of the drug entries in this chapter. In all cases detailed specialist literature should be consulted.

Prescriptions should not be repeated except on the instructions of a specialist.

Cytotoxic drugs fall naturally into a number of classes, each with characteristic antitumour activity, sites of action and toxicity. A knowledge of sites of metabolism and excretion is important because impaired drug handling as a result of disease is not uncommon and may result in enhanced toxicity.

Appendix 2 - Search strategies to identify studies on the effectiveness of fludarabine in treating CLL

MEDLINE (Ovid) 1966-Sept 2000

1   randomised controlled trial.pt.
2   controlled clinical trial.pt.
3   randomised controlled trials/
4   random allocation/
5   double blind method/
6   single blind method/
7   or/1-6
8   (animal not human).sh.
9   7 not 8
10   clinical trial.pt
11   exp clinical trials/
12   (clin$ adj25 trial$).ti,ab.
13   ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14   placebos/
15   placebo$.ti,ab.
16   random$.ti,ab.
17   research design.sh.
18   or/10-17
19   18 not 8
20   19 not 9
21   comparative study/
22   exp evaluation studies/
23   follow up studies/
24   prospective studies/
25   (control$ or prospectiv$ or volunteer$).ti,ab.
26   or/21-25
27   26 not 8
28   26 not (9 or 20)
29   9 or 20 or 28
30   exp leukemia b cell chronic/
31   cll.ti,ab.
32   b-cll.ti,ab.
33   chronic lymphocytic leuk?emia$.ti,ab.
34   or/30-33
35   fludara$.ti,ab.
36   29 and 34 and 35

EMBASE (Ovid) 1980-Sept 2000

1   controlled trial/
2   randomised controlled trial/
3   clinical trial/
4   prospective study/
5   double blind procedure/
6   randomisation/
7   major clinical study/
8   trial$.ti,ab.
9   or/1-8
10   exp lymphatic leukemia/
11   chronic lymphocytic leuk?emia$.ti,ab.
12   cll.ti,ab.
13   b-cll.ti,ab.
14   or/10-13
15   fludara$.mp.
16   9 and 14 and 15

Science Citation Index (Web of Science) 1981-Oct 2000

fludara*
(leukemia* or leukaemia* or CLL or BCLL)
1 and 2
Cochrane Library 2001, Issue 3

Appendix 3 - Quality Assessment strategy for Assessing quality of RCTs identified in this review

Quality assessment for RCTs on Fludarabine in CLL

A. Randomisation procedure

A1 Was the trial truly randomised   N   Y
A2 Was allocation truly random?   A
    Was allocation quasi-random or   B
    Was allocation systematic (alternate) or   C
    Was the method of randomisation not stated or unclear?   D

B. Allocation concealment

B1 Was concealment adequate?   A
    (Central allocation at trials office or pharmacy, sequentially numbered or coded vials, other methods where the trialist allocating treatment could not be aware of the treatment) or

    Was concealment inadequate?   B
    (Allocation was alternate - by patient, day of week, admission ward, etc - or based on information such as date of birth, already known to the trialist) or,

    Was concealment unclear (inadequate information given)   C

C. Methods of blinding

C1 Was the trial described as double blind?   N   Y
C2 Was the treatment allocation masked from the participants?
    (either stated explicitly, or an identical placebo used)   U   N   Y
C3 Was the treatment allocation masked from the investigators?   U   N   Y

C4 Was the treatment allocation masked at the outcome   U   N   Y
assessments?

D. Completeness of the trial

D1 Were the numbers of withdrawals in each group stated?   U   N   Y

D2 Was there an intention-to-treat analysis (analysis according the allocation) performed?

                                                                 U   N   Y

D3 What were the drop-out rates in each group of the trial for each of the main outcomes (unclear? Not stated?)

Group	Clinical response	Progression-free survival	Adverse events	Survival analysis	Quality of life
1					
2					
3					
4					
5					

D4 Are there substantial differences in completeness between the
Groups   U   N   Y

Jadad Scale

Circle when point awarded

Score 1 point if the answer to A1 is YES   +1

Score 1 point if the answer to C1 is YES   +1

Score 1 point if the answer to D1 is YES   +1

Score 1 point if the answer to A2 is A   +1

    and the answer to B1 is A

Deduct 1 point if the answer to A1 is Y   -1
    and the answer to A2 is B or C *or* the answer to B1 is B

Score 1 point if the answer to C2 is YES   +1
    and the answer to C4 is YES

Deduct 1 point if the answer to C1 is YES   -1
And the answer to C2 is NO or the answer to C4 is NO

Total score (between 0 and 5)

Appendix 4 - Data Extraction forms

Table 13 - Data Extraction forms for outlining characteristics of RCTs comparing first-line treatment with fludarabine for other first-line treatments for B-CLL

First author, year	
Aim	
Number randomised	
Inclusion criteria	
Exclusion criteria	
Demographics	
Follow-up: Adequate (target <10% unreported) Length	
Intervention	
Comparator	
Concomitant Rx:	
Pre-treatment tests:	
Outcome measures	
Response definitions CR = Complete remission PR = Partial remission PD = Progressive disease SD = Stable disease	

Table 14 - Data Extraction forms for results of RCTs comparing first-line treatment with fludarabine for other first-line treatments for B-CLL

	Fludarabine	Chlorambucil	Fludarabine plus Chlorambucil	Comments
Number entered into study				
Drop-outs/exclusions before assessment				
Losses to follow-up				
Number randomised				
Number of patients evaluated for response				
Evaluated as intention-to-treat				
Clinical response rates (CR + PR)				
Follow-up period				
Median duration of response				
Median time to progression				
Median overall survival				
Patients evaluated for adverse events[ξ]				
Deaths during Rx				
Thrombocytopenia				
Neutropenia				
Infection				
Differences in side effects				

Appendix 5 - Fludarabine compared with chlorambucil (intermediate dosage) plus prednisone

Number of trials

One RCT contributed information on this comparison.[22] The results, described as a "first interim report", have only been published in limited form as a conference abstract.

Included study characteristics

Fludarabine (given intravenously) was compared to oral chlorambucil plus intramuscular prednisone in previously untreated CLL patients, who presented with B-CLL classified as Rai stages intermediate and high risk. 73 patients were allocated to fludarabine, which was given in standard dosage ($25mg/m^2/d$ for 5 days repeated every 28 days) for 6 cycles initially. A total of 74 patients were allocated to chlorambucil, which was given at a slightly higher than normal dosage ($30mg/m^2$ twice every 28 days) combined with intramuscular prednisone ($40mg/m^2/day$ for 5 days, repeated twice every 28 days). The chlorambucil plus prednisone regime was again given for 6 cycles initially. In both arms the regimes were stopped if there was disease progression or stable disease after three or six cycles. Two additional cycles were allowed if a complete remission was achieved; three if a partial response was obtained. There was no information on any prophylactic regime, or on switching in the event of failure of the initially allocated treatment.

Specified outcomes had to be inferred from the results reported. These were limited to disease response and toxicity. There was no information on whether a power calculation had been carried out.

Included study quality

Assessment of quality of this study is greatly limited by the early nature of the report. Of particular concern is that quality of randomisation cannot be assessed and 42 (29%) of the 147 participants do not appear to be accounted for in the results reported.

Included study results

The conference abstract reports that the overall response rate was 70% for fludarabine and 66% for chlorambucil plus prednisone. It important to note that these results are only based on 60 out of 73 participants (able to be evaluated) in the fludarabine arm and 55 out of 74 in the chlorambucil plus prednisone arm. The reporting of results on toxicity is limited to the statement, "Toxicity was acceptable and comparable in the two treatment arms", which does not allow us to draw any further conclusions about the treatments with regard to this outcome of interest.

Full publication of the results of this trial precludes making robust conclusions on the effectiveness of fludarabine relative to chlorambucil plus prednisone. Nonetheless, provided this trial is fully published, it should provide useful information on the relative effectiveness of fludarabine in CLL in the future.

Appendix 6 - Fludarabine compared to high dosage chlorambucil

Number of trials

One RCT contributed information on this comparison. [21] The results are currently only available as conference abstracts and posters. Further information was derived from the published protocol for this study

Included study characteristics

Fludarabine (given intravenously) was compared to oral chlorambucil in previously untreated CLL patients with advanced disease (on the basis of Total Tumour Mass (TTM) scores or bone marrow failure). Approximately 40 participants were allocated to fludarabine. The regime was slightly different to that employed in other RCTs; $25mg/m^2$/day for four days repeated every 21 days for six cycles. Approximately 36 participants were allocated to chlorambucil. This regime is clearly
different from that normally used; i.e., $10mg/m^2$/d continuously for 18 weeks. Dose modification was specified for each regimen. A prophylactic regime was also specified allowing use of gammaglobulin infusions and corticosteroids. Switching from fludarabine to chlorambucil or vice versa was permitted if there was no response or disease progression at nine or 18 weeks, or if there was a minor response at 18 weeks. Treatment with the crossover regime was not to exceed 18 weeks.

The primary outcome was stated to be response rate. Additional specified outcomes were disease response, overall survival, toxicity and quality of life. The quality of life measurements consisted of number of nights in hospital and frequency of admission; frequency and nature of infectious episodes; and number of red blood cell and platelet transfusions. A power calculation was done; the target number of patients for the trial was stated to be 260. However, with 80 participants the "feasibility" study reported is hence underpowered, which needs to be considered when interpreting the results of this trial.

Included study quality

Given the limits of the reporting, the study was reasonably well conducted. Allocation in particular was likely to have been concealed. Loss to follow-up was probably minimal, as 76 participants are accounted for in the results and the maximum number said to have been randomised was 82. The study was open to detection bias through lack of blinding. There were no features off-setting this apart from clear definition of most outcomes. As mentioned in the preceding section, the fact that the study is under-powered also needs to be taken into account in its interpretation.

Included study results

Given that the study is underpowered, the benefit shown in this trial in favour of high dose continuous chlorambucil compared to fludarabine (at the expense of higher levels of adverse events) needs to be interpreted very cautiously. A full assessment of the potential of high dose continuous chlorambucil to deliver similar or improved response rates relative to fludarabine should await the results of larger trials with fully reported data on impact on quality of life. The results are shown in Table 15 below.

Table 15 - Results of RCT comparing intravenous fludarabine with oral chlorambucil (high dose continuous)

Outcome		Fludar-abine	Chlor-ambucil	Difference (Fl – Chl)	Comment
Response rates (complete + partial responses)		30/40 75%	31/36 86%	-11% (95% CI -29% to 6%)	Favours Chl-HD; results could have occurred by chance alone
Progression-free survival - median [I]		No detail available from reports		No detail bar (p [log rank] = 0.92)	Unable to assess direction of effect
Overall survival - median [I]		No detail available from reports [II]		No detail bar (p [log rank] = 0.207)	Unable to assess direction of effect
Toxicity – deaths		?0/40 [III]	?0/36 [III]	No difference	No difference
Toxicity - severe adverse events [IV]	Anaemia	11/40 28%	13/36 36%	-9% (95% CI -29% to 12%)	Generally favours Fl; all results except thrombocytopaenia could have occurred by chance alone
	Thrombocytopaenia	3/40 8%	13/36 36%	-29% (95% CI -46% to -11%)	
	Neutropaenia	14/40 35%	16/36 44%	-9% (95% CI -31% to 13%)	
	Infections	2/40 5%	2/36 6%	-1% (95% CI -11% to 10%)	
Impact on quality of life		Measured but not yet reported			
Notes: I - Unknown if the data included patients who did not respond to first-line therapy II - Unable to read off detailed results from Kaplan-Meier curve because of poor quality of reproduction in published abstract III - No mention made of any deaths despite relatively full reporting on other toxicity events IV - Proportion of patients with WHO grade III or IV adverse events; information on other events also reported					

Given that the study is underpowered, the benefit shown in this trial in favour of high dose continuous chlorambucil compared to fludarabine (at the expense of higher levels of adverse events) needs to be interpreted very cautiously. A full assessment of the potential of high dose continuous chlorambucil to deliver similar or improved response rates relative to fludarabine should await the results of larger trials with fully reported data on impact on quality of life.

Appendix 7 - Fludarabine compared with CAP or ChOP

Number of trials

Two trials were identified where fludarabine was compared with CAP, a combination of cyclophosphamide, prednisone and doxorubicin.[15,23] One of these trials had a third arm consisting of treatment with ChOP.[23]

Included study characteristics

The study by The French Cooperative Group on CLL[15] compared fludarabine using a standard regime with CAP in patients with Binet stage B & C B-cell CLL. The randomisation was stratified by whether patients had either had no prior therapy, or had received prior therapy with chlorambucil or a similar therapy. Thus the study provided information directly relevant to this review on 100 patients (52 receiving fludarabine; 48 receiving CAP). The outcomes measured in these subjects were clinical response, adverse events, survival, time to progression and duration of response. The only outcome of interest not measured by this trial was impact on quality of life. In both cases 4 further cycles were allowed in the case of incomplete but continuing response. A prophylactic regime was not mentioned. Patients relapsing after initial response to fludarabine or CAP could be switched to the alternative regime; no information is given on switching where the participant was chemorefractory.

Leporrier et al,[23] also conducted under the auspices of the French Cooperative Group on Leukaemia, compared fludarabine (given intravenously) with CAP or ChOP in untreated CLL patients, Binet stages B and C. 341 patients received fludarabine, which was given in standard intravenous dosage ($25mg/m^2/d$ for 5 days repeated every 28 days) for 6 cycles. 240 patients were allocated to CAP for 6 cycles and 357 patients were allocated to ChOP. Recruitment to the CAP arm of the study was stopped in February 1996 after the third planned interim analysis showed an excess of deaths. The CAP regime consisted of cyclophosphamide intravenously $750mg/m^2$ on day 1; doxorubicin intravenously $50mg/m^2$ on day 1 (50% decrease if in remission); oral prednisolone $40mg/m^2/d$ on days 1-5. The ChOP regime consisted of vincristine (intravenous dose) $1mg//m^2$ on day 1; doxorubicin (intravenous dose) 25mg on day 1; cyclophosphamide (oral dose) $300mg/m^2$ days 1-5; prednisone (orally) $40mg/m^2$ days 1-5, repeated every 28 days for six cycles then every three months, for six cycles. Patients were switched to fludarabine if they had progression after three months. A further 6 cycles at 3 monthly intervals could also be given. A prophylactic regime was not mentioned. In the event of treatment failure, during the first 3 cycles, fludarabine or CAP could be switched to the alternative regime after the third cycle.

Specified outcomes were disease response, progression-free survival, overall survival and toxicity. Overall survival was stated to be the primary outcome.

Table 16 - Characteristics of RCTs comparing fludarabine to CAP or ChOP

First author, year	French Co-operative Group 1996[15]	Leporrier et al[23]					
Number randomised	100 (52 untreated/48 previously treated) to fludarabine 96 (48 untreated/48 previously treated) to CAP	341 to fludarabine 240 to CAP 357 to ChOP					
Inclusion criteria	>18 years of age, No Prev R_x B-CLL, Binet stage B or C. Relapsed B-CLL pre-treated Chl or other anthracycline /anthrachinone regimen for >6months <3 years, Req R_x : impairment of normal haematopoiesis, B-symptoms or pd.	B-CLL, previously untreated, Stage: Binet B & C, under 75 yrs					
Exclusion criteria	WHO ps =4, Abnormal renal/liver function Uncontrolled autoimmune haemolytic anaemia and thrombocytopenia HIV-related disease, T-CLL, Richter's syndrome	AIHA, concomitant neoplasm, prolymphocytic leukaemia, diagnosis of B-CLL according to IWCLL					
Demographics	Age: Median 63 (39-70) fludarabine arm Median 62 (43-78) CAP arm Sex: 74% male fludarabine arm, 66% male CAP arm Demographics not given for sub-set of cohort most relevant	Flu Stage B	Flu Stage C	CHOP Stage B	CHOP Stage C	CAP Stage B	CAP Stage C
		236	105	240	117	175	65
		62 yrs (53-67)	63 yrs (56-68)	62 yrs (55-67)	64 yrs (59-68)	60 yrs (55-67)	65 yrs (58-71)
		74% male	69% male	76% male	66% male	69% male	53% male
Intervention	Flu: (25mg/m² tbsa IVD, d 1-5, p/ 28d, 6 cycles) (+4 if incomplete but continuing response). Prophylactic regime not mentioned. Switch to CAP if chemorefractory	Flu: (25mg/m² tbsa IVD, d 1-5, p/ 28d, 6 cycles) and then every 3mths for 6 cycles or not (50/50 randomly allocated if responders. Prophylactic regime not mentioned. Sw to CAP after Rx failure if no resp					
Comparator	CAP: cyclo (750mg/m² p/d, d 1-5, p/ 28 d), pred (50mg/m² p/d, d 1-5, p/ 28 d) and doxo (40mg/m² p/d, d 1of 5 d course), rpt p/28d for 6 cycles (+4 if incomplete but continuing response). Prophylactic regime not mentioned. Sw to Flu in chemorefractory cases	CAP: cyclo (750mg/m² p/d, d 1-5, p/ 28 d), pred (50mg/m² p/d, d 1-5, p/ 28 d) and doxo (40mg/m² p/d, d 1of 5 d course), rpt p/28d for 6 cycles, then every 3 months for 6 cycles. Prophyl reg not mentioned. Sw to Flu after 3 mths if Rx failure with CAP CHOP: vincristine iv 1mg//m2 d1; doxo iv 25mg d1; cyclop po 300mg/m2 d1-5; pred po 40mg/m2d1-5, rptd every 28d for 6 cycles then every 3 mts, for 6 cycles. Prophyl reg not mentioned. Sw to Flu if prog disease after 3 mths					
Concomitant Rx: Corticosteroids Other Rx allowed	No statement on banning of use or of prophylaxis taken	Not stated					
Pre-treatment tests:	Serum chemistries; blood counts; physical examination; pathology specimen; bone marrow tests	Not stated					
Outcome measures (* = primary outcome)	Disease response (rates)* progression-free survival, overall survival, toxicity	Overall survival* disease response (rates and stage at 6 months) progression-free survival, time to re-treatment, toxicity					
Response definitions CR = Complete remission PR = Partial remission PD = Progressive disease SD = Stable disease	CR: Disappearance of all palpable disease and return to normal of blood counts, granulocytes >1500μL, thrombocytes > 100000/μL, Hb >11g/dL, BM lymphocyte %< 30%. PR: >50% reduction measurable disease and >50% improvement of all abnormal blood counts. SD: No change in parameters PD: Lymphocytes >10000/μL, >25% increase above remission values or >50% increase in BM infiltration or corresponding enlargement of lymph nodes, liver or spleen	CR:Absence of lymph node, spleen and liver enlargement; Lymphocytosis <4.10⁹/L, neutrophils> 1.5 10⁹/L; platelets>100 10⁹/L; haemoglobin level >110 g/L PR: decrease>50% of lymph node, spleen and liver enlargement; decrease lymphocytosis 50% of baseline value; neutrophils> 1.5 10⁹/L or increase>50% of baseline value; platelets>100 10⁹/L or increase>50% of baseline value; haemoglobin level >110 g/L or increase>50% of baseline value SD: Absence of response or progression PD: increase volume> 50% lymph node, spleen and liver enlargement (or new involvement of these organs) decrease lymphocytosis 50% of baseline value; neutrophils> 1.5 10⁹/L or decrease>50% of baseline value; platelets<100 10⁹/L or decrease>50% of baseline value; haemoglobin level <110 g/L or decrease>50% of baseline value					

Study Quality

Both studies were well conducted, especially with reference to follow-up of patients, allocation concealment and randomisation of patients. However, they were open to detection bias through lack of blinding of patients, investigators and assessors.

Table 17 - Quality assessment RCTs comparing fludarabine to CAP or ChOP

Elements of Jadad score	French Cooperative Group[15]	Leporrier et al[23]
A. Generation of allocation schedule		
A1 *Was the trial described as randomised?*	Yes	Yes
A2 *Was allocation truly random? or*	Yes	Yes
Was allocation quasi-random? or	No	No
Was allocation systematic? or	No	No
Was the method of randomisation not stated or unclear?	No Note: Randomisation was stratified by prior treatment	No
B. Concealment of treatment allocation		
B1 *Was concealment adequate? or*	Yes	Yes
Was concealment inadequate? or	No	No
Was concealment unclear?	No	No
C. Implementation of masking		
C1 *Was the trial described as "double-blind"?*	No	No
C2 *Was the treatment allocation masked from the participants?*	No	No
C3 *Was the treatment allocation masked from the investigators?*	No	No
C4 *Was treatment allocation masked at the outcome assessments?*	Unclear	No
D. Completeness of the trial		
D1 *Were the number of withdrawals in each group stated?*	Yes	Yes
D2 *Was an intention-to-treat analysis performed?*	Yes	Yes
D3 *What were the drop-out rates in each group of the trial for each of the main outcomes?*	Generally: Fludarabine 6/106 (6%) CAP 6/102 (6%)	Generally: Fludarabine 5/341 (1%) ChOP 6/357 (2%) CAP 3/240 (1%)
D4 *Are there substantial differences in completeness between the groups?*	No Note: Assessment of response duration restricted to responders	No
Total Jadad score (maximum 5)	**3**	**3**

An important issue needing to be taken into account in the interpretation of the results of the effectiveness of fludarabine relative to CAP is the possibility of duplication between the two studies. It is unclear the extent to which previously untreated CLL patients in the Leporrier et al study,[23] were also represented in the treated sub-group (previously untreated patients) of the French Cooperative Group on CLL et al{Johnson} study. Both studies began in 1990 and both involved the French Cooperative Group on CLL. The duplication is unlikely to be complete because the study by Leporrier et al is of longer duration, and other European countries contributed patients to the French Cooperative Group on CLL et al study.[23] However, the possibility of duplication of the results from some patients remains. If information should emerge that the number of subjects duplicated in the fludarabine and CAP arms is larger than expected, a reassessment of the results may be necessary in the future.

Results for French Cooperative Group, 1996 study comparing fludarabine to CAP[15]

Response rate

The rates of complete response in previously untreated patients were 71% for the fludarabine group and 60% for the CAP group. The difference in CR was thus 11%, and this difference in response rate was not statistically significant. The partial response rates were 48% and 43% for fludarabine and CAP, respectively.

Time to progression

For previously untreated patients the median time to progression had not been reached at time of evaluation for the patients treated with fludarabine, and the time to progression was a median of 208 days for CAP. This difference was statistically significant (p=0.0001). It is important to note that the figures given for this outcome refer to patients who had either a partial or complete response to treatment. Data for the patients who did not respond to treatment were not included in this analysis.

Overall survival

In previously untreated patients, the median overall survival for the fludarabine treated patients had not been reached at the point of evaluation, but was 1580 days with CAP treatment. The difference, although favouring fludarabine, was not statistically significant (p= 0.087).
Quality of life

No direct measure of impact on quality of life was provided. It should be noted however, that the definition of complete response in particular, does capture features of the disease which are likely to impinge on quality of life i.e. disappearance of all palpable disease.

Adverse events and toxicity

It was only possible to consider the results of the study as a whole (previously treated combined with previously untreated participants). On this basis 33 patients did not complete the course of treatment in the fludarabine group and 35 in the CAP group. The most common reasons for failure to complete treatment in the fludarabine group were progressive disease (9 patients), intercurrent illness (15 patients) and death (9 patients). The causes of death were from infection (4), from progression (2), from myocardial infarction (1) and from a stroke related to severe thrombocytopenia (1). The reasons for failure to complete treatment in the CAP group were progressive disease (21 patients), additional or intercurrent illness (10 patients) and death (3 patients). The causes of death during treatment in the CAP group were from infection (3). The difference in deaths during treatment (fludarabine 9 vs CAP 3) is not statistically significant.

Adverse events other than death appeared extremely common in both treatment arms. There were 598 mild/moderate adverse events in the fludarabine group and 799 in the CAP group. There were 227 severe adverse events in the fludarabine group and 308 in the CAP group. Although not explicitly stated, it seems likely that most of the 196 patients in the trial would have experienced not just several mild to moderate adverse events, but at least one severe

adverse event too. The majority of adverse events were haematological. In this category granulocytopenia was the most common problem, but not greatly different from other haematological adverse events such as anaemia, thrombocytopenia and infection.

However there were some important differences between the level and profiles of adverse events in the fludarabine and CAP arms. They were less common in the fludarabine arm; the CAP arm in particular had statistically significantly higher adverse event rates in the non-haematological categories of nausea and vomiting, and alopecia and hair loss, which are side effects likely to be subjectively important to patients

Overall effectiveness

The study is small. However, even given this proviso, fludarabine appears to be more effective than CAP particularly with respect to increased duration of response and reduced alopecia and nausea. Absence of any direct measurement of impact on quality of life makes quantification of the net effect over the whole treated population (including non-responders) difficult.

Table 18 - Results from study by French Cooperative Group et al

	Fludarabine	CAP	Differences
Number entered into study**	106	102	
Drop-outs/exclusions before assessment**	6 excluded for protocol violation (33 patients did not complete treatment but were included in assessment; 9 of these were deaths during treatment)	6 excluded for protocol violation (35 patients did not complete treatment but were included in assessment;3 of these were deaths during treatment)	
Losses to follow-up**	6/106	6/102	
Number randomised	100 (52 untreated, 48 previously treated)	96 (48 untreated, 48 previously treated)	
Number of patients evaluated for response	52 previously untreated	48 previously untreated	
Evaluated as intention-to-treat	Yes	Yes	
Clinical response rates (RR=CR+PR) for untreated patients	37/52 = 71%	29/48 = 60%	Difference = 11% favouring fludarabine P=0.26.
Follow-up period**	Median follow-up period = 34 months (1-61 months)		
Median duration of response$^{\xi}$	Median not yet reached at time of evaluation	208 days (60-412 days)	Favours fludarabine P<0.001
Median overall survival$^{\xi}$	Median not yet reached at time of evaluation	1580 days	Favours fludarabine P= 0.087
Patients evaluated for adverse events**	100	96	
Total adverse events** Mild/moderate adverse events** Severe and fatal adverse events**	N/S Haematological (357) Non-haematological (143) Infections (98) Haematological (194) Non-haematological (12) Infections (21)	N/S Haematological (332) Non-haematological (369) Infections (98) Haematological (191) Non-haematological (105) Infections (12)	Favours fludarabine in respect of non-haematological adverse events, particularly nausea and vomiting and alopecia. These differences statistically significant
Deaths during treatment	9	3	Favours CAP Not statistically significant
Quality of life	Not measured	Not measured	
NOTES: **Indicates results extracted for both previously treated and untreated patients ξ Only includes data for responders to first-line therapy			

Results for RCT by Leporrier et al comparing fludarabine to CAP

Disease response rates

The complete response rates for were 40% and 15 % for fludarabine and CAP respectively. The difference of 25% in favour of fludarabine was statistically significant (p<0.0001).

Duration of response/time to progression

The median time to disease progression was 31.7 months and 27.7 months for fludarabine and CAP respectively. Although there was a trend favouring those treated with fludarabine this was not statistically significant. The time to second-line therapy for fludarabine patients was 45.4 months, which was significantly better than the time to second-line therapy with CAP (25.7 months).

Overall survival (primary outcome)

The median overall survival was 69 months and 70 months for fludarabine and CAP respectively. The difference was not statistically significant, nor was there any statistically significant difference in the 5-year survival rates.

Toxicity/Side effects

The numbers of deaths (during treatment) were similar with seven deaths occurring in the fludarabine group and eight deaths in the CAP group.

Lower rates of nausea (p=0.003) and no alopecia (p<0.001) was observed in the fludarabine group, compared to the groups of patients treated with CAP. However, a higher incidence of thrombocytopenia was observed in the fludarabine group compared to CAP. There was significantly more anaemia, neutropenia and infection in the fludarabine group compared to the CAP group.

Overall effectiveness

The pattern of results for fludarabine in comparison with CAP in this study is generally consistent with that identified in the much smaller trial by the French Cooperative Group et al.[15] More responses of longer duration are achieved with less nausea and alopecia. This study indicates that the incidence of haematological side effects is greater. Quantifying the net effects over the whole treated populations is difficult in the absence of direct measures of impact on quality of life. The study does provide good evidence that the overall survival is unchanged, but when interpreting this account needs to be taken that the drugs allocated first line, are likely to have been received by participants in other arms in second and subsequent lines of therapy.

Table 19 - Results from RCT by Leporrier et al comparing fludarabine to CAP and ChOP)

	Fludarabine	ChOP	CAP	Differences
Number entered into study	341	357	240	Accrual to CAP group stopped when interim analysis showed significant decreased response rates in CAP group for ethical reasons.
Drop-outs/exclusions before assessment	1	2	1	
Losses to follow-up	4	6	3	
Number randomised	341	357	240	
Number of patients evaluated for response	336	351	237	
Complete response for all patients (CR)	135/341 =40.0%	104/357 = 29.1%	36/240 =15.0%	Flu and ChOP both sig. more CRs than CAP (p<0.0001 each). Sig. advantage of flu over ChOP (p=0.004)
Overall response rates (CR + PR)	239/341 = 70.1%	251/357 = 70.3%	138/240 = 57.5%	Significant advantage of flu and ChOP over CAP<0.0001)
Follow-up period	Median follow-up time was 70 months			
Time to disease progression (median)	31.7 months	29.5 months	27.7 months	P [log rank] = 0.09 Non statistically significant trend favouring fludarabine
Time to second-line therapy	45.4 months	32.2 months	25.7 months	P [log rank] <0.0001 Statistically significantly favours fludarabine over remaining two treatments
Median overall survival[ξ]	69 months	67 months	70 months	No significant difference
5 year survival rates	58.4% (95% CI 51.9%, 64.9%)	57.3% (95% CI 51.0%, 63.6%)	59.8% (95% CI 53.4%, 66.2%)	P [log rank] = 0.38 No significant difference between the three treatments
Patients evaluated for adverse effects	341	357	240	
Deaths during treatment	7	5	8	Similar between groups
Anaemia	57	57	25	No sig. difference between flu and ChOP. Favours CAP over fludarabine (P=0.04)
Auto-immune haemolytic anaemia	6	3	0	Favours CAP over fludarabine (P=0.07)
Neutropenia	122	131	71	Generally favours CAP, but not stat significant
Thrombocytopenia	49	29	18	Favours CAP over fludarabine (P=0.04) & favours ChOP over fludarabine (P<0.0001)
Infection	16	17	10	Generally favours CAP, but not stat significant
Alopecia	0	54	35	Favours fludarabine over ChOP, CAP (P<0.0001)
Nausea, vomiting	3	6	13	Favours fludarabine

Results for RCT by Leporrier et al comparing fludarabine to ChOP

Disease response rates

The complete response rates were 40% and 27% for fludarabine and ChOP. The 13% difference was statistically significant (p=0.004).

Duration of response/time to progression

The median time to disease progression was 31.7 months and 29.5 months for fludarabine and ChOP respectively. Although there was a trend favouring those treated with fludarabine this was not statistically significant. The time to second-line therapy for fludarabine patients (who responded to treatment) was 45.4 months, significantly better than the time to second-line therapy for patients who responded to treatment with ChOP (32.2 months).

Overall survival (primary outcome)

The median overall survival for the three groups was 69 months for fludarabine and 67months for ChOP. The difference was not statistically significant.

Toxicity/Side effects

The numbers of deaths (during treatment) recorded were similar with seven deaths in the fludarabine group and five deaths in the ChOP group.

Lower rates of nausea (p=0.003) and no alopecia (p<0.001) was observed in the fludarabine group, compared to the groups of patients treated with ChOP. However, a higher incidence of thrombocytopenia was observed in the fludarabine group compared to the ChOP group. The incidences of anaemia, neutropenia and infection were similar for the fludarabine and ChOP groups.

Overall effectiveness

The study indicates that fludarabine is probably more effective than ChOP particularly with respect to complete response rate, time to re-treatment and reduced levels of alopecia. There was no difference in the primary outcome of overall survival, but interpreting this needs to be take account of the fact that the drugs allocated first line are likely to have been received by participants in other arms in second and subsequent lines of therapy.

Appendix 8 - Search strategy for Cost and Quality of Life studies

- The NHS Economic Evaluation Database was searched using the following terms: Fludara$, leuk?emia, chronic, lymphocytic.

- Internet sites of the following health economics units were also searched: University of York Centre for Health Economics, Health Economics Research Unit, Health Economics Research Group.

The following strategy was executed in MEDLINE

1   economics/
2   exp "costs and cost analysis"/
3   cost of illness/
4   exp health care costs/
5   economic value of life/
6   exp economics medical/
7   exp economics hospital/
8   economics pharmaceutical/
9   exp "fees and charges"/
10   (costs or cost or costed or costly or costing).tw.
11   (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
12   or/1-11
13   fludara$.mp.
14   12 and 13
15   quality of life/
16   life style/
17   health status/
18   heath status indicators/
19   treatment outcome/
20   "outcome assessment (health care)"/
21   or/15-20
22   b cell lymphocytic.ti,ab.
23   or/21-22
24   exp leuk?emia b cell chronic/
25   cll.ti,ab.
26   b-cll.ti,ab.
27   chronic lymphocytic leuk?emia.ti,ab.
28   or/24-27
29   28 and 23

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