FLUDARABINE as SECOND LINE THERAPY for B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA

Report commissioned by: NHS R&D HTA Programme

On behalf of: The National Institute for Clinical Excellence

Produced by: Department of Public Health & Epidemiology
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Date completed: 9/1/2001

Expiry Date: 1/1/2002

[A small amount of commercial-in-confidence data, obtained from the manufacturer of fludarabine, has been removed from pages 30 and 32 of this document.]

HOW TO CITE THIS REPORT

Wake BL, Bryan S, Barton P, Fry-Smith A, Davenport C, Song F, Hyde C. *Fludarabine as second line therapy for B-cell chronic lymphocytic leukaemia.* Birmingham: University of Birmingham, Department of Public Health and Epidemiology, January 2001.

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CONFLICTS OF INTEREST

Source of funding

This report was commissioned by the NHS R&D HTA programme.

Relationship of reviewer(s) with sponsor

No members of the review team or the units to which they belong at the University of Birmingham have any pecuniary relationship with sponsors, specific and non-specific.

ACKNOWLEDGEMENTS

Prof. A.K. Burnett:	Peer review and general advice
Dr. C. Fegan:	Peer review and general advice
Dr. A. Jacob:	Peer review and general advice
Dr. S. Johnson:	Peer review and general advice
Dr. T.A. Lister:	Peer review and general advice
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West Midlands Cancer Intelligence Unit:	Advice on incidence and prevalence of CLL

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SUMMARY

- Description of proposed service

Fludarabine is a recently developed chemotherapeutic agent. What is under consideration is whether the already well established use in its current licensed indication should be supported and further encouraged. The current licence is for use in patients with B-cell CLL 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 ie as a second line of treatment.

- Epidemiology and background

CLL is a cancer of lymphocytes, one of the types of white blood cell. It is slowly progressive with gradual accumulation of malignant cells in blood, bone marrow and lymph nodes. This gives rise to anaemia, thrombocytopenia and immunosuppression, among other effects. The disease is widely acknowledged to be incurable, although median overall survival is 10 years. An average HA of 500,000 may have approximately 16 new patients presenting each year, most of whom will be over 60 years of age and asymptomatic. Only approximately 50% will require treatment at some stage during the course of their disease.

Specific anti-cancer treatment does not commence until the disease becomes symptomatic. The main aim of treatment is to maximise quality of life by inducing remission, abolishing symptoms associated with relapse, with minimal treatment side-effects. First line therapy is usually oral chlorambucil (or an equivalent alkylating agent). Second line treatment is usually an anthracycline containing chemotherapy regimen such as CHOP, or fludarabine.

- Number and quality of studies, and direction of evidence

The systematic review of effectiveness identified two RCTs but only one of these contributed data to the analysis. Although well conducted this RCT was small comparing disease progression, survival and adverse events in 48 previously treated patients given fludarabine with 48 given CAP. Overall response rates were 48% (fludarabine) vs 27% (CAP) - difference 21% (95%CI: 2 to 40). Improvements in response rate were seen in both complete and partial response categories. The time to progression in responders was increased from a median of 179 days (CAP) to 324 days (fludarabine) but this was not statistically significant (p=0.22). No difference was seen in overall survival. In the whole trial, which included a further 100 previously untreated patients (total 196; 100 fludarabine; 96 CAP), adverse events were common in both arms, but nausea and vomiting, and alopecia and hair loss were markedly less for fludarabine. Deaths during the treatment period were greater for fludarabine than for CAP (9 vs 3), but this difference was not statistically significant.

7 case-series with more than 50 patients were also considered. The variability of the results for response rates and times to progression suggested a cautious interpretation of the results of the evidence on effectiveness provided by the single small RCT identified was appropriate.

- Summary of benefits

On the evidence provided by the single small trial, qualitatively it appears reasonably clear that the balance between beneficial effects and adverse events favours fludarabine over CAP. However, the degree to which beneficial effects are outweighed by adverse events is difficult to quantify, particularly in the absence of any direct measures of the impact on quality of life of fludarabine.

- Costs

The drug cost of a recommended course of iv fludarabine is £3,900. The wider cost of administration is estimated to be £6,000. This estimate could be subject to variation depending on what the true incidence, severity and costs of treating adverse events are judged to be. The total annual budget impact is highly uncertain; we derived an approximate upper estimate of £5.5 m per annum for the NHS in England and Wales. This equates to an additional cost of £50,000 per annum for an average HA of 500,000 persons.

- Cost-effectiveness and cost-utility

Apparently favourable estimates of the incremental cost-effectiveness of fludarabine relative to CHOP were identified. However they need to be interpreted very cautiously. The cost-utility of fludarabine cannot be accurately calculated and so cannot assist a judgement on whether for a given investment of resources, encouraging use of fludarabine is likely to achieve more net benefit than investing in other areas of health care.

- Other important issues regarding implications

The recent licensing of an oral preparation of fludarabine has implications for cost and patient acceptability. Its effectiveness, cost and cost-effectiveness will need to be assessed, as this could not be covered in this report.

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- Need for further research

Ideally there should be further RCTs on second line therapy with fludarabine in relapsed/refractory CLL. Realistically, attention has now focused on the effectiveness of fludarabine as a first line therapy in CLL. Arguably the priority should be support and amplify on-going RCTs to ensure an adequate evidence-base for likely future NICE decisions on the use of fludarabine. Future RCTs must assess impact on quality of life directly.

ABBREVIATIONS

AML	Acute myeloid leukaemia
BM	Bone marrow
BNF	British National Formulary
BNLI	British National Lymphoma Investigation
CAP	Cyclophosphamide, doxorubicin, prednisolone
CCST	Corticosteroids
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CLL	Chronic lymphocytic leukaemia
CML	Chronic myelogenous leukaemia
CR	Complete response/remission
CT	Computerised tomography
CVP	Cyclophosphamide, vincristine, prednisolone
EBMT	European Group for Bone and Marrow Transpantation
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research on the Treatment of Cancer
ESR	Erythrocyte sedimentation rate
FUO	Fever of unknown origin
HA	Health Authority
HIV	Human Immunodeficiency Virus
ICER	Incremental cost-effectiveness ratio
iv	Intravenous
LDH	Lactate dehydrogenase
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NEED	NHS Economic Evaluations Database
NHL	Non-Hodgkin’s lymphoma
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
Conditioning agent	In this instance fludarabine is used to prepare BM for transplant by depletion of T-cells
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
Mini-transplants	Partial replacement of bone marrow from matched donor
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

AIM OF THE REVIEW

Despite undoubted improvements in the treatment of haematological malignancies, a number of conditions remain difficult to treat. Chronic lymphocytic leukaemia (CLL) is such a condition and consequently the search continues for therapeutic agents that might improve its management. Fludarabine is a novel chemotherapeutic agent that was licensed in 1994.

The research question addressed by this report is, "What is the clinical effectiveness and cost-effectiveness of fludarabine in 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?" these being the circumstances for which fludarabine is currently licensed.

1. BACKGROUND

1.1 Description of underlying health problem

1.1.1 Nature of the condition

CLL is a malignant disorder of circulating blood cells. There are several types of blood cells but the ones which proliferate in CLL are lymphocytes, a type of white blood cell. Lymphocytes are of two main types – B-lymphocytes and T-lymphocytes. The vast majority of CLL is of B-cell origin, and the term B-cell CLL is sometimes used to distinguish the most common type of CLL from the minority derived from other lymphocytes. The effect of the proliferation of the abnormal lymphocytes is to impair the production and function of normal blood cells, particularly the red blood cells, giving rise to anaemia, and platelets (thrombocytopenia) predisposing to bleeding and the white cells giving rise to immunosuppression. The disease can also cause enlargement of lymph nodes. The disease is often diagnosed by chance when a routine blood test reveals very high levels of lymphocytes in the blood – lymphocytosis. The severity of the disease is gauged by the number of main effects present in a patient. This is the basis of staging systems, the most commonly used of which are the Binet [1] system and the Rai [2] system given below in Tables 1 and 2.

Table 1 Binet staging system for CLL [1]

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 <100x10^9/L

Table 2 Rai staging system for CLL [2]

Low risk	Stage 0	Lymphocytosis in blood (>5x10^9/L) and marrow (>30%)
Intermediate risk	Stage I	Lymphocytosis in blood & marrow with enlarged lymph nodes
	Stage II	Lymphocytosis in blood & marrow with enlarged spleen and/or liver (with or without enlargement of nodes)
High risk	Stage III	Lymphocytosis in blood & marrow with anemia (Hb <110g/L)
	Stage IV	Lymphocytosis in blood & marrow with thrombocytopenia (platelets <100x10^9/L)

The International Workshop on CLL 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 [3].

1.1.2 Epidemiology

CLL is the most common leukaemia in adults [4]. In 1998 there were 824 deaths from CLL in England and Wales [5]. There were approximately 1,700 new cases of CLL per year in the UK in 1989 and it is most common in older persons [6], with the average age of diagnosis being 64 years [4]. It is more common in men than women. The overall incidence rate in England and Wales in 1992 was 3.8 and 2.7 per 100,000 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 16 new cases each year. The prevalence is considerably in excess of this due to the long median survival times of patients – overall approximately 10 years (more than 10 years in $^2/_3$ patients) [4]. Thus, again approximately, there are likely to be about 160 patients with CLL in the average HA at any one time [7]. However, it should be noted that any time only half of these will be being actively treated – see next section.

1.1.3 Aetiology and prognosis

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 [6]. Migrant studies of Japanese moving to the USA [8], and retaining their low rates of CLL, seems to confirm a genetic component.

As the word “chronic” in CLL implies, the disease is slowly progressive. Symptoms appear as the number of malignant cells accumulates in blood, bone marrow and lymphatic tissue. The motive of treatment is to induce remission, abolish symptoms and restore quality of life. The survival may be as long as 10 years from diagnosis. Indeed many patients die of unrelated diseases [4]. However, at the present time CLL remains incurable, as it is extremely difficult with currently available therapies to eliminate the malignant lymphocytes entirely from the body. Stage is the most important prognostic factor, with over 90% of early stage patients (Binet stage A), which is also the commonest category at presentation, surviving 5 years [9]. 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 [4]. More than 25% patients with low risk disease as described above die of unrelated causes, while in 40% the disease progresses to a more advanced stage. Ultimately 50% patients require treatment [10].

1.1.4 Prognostic factors

A systematic search was undertaken of cohort studies that might provide accurate information on the natural history of CLL. The search strategy used is given in Appendix 1. Five articles were collected for prognostic factors in CLL; 3 reviews and 2 by the same authors about laboratory factors.

Tefferi et al suggested that the major prognostic factor in B-CLL is the clinical stage of the disease [11]. Molica et al listed other prognostic parameters, including age and gender, peripheral blood lymphocyte count and lymphocyte doubling time, pattern of bone marrow involvement, cytogenetics, and immunopenotype [12]. They cited results from the French Cooperative Group for CLL Study: the 5 year survival rate was 89% for stage A(0) and 77% for stage A (I-III) using the International Workshop on CLL system.

In a different study by Molica et al, 93 patients with CLL were followed up for a median time of 49 months [13]. It was found that patients with low CD20 antigen expression have a better survival outcome than those with the high CD20 antigen expression (relative risk 0.51, 95% CI: 0.24 to 1.04). In multivariate analysis, only absolute peripheral blood lymphocytosis and Binet clinical stages remained independent prognostic factors. They concluded that "although variability of CD20 and SmIg expression make it possible to appreciate biological heterogeneity of B-cell CLL better, they cannot substitute well-established clinico-hematological features in the prognostic assessment of B-CLL patients".

In another paper by Molica et al, they found that beta2-microglobulin and soluble CD23 contribute individually to prognosis of B-CLL[14]. In addition, a combination of beta2-microglobulin and soluble CD23 was a strong prognostic system because their combined use integrates different clinical and biological aspects of CLL and therefore provides prognostic information superior to those of a single marker.

This analysis confirms that clinical staging remains the most important prognostic factor, but alerts to the possibility that newer markers may improve assessment of prognosis.

1.1.5 Significance in terms of ill-health (burden of disease)

The nature of CLL and the duration of the diseases, suggests that individually and at a population level it is responsible for a considerable amount of morbidity and mortality.

1.2 Current service provision

1.2.1 Objectives of treatment and important health outcomes

There are at least five potential objectives in treating CLL, or indeed any other cancer:

- Eradicating the cancer, and so effecting a long-term cure
- Achieving long term cancer stasis or regression, with the aim of prolonging life
- Treating symptoms, particularly those arising from disease progression, so improving quality of life
- Helping patients come to terms with their condition, again improving quality of life
- Managing the terminal stages of the disease, so allowing dignified death free of discomfort and distress

This predicts that the following health outcomes are likely to be of potential importance:

- Absence of cancer at given points in time following diagnosis
- Mortality, particularly cancer specific mortality
- Duration of survival
- Quality of life
- Patient and carer satisfaction

However in CLL, because the prospect of cure with current treatments is acknowledged to be rare (and there has been no claim that fludarabine substantially alters this), the main focus of specific cancer therapy is on treating symptoms arising from progression, so maximising quality of life during the period of survival.

Specific events that contribute to this end, and so might act as proxies for the main objective, can thus be identified as:

- Number of episodes of symptomatic progression
- Duration of these episodes
- Severity of symptoms associated
- Ability to bring about a remission
- Speed of induction of remission
- Reduction of symptoms associated with the remission
- Adverse events associated with induction of the remission
- Duration of remission

1.2.2 Established treatments

There is clear consensus that active cancer specific treatment is generally unjustified until patients become symptomatic. Such watchful waiting may extend over many years. Once symptomatic disease progression occurs a hierarchy of treatments is invoked. The order 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 response.

First line: This may involve the use of an oral alkylating agent such as chlorambucil with or without corticosteroids. Occasionally cyclophosphamide may be used as an alternative. Fludarabine is increasingly also being considered as a first line therapy.

Second line: This usually involves combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine & prednisolone) or other anthracycline containing regimens such as CVP (cyclophosphamide, vincristine & prednisolone) or CAP (cyclophosphamide, doxorubicin & prednisolone). Fludarabine is an alternative, which may also be used before or after regimens such as CHOP.

1.2.3 Evidence on the effects and effectiveness of existing treatments for CLL

A systematic search was undertaken targeting systematic reviews of randomised trials and other rigorous research on the effectiveness of existing treatments for CLL. The search strategy is detailed in Appendix 2. One meta-analysis, and 8 narrative reviews were considered. Further detail on these is provided in Appendix 3. The key points arising were:

- In the meta-analysis [15], immediate chemotherapy was compared with deferred chemotherapy (6 RCTs), and combination chemotherapy was compared with single agent chlorambucil as first line treatment for more advanced CLL (10 trials).
- The conclusion concerning early vs deferred chemotherapy for early disease, was that early treatment offers no advantage in terms of overall survival.
- Concerning first line treatment the value of single agent chlorambucil as the first line of treatment for most patients with advanced disease was confirmed, with no evidence of benefit from early inclusion of an anthracycline
- 5 narrative reviews considered treatment options in CLL, but only two reviews mentioned second line therapy [16], or treatment for 'patients failing front-line therapy' [17]
- Kalil & Cheson [16] writing in the context of US practice, recommended that 'the most appropriate treatment for patients with CLL who relapse after, or are refractory to, initial treatment is referral to a clinical research study. Many could be retreated with alkylating agent; fludarabine has become the standard agent for patients initially treated with an alkylating agent based regimen (overall response rate 40-50%). Combination of fludarabine with alkylating agents, antracyclines or related compounds, cytarabine and interferon-alpha are not clearly better than fludarabine alone.'
- Similarly, Montserrat & Rozman [17] suggested that 'patients failing front-line therapy should be treated with combination chemotherapy or fludarabine'.
- 3 of the 8 narrative reviews were about purine analogues (mainly fludarabine) for CLL.

1.2.4 Current service cost

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.

1.2.5 Variation in services

There seems to be remarkable consensus about the treatment of CLL, predicting that variation in treatment, although constituting only one part of services to help patients with CLL, is likely to be limited. Of note is the well-established place of fludarabine in current treatments, indicating that in most 'clinicians' minds this treatment may no longer be considered new.

1.3 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.

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' ie 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 4), the BNF [18] 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."

For mild renal impairment, dose reduction is suggested; and avoidance is suggested if creatinine clearance is <30ml/min. Specific interacting drugs are given as:

- Dipyridamole: Efficacy of fludarabine possibly reduced
- Pentostatin: Increased pulmonary toxicity with pentostatin (unacceptably high incidence of fatalities.

The recommended dosage is 25mg/m^2 daily for 5 consecutive days in every 28 days by the intravenous route. It should be administered up to the achievement of a maximal response (usually 6 cycles) and then discontinued. The quoted cost per 50mg vial is £130.00 [18]. This suggests a net drug cost of a 6 cycle treatment will be approximately £3,900.00 (5x6x£130.00). This would be sufficient to treat a person up to a surface area of 2m^2 (average for UK adult approximately 1.7m^2).

The drug acquisition costs are considerably greater than alternative first and second line therapies such as chlorambucil and CHOP.

The Schering submission to NICE refers to an oral version of fludarabine which "has recently been approved and will be available by the end of the year". It should be noted that this technology appraisal has not formally considered this preparation.

1.4 Summary of key points from background

Disease:

- CLL is a cancer of lymphocytes (white blood cells); the vast majority are of B-cell origin
- It is slowly progressive with gradual accumulation of malignant cells in blood, bone marrow and lymph nodes
- This gives rise to anaemia, thrombocytopenia and immunosuppression, among other effects
- The disease is widely acknowledged to be incurable
- It mainly affects persons older than 60 years
- The average HA may have approximately 16 new patients presenting each year
- The median overall survival is 10 years
- The average HA may have approximately 160 patients with CLL at any time
- Only a maximum of 50% of these will require treatment
- Prognosis varies by clinical stage; using the Binet classification median survival is more than 10 years for stage A; 7-9 years for stage B; and 5 years for stage C
- Most patients at presentation are asymptomatic and stage A
- 25% of low risk patients die of unrelated causes

Existing treatments:

- Specific anti-cancer treatment does not commence until the disease progresses to the point that it is symptomatic

- The main aim of treatment is to maximise quality of life by inducing remission, abolishing symptoms associated with relapse, with minimal treatment side-effects
- First line therapy is usually oral chlorambucil (or an equivalent alkylating agent), with or without steroids
- Second line treatment is usually an anthracycline containing chemotherapy regimen such as CHOP, or fludarabine
- The effectiveness of current first line treatment strategies has a good evidence base; less is known about the effectiveness of second line treatments.
- Failure to improve overall survival has been a consistent feature of past randomised trials

New treatment:

- Fludarabine is a cytotoxic agent of the antimetabolite class
- It is currently licensed for "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" ie as second line therapy
- It is administered as a course of 5 injections over 5 days, repeated every 28 days for 6 cycles
- The cost of the drug is approximately £3,900 per course
- This is considerably greater than other treatments such as chlorambucil and CHOP
- The use of fludarabine in CLL is already well established as a second line treatment for B-cell CLL
- It is increasingly being considered as a first line treatment
- An oral preparation of fludarabine has recently been approved; this has not been considered in this technology appraisal

2. EFFECTIVENESS

2.1 Objective

To systematically review the evidence of the effectiveness of fludarabine in 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.

2.2 Methods for reviewing effectiveness

2.2.1 Protocol

The review was undertaken in accordance with a pre-defined protocol (see Appendix 5).

2.2.2 Search strategy

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

- Electronic bibliographic database searches ; MEDLINE (Ovid) 1966-Sept 2000; Embase (Ovid) 1980-Sept 2000; Science Citation Index (Web of Science) 1981- Oct 2000; Cochrane Library 2000 Issue 3 (see Appendix 6 for detail on search terms used)
- Citation checking of studies and reviews obtained
- Citation checking of the reference list of the single industry submission
- Contact with experts in the field (see Appendix 7 for list)

- Internet search engines

This search strategy was amplified by identification of potentially relevant citations in the systematic searches conducted for:

- Evidence on the effectiveness of treatments other than fludarabine for CLL (see Appendix 3 for further details)
- Identification of on-going and unpublished trials involving fludarabine (see Appendices 8 and 9 for further details). This included extensive interrogation of relevant Internet web-sites which are listed in Appendix 8 and a search of the National Research Register (2000, Issue 4)

In the initial protocol we indicated that we would attempt to search conference abstracts. This however was not feasible in the time available.

2.2.3 Inclusion and exclusion criteria

Intervention: Fludarabine at the dose given on the product information sheet i.e. 25 mg/m^2 daily for 5 consecutive days in every 28 days iv for approximately 6 cycles.

Population: 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, as indicated in the UK licensing information.

Comparator: Any, which also includes no treatment and any of the current recommended treatments.

Outcomes : No restriction was made according to the outcomes measured. However, survival, quality of life and adverse events were the outcomes designated a priori as those of greatest interest.

Design : The initial inclusion criteria specified RCTs. In our protocol, in the absence of RCTs we indicated an intent to extend our inclusion criteria to include non-randomized CCT and studies with no parallel control arm ie case-series. In the event as only a very limited number of RCTs were identified, the inclusion criteria with respect to design were extended for completeness. However, to limit work, without introduction of bias, case-series studies with fewer than 50 patients were not considered. Where case-series were included, the inclusion criterion relating to presence of a comparator was inevitably dropped

Application of inclusion/exclusion criteria was undertaken by two reviewers (BW & CD). Decisions were made independently of the data extraction and prior to the scrutiny of results.

2.2.4 Data extraction strategy

Data concerning study characteristics, study quality and results were extracted independently by two reviewers (BW and CD) using a series of proforma. Any differences were resolved by consensus.

2.2.5 Quality assessment strategy

A generic framework, as suggested by the Cochrane Collaboration assessing selection, performance, detection and attrition biases was employed to describe the strengths and weaknesses of the included studies [19].

The RCTs were assessed using the Jadad checklist [20].

In relation to case-series the strengths and weaknesses of the included studies were assessed using a pre-specified framework incorporating:

- Need to indicate that they were conducted prospectively
- Ideally present the results of a consecutive series
- Give clear indications of the patient characteristics particularly with regard to stage of disease and previous treatments
- That losses to follow-up with respect to particular outcomes of interest are <10%

These had been developed by two of the authors in a previous systematic review on a different topic [21].

This was performed independently by two reviewers (BW and CD) and any differences resolved by consensus.

2.2.6 Analysis

As pre-stated the main method of analysis was qualitative. Meta-analysis was not employed and no sub-group analysis was performed.

2.3 Results

2.3.1 Quantity and quality of research available

- Number of studies identified

The search identified 596 studies. By applying the inclusion criteria documented above 38 studies were selected as potentially relevant on the strength of their abstract. Studies clearly identifiable as reviews from the abstract were also excluded at this stage. The 38 studies selected were obtained in full text.

- Number and type of studies included

9 studies were finally included. 2 studies are randomised controlled trials [22, 23] and 7 case series [24, 25, 26, 27, 28, 29, 30] (6 prospective, 1 retrospective).

- Number and type of studies excluded, with reasons for specific exclusions

29 of the potentially included 38 studies were excluded, most were excluded either because patient population was < 50 or that the study was restricted to untreated patients. Full details of excluded studies and reasons for exclusion are available in Appendix 10.

2.3.2 Effectiveness evidence from randomised controlled trials

- Included study characteristics (see Table 3)

The study by The French Cooperative Group on CLL [22] 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 96 patients (48 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 the study by Tondini [23] it was noted that although the stated population was indolent NHL, it included IWF type A, which has some overlap with B-cell CLL. B-cell CLL was not specifically excluded, and following contact with the authors it seems likely that some of the 43% of IWF type A patients were indeed CLL. However, it also seems very likely that the number of these is small and that the results for this sub-group were not readily available. For this reason the results of this study are not presented further, although potentially of great interest being the only study identified comparing fludarabine with another new antimetabolite cytotoxic agent cladribine.

Table 3 Characteristics of included fludarabine RCTs

	French Cooperative Group 1996 [22]	Tondini 2000 [23]
Aim of study	Two-arm comparison of fludarabine with CAP for patients with B cell CLL	Evaluate tolerability and cross-over activity of fludarabine and cladribine in NHL
Number randomised	100 (52 untreated/48 previously treated) to fludarabine 96 (48 untreated/48 previously treated) to CAP	Originally 60 (2 excluded before Rx) → 26 randomised to fludarabine, 32 to cladribine
Demographics	Age: Median 63 (39-70) fludarabine arm Median 62 (43-78) CAP arm Sex: 74% male fludarabine arm, 66% male CAP arm	Age: N/S Sex: N/S
Inclusion/exclusion criteria given :		
Condition	Yes – B cell CLL	Yes – *Relapsed indolent lymphoma* (but includes IWF A, some of which is CLL)
Stage	Yes – Binet stage B or C in untreated patients	No
Prior Rx	No – untreated and previously treated with chlorambucil or similar Rx eligible	Yes – must have received at least one previous Rx and be relapsed or refractory
Age	Yes – must be 18 years or above	Yes – aged 17-75
Sex	No – male and female included	No – demographics not given
Performance status	Yes – WHO scale 4 excluded	Yes – must have Karnofsky PS of 60 or above
Pregnancy/lactation	No – N/S	No
Other serious disease/infection	Yes – abnormal liver or renal function, haemolytic anaemia, thrombocytopenia excluded	No
HIV/Hepatitis	Yes – HIV related disease excluded	No
CNS involvement	No – N/S	No
Other anti-cancer therapy	No – N/S	Yes – must not be receiving other anti-cancer Rx incl. Corticosteroids
Other	Must be 'in need of therapy'	Must have active disease as defined by Cheson 1988, life expectancy > 3 months.
% of cohort relevant to review	49% evaluated patients are previously treated with alkylating agent	43% have IWF A; unknown % of these who are CLL; all have probably previously received alkylating agent
Demographics	Not given for sub-set of cohort most relevant	Not given for sub-set of cohort most relevant
Follow-up: Adequate (target <10% unreported)	Yes – $^{12}/_{208}$ = 6%	N/S
Length	Yes – Median 36 months (1-61)	N/S
Intervention	Fludarabine 25mg/m^2 per day over 5 consecutive days by 30 minute infusion repeated every 28 days for 6 cycles	Fludarabine 25mg/m2 30 min IV infusion on 5 consecutive days every 4 weeks
Comparator	CAP Cyclophosphamide 750mg/m^2 per day; doxorubicin 50mg/m^2 per day IV on day 1; oral prednisone 40mg/m^2 per day on days 1-5 repeated every 28 days for 6 cycles	Cladribine 0.14mg/kg 2 hour IV infusion on 5 consecutive days every 4 weeks
Concomitant Rx:		
Corticosteroids	Banning of use not stated	Stated as being banned
Other Rx allowed	N/S	Prophylactic cotrimoxazole and itraconazole
Pre-treatment tests:	Serum chemistries; blood counts; physical examination; pathology specimen; bone marrow tests	Serum chemistries; blood counts; physical examination; pathology specimen; bone marrow tests
Outcome Measures:		
Clinical Response	Yes (Primary)	Yes
Adverse Events	Yes	Yes
Survival analysis	Yes	No
Quality of Life	No	No
Time to progression	Yes	Yes
Duration of response	Yes	No
Other	None	None
Clinical response definitions: CR = Complete response PR = Partial response SD = Stable disease PD = Progressive 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: Disappearance of all clinical evidence of tumor for a period of at least 2 months. No lymphadenopathy, hepato/ splenomegaly, constitutional symptoms, ANC > 1.5 x 10^9/L, Plts > 100 x 10^9/L, Hb > 11.0 lymphocytes (PBL) ≤4 x 10^9/L.Bone marrow normocellular for age with <30% of mature lymphocytes at least 2 months after clinical complete remission PR: >50% decrease in PBL from baseline value and>50% reduction in lymphadenopathy, +/->50% reduction in the size of liver and/or spleen;and one or more of: ANC ≥ 1.5 x 10^9/L or 50% improvement; Plts > 100 x 10^9/L or 50% improvement; Hb >11.0 gr/dL or 50% improvement SD: Patients with no response / not progressive PD: Not stated

- Included study quality (see Table 4)

Table 4 Quality assessment of included RCT for fludarabine

	French Cooperative Group 1996 [22]
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 Note: randomisation was stratified by prior treatment
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 descibed as "double-blind"?	No
C2 Was the treatment allocation masked from the participants?	No
C3 Was the treatment allocation masked from the investigators?	No
C4 Was treatment allocation masked at the outcome assessments?	Unclear
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 6/106 (6%) CAP 6/102 (6%) Assessment of response duration restricted to responders
D4 Are there substantial differences in completeness between the groups?	No
Jadad score	3

Quality assessment considering the main included RCT overall (not just the sub-groups of most relevance to this review) suggests it was well conducted with respect to randomisation. Its main short-coming related to avoidance of detection bias. Clearly it is difficult to devise a double-blinded study; but in such a situation it is possible to reduce the possibility of detection bias by independent single blind assessment of response, particularly in assigning clinical response definitions. It was not clear that this was done for the outcomes most at risk ie those relying directly or indirectly on assessment of clinical response. Arguably this short-coming would have least impact on assessment of outcome based on death, particularly overall survival

- **Results (see Table 5)**

Clinical response - overall response rates (RR)
Overall the response rate was 60% in the fludarabine group and 44% in the CAP group. The difference of 16% was statistically significant (95% CI: 2% to 30%). For the most relevant subset, previously treated patients, the overall RR was 48% in the fludarabine group and 27% in the CAP group. The difference in response was thus 21% (95% CI: 2% to 40%).

Table 5 Results from included RCT for fludarabine [22]

	Fludarabine	CAP
Number entered into study	106	102
Follow-up period	Median 36 months (range 1-61)	
Losses to follow-up	N/S	N/S
Drop-outs/exclusions before assessment	6 excluded for protocol violation (33 patients did not complete Rx but were included in assessment; 9 of these were deaths during Rx)	6 excluded for protocol violation (35 patients did not complete Rx but were included in assessment;3 of these were deaths during Rx)
Number randomised	100 (52 untreated, 48 previously treated)	96 (48 untreated, 48 previously treated)
Patients evaluated for response	100	96
Evaluated as intention-to-treat	Yes	Yes
Clinical response rates (RR=CR+PR)	60% (95%: CI 50 to70%)	44% (95%: CI 34 to54%) (p=0.023)
Patients evaluated for adverse events	100	96
Deaths during Rx	9 patients died during Rx	3 patients died during Rx
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)
Differences	Significantly greater numbers nausea/vomiting and hair loss in CAP arm	
Other outcomes Time to progression -in responders Quality of life Survival analysis -in responders	 Median 817 days (95% CI: 453 to 996) No Median overall survival 1348 days (95% CI: 936 to >1661)	 270 days (95% CI: 136 to 445) (p=0.0001) No Median overall survival 999 days (95% CI: 774 to 1537) (p=0.27)
Nearest subset of relevant patients	Previously treated (n=48)	Previously treated (n=48)
Response rates for relevant subset	CR : 13% PR : 35% RR : 48%	CR : 6% PR : 21% RR : 27% (p=0.036)
Other outcomes for relevant subset Time to progression -in responders Quality of life Survival analysis -in responders	 Median 324 days (95% CI 272-459) No Median overall survival 728 days (95% CI: 392 to 939)	 179 days (95% CI 56-567) (p=0.22) No Median overall survival 731 days (95%: CI 409 to 999) (NS)
* Denotes statistical significance at 5% level of fludarabine vs CAP		

Clinical response – complete response rates (CR)

The rates of complete response in the most relevant subset were 13% for the fludarabine group and 6% for the CAP group. The difference in CR was thus 7% (95% CI: 5% to 19%).

Clinical response – partial response rates (PR)

The rates of partial response in the most relevant subset were 35% for the fludarabine group and 21% for the CAP group. The difference in PR was thus 14% (95% CI: 4% to 32%).

Time to progression

Overall the time to progression was a median of 817 days for fludarabine and 270 days for CAP. This difference was statistically significant (p=0.0001).

For previously treated patients the time to progression was a median of 324 days for fludarabine and 179 days for CAP. This difference although consistent in magnitude with the difference observed in the overall group, was not statistically significant (p=0.22).

It should be noted that these figures are not mean or median durations of response for all patients exposed to either fludarabine or CAP. They refer to responders alone.

Overall survival
The overall survival, considering the trial in its entirety was a median of 1348 days (95% CI: 936 to >1661) in the fludarabine group and 999 days (95% CI 774 to 1537) in the CAP group. The difference in the survival curves for fludarabine and CAP was not statistically significant (p=0.27 using the log-rank test).

For previously treated CLL patients the median overall survival was 728 days (95% CI: 392 to 939) in the fludarabine group and 731 days (95% CI: 409 to 999) in the CAP group. The survival curves were virtually identical, and inevitably any differences were clearly not statistically significant.

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 ie disappearance of all palpable disease.

Adverse events and toxicity
Considering the study as a whole, 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 CVA related to severe thrombocytopenia (1). The reasons for failure to complete treatment in the CAP group were progressive disease (21 patients), 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 whether severe or mild to moderate 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

- **Discussion of results**

The study by The French Cooperative Group on CLL [22] is critical to the assessment of effectiveness of fludarabine in 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. It was the only rigorous, directly relevant study identified, for which published data were available for the population of interest. As such it deserves close scrutiny.

The key points identified were:

- This is a small trial. Considering the population of interest, there are only 96 patients, 48 per arm.
- The comparison of fludarabine to CAP is relevant, although CAP is not the anthracycline containing regime most used, this probably being CHOP.
- This is a generally well conducted RCT, particularly with respect to quality of randomisation and allocation concealment.
- There was a clear 21% difference in the overall response rates in favour of fludarabine. However, the 95% CI on this difference comes close to zero, ranging from + 2% to +40%.
- The additional responses in the fludarabine group occurred in both the CR and PR categories.
- In responders the time to progression was considerably greater in the fludarabine group: 324 days vs 179 days. However, this impressive result does have to take account that non-responders constitute a considerable proportion of those involved in the trial, and it needs to be confirmed that non-responders in the fludarabine arm fare no worse than those in the CAP arm. Clearly they can be no worse with respect to time to progression which by definition is 0. However, with respect to death during the treatment period, we know that they did fare worse (9 deaths during treatment in fludarabine vs 3 deaths in CAP). Thus concentrating on responders, although understandable, needs to be accompanied by confirmation concerning outcome in non-responders.
- There is no difference in overall survival, although the interpretation of this is complex where cross-over from CAP to fludarabine and vice versa occurs during the period of follow-up, as is the case in this trial.
- The level of adverse events for each group is high (this can only be considered for the whole trial, not just the most relevant subset); it appears likely that at least one serious adverse event was experienced by every patient in both the fludarabine and CAP arms.
- Deaths during the treatment period (again for the whole trial) were higher in the fludarabine arm than the CAP arm (9 vs 3) but this difference is not statistically significant
- In other respects the level of adverse effects was markedly and statistically significantly less in the fludarabine arm, particularly for the non-haematological adverse events of nausea and vomiting and alopecia and hair loss.
- There is no directly measured information on impact on quality of life, so it is difficult to translate the results concerning response into the outcome of true interest, the patient's freedom from symptoms and ability to function. The lack of direct measure of impact on quality of life also makes it extremely difficult to gauge the degree to which benefits are offset by the adverse events during treatment, which appear to be frequent. This is equally true for both fludarabine and CAP.
- Qualitatively it is clear that the balance between clinical response and adverse events favours fludarabine over CAP.
- The findings from this small trial do not appear to have been verified in other RCTs.

In summary, concerning the evidence on effectiveness, at face-value the results from the study by the French Cooperative Group on CLL [22] provide good evidence for the advantage offered by fludarabine, and it appears that many have reacted to it at this level. Close examination of the results, however, suggests some notes of caution needing to be observed in translating the trial data into an assessment of overall effectiveness. Ideally the results should have been corroborated in another trial, if nothing else to provide a more precise estimate of the difference in response rates.

2.3.3 Effectiveness evidence from case-series

- **General introduction**

The purpose of including case-series in the systematic review of effectiveness was to corroborate key findings from the small RCT identified, rather than as the substantive evidence-base for our conclusions on effectiveness. In consequence, although they are detailed in full in the appendices, their presentation and discussion in this section of the technology appraisal has been deliberately curtailed.

- **Included study characteristics** (see Appendices 11, 12 & 13)

The seven case-series with >50 patients, varied in size. Most considered between 50 and 100 patients. One was larger than this [29] with 137 patients; another was considerably larger than this [28] with 791 patients, of which 724 received treatment. Not all the included patients in the case-series were directly relevant to the review question, particularly with respect to the condition of interest, and the amount and nature of prior treatment. In two of the case-series, it was clear that all included patients were directly relevant [26 28]. All studies collected information on clinical response and all bar one [26] some information on adverse events. No studies collected information on impact on quality of life.

- **Included study quality** (see Appendix 14)

As might be expected from the study design, all case-series were highly susceptible to bias. Detection bias in uncontrolled studies is of particular concern. The absence of control groups also clearly limits what can be concluded directly about the relative effectiveness of fludarabine. Failure to give any information about how included patients were drawn from the whole population meeting the inclusion criteria at the institutions involved in the studies, lays them open to the possibility of selection bias.

- **Results** (see Appendix 15 & 16)

Response rates (RR overall)

The overall response rates varied markedly across the six case series. The range was from 28% [27] to 73% [25].

Time to progression (in responders)

This was available for four studies [24, 25, 28, 30] who reported median times of 8 months (≈240 days), 7 months (≈210 days), 7.5 months (≈225 days) and 13 or 21 months (≈390 or 630 days) respectively. In the last study [30] the two figures given consider time to progression in PR, and CR + nodular PR respectively.

Adverse events

The adverse events data was generally poorly reported. Concerning severe adverse events most case-series suggested relatively low adverse event rates [29, 30]. An exception was the largest study [28] indicating that many of patients suffered severe haematological adverse events ie aneamia 37%, leucopenia 46%, thrombocytopenia 46%.

- **Discussion of results**

The results of the included case-series clearly need to be regarded with considerable circumspection, taking into account the considerable biases to which uncontrolled studies are open. The variability of the results is the key observation. With this in mind the results do confirm that caution is

appropriate concerning the interpretation of the results of the evidence on effectiveness provided by the single small RCT identified [22].

The case-series identified provided no further information on a key outcome absent from the RCT, impact on quality of life.

2.3.4 Assessment of effectiveness

Overall effectiveness can only be assessed if accurate information on all the main areas of expected impact has been assessed. In the introduction we highlighted the importance of impact on quality of life. This is important to confirm that inducing remission following symptomatic progression truly abolishes the unpleasant associated symptoms to a degree that offsets the side effects of the treatment itself. That quality of life has not been measured directly, must therefore be considered a handicap to assessing the effectiveness of fludarabine. The fact that response rates, in general incorporate direct measurement of haemoglobin, platelets and white blood cells off sets this criticism to some degree, but not completely.

We do have high quality information from an RCT, albeit on a limited number of patients indicating clinical response rate and time to progression comparing fludarabine with CAP another commonly used treatment option when CLL has failed to respond to first line therapy.

To reiterate, in previously treated patients in the study by The French Cooperative Group on CLL [22]:

- Overall response rates are 48% (fludarabine) vs 27% (CAP)
- The 95% CI for the difference is +2% to +40%
- The improvements in response rate are seen in both CR and PR categories
- The time to progression in responders is markedly increased from a median of 179 days (CAP). to 324 days (fludarabine). This difference was not statistically significant (p=0.22).
- The survival time in all patients was identical with a median of 728 days for fludarabine to 731 days for CAP.
- Adverse events appear common. Severe adverse events are probably universal in both the fludarabine and CAP.
- Deaths during the treatment period were greater for fludarabine (9 deaths) than for CAP (3 deaths). This difference is not statistically significant.
- The non-haematological adverse events of nausea and vomiting, and alopecia and hair loss were markedly and statistically significantly less in fludarabine.

The results which, at face value are favourable with regard to the effects of fludarabine relative to CAP on response rates and duration of response, need to be tempered by:

- The small size of the RCT and the fact that it is the only RCT
- Observations about the confidence intervals around the difference in response rate
- The possibility that greater numbers of fatal adverse events during treatment with fludarabine may to some extent offset both the benefits observed and the advantage of fludarabine relative to CAP concerning non-haematological adverse events
- The variability of the results observed in the case-series reviewed

However, qualitatively it appears reasonably clear that the balance between beneficial effects and adverse events favours fludarabine over CAP. Clinical experience, particularly regarding adverse event profiles, supports this, and suggests that it is also true for fludarabine in comparison with CHOP.

Concerning how our conclusions on effectiveness compare with others who have summarised the evidence on effectiveness of fludarabine as second line treatment in CLL, we identified no other systematic reviews. Many other assessments of the value of fludarabine, based on the single available RCT, have been positive. In our systematic review we have possibly placed greater emphasis on the limitations of the available evidence than others, but we believe the systematic consideration of bias and wider consideration of other types of evidence on effectiveness provides explicit support for this more cautious interpretation.

In comparison with the Schering submission to NICE on this topic, there was little disagreement concerning the included studies providing the best evidence of effectiveness. No new unpublished data was revealed. There was no disagreement about absence of conclusive evidence that overall survival is improved in fludarabine relative to CAP. Conclusions concerning the advantages of fludarabine over CAP with respect to clinical response, duration of response in responders and fewer non-haematological adverse events were also similar. There was however, difference in the emphasis placed on some aspects of the RCT. Little attention was paid to the role that chance might have played in accounting for the results observed. The high levels of adverse effects and the presence of fatal adverse events during the fludarabine treatment period were not given great attention, particularly in the context of drawing conclusions concerning net benefit.

2.4 Summary of effectiveness

- A systematic review of effectiveness was undertaken
- The review question was, what is the effectiveness of fludarabine 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
- 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)
- Two RCTs were identified; one could not be incorporated into the analysis because probably only a small proportion of the included patients were directly relevant to review question
- The RCT included in the analysis included 96 directly relevant patients (48 fludarabine and 48 CAP)
- In most clinical conditions the size of the trial alone would suggest that confirmation of results would be prudent
- 7 case-series were also considered to corroborate key findings from the RCT; these included in excess of 1,000 patients
- The RCT was well conducted particularly with respect to method of randomisation and allocation concealment
- The case-series were open to substantial bias
- No information was available on impact on quality of life from any of the studies considered
- The main findings were based on the results of the single small RCT
- Overall response rates are 48% (fludarabine) vs 27% (CAP)
- The 95% CI for the difference is +2% to +40%
- The improvements in response rate are seen in both CR and PR categories
- The time to progression in responders is markedly increased from a median of 324 days (fludarabine) to 179 days (CAP). This difference was not statistically significant (p=0.22).
- The survival time was identical with a median of 728 days (fludarabine) to 731 days (CAP)
- Adverse events appear common. Severe adverse events are probably universal in both the fludarabine and CAP.

- Deaths during the treatment period were greater for fludarabine (9 deaths) than for CAP (3 deaths). This difference is not statistically significant.
- The non-haematological adverse events of nausea and vomiting, and alopecia and hair loss were markedly and statistically significantly less in fludarabine.
- Closer inspection suggests some areas for concern:
  - The confidence intervals around the difference in response rate
  - The small excess of fatal adverse events during treatment with fludarabine
  - The variability of the observed results in the included case-series
- Qualitatively it appears reasonably clear that the balance between beneficial effects and adverse events favours fludarabine over CAP.
- However, the degree to which beneficial effects are outweighed by adverse events is difficult to quantify.
- Although we have probably placed greater evidence on some of its limitations, our conclusions on effectiveness appear to be consistent with others summarising research in this area.

3. ECONOMIC ANALYSIS

3.1 Objectives

The original objectives defined in the protocol were re-stated slightly:

- To systematically review the evidence on costs and health economic impact of fludarabine in 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
- To identify strengths and weaknesses of available cost-effectiveness studies and identify areas that might be revised or extended
- To selectively undertake some further analysis using published data

3.2 Methods

A priori we anticipated that the quality of evidence on effectiveness would be the main limiting factor to an accurate assessment of health economic impact. The pre-specified method was designed on this basis. Following confirmation from the systematic review of effectiveness that the prior assumption about quality of evidence on effectiveness was confirmed, no amendments to the protocol concerning economic analysis were made.

3.2.1 Search strategy

A specific search strategy for information on costs, cost-effectiveness and quality of life involved searches of:

- Bibliographic databases – Medline (Ovid) 1966-September 2000 and the NHS Economic Evaluation Database (NEED)
- Internet sites of UK health economics units

Details of the search terms used are given in Appendix 17. The search for economic information on fludarabine and the intervention in the accompanying report, rituximab was conducted jointly. The industry submission from Schering to NICE in support of fludarabine, was considered as one of the included existing economic evaluations considered in our economic analysis. In addition to the specific search strategy for economic evaluation above, all studies encountered in the searches for effectiveness referring in any way to cost, were also considered.

3.2.2 Handling information identified

The inclusion criteria allowed all information on costs, quality of life or previous health economic evaluations of fludarabine in the treatment of CLL to be included. The quality of all included studies was assessed. In the case of full economic evaluations the criteria used were based on the BMJ guidelines for economic appraisals. All the data in the included studies was abstracted into tables for presentation in this report and for consideration of conclusions.

3.3 Results

3.3.1 Estimation of net benefits (i.e. taking account of disbenefits)

The results and conclusions of the systematic review of effectiveness contain our assessment of net benefit - see section 2.4. It is important to reiterate that no directly collected information on impact on quality of life (QoL) was identified in the included effectiveness studies and that this absence was confirmed by the further searches undertaken as part of the economic evaluation. Our statement on the difficulty of quantifying the degree to which beneficial effects of second line fludarabine treatment for CLL are outweighed by adverse events thus stands.

In the Wessex DEC report no 44 [31], an attempt was made to *estimate* the impact of fludarabine treatment relative to CAP in terms of QoL. Their estimates of QoL were based on gauging where patients in four states might be on the IHQL measure of QoL. Their estimates were as follows:

1. QoL in remission	= D2 P1 E2	= 0.96
2. QoL with disease	= D3 P2 E8	= 0.81
3. QoL during 6 month treatment with fludarabine	= D3 P2 E3	= 0.81
4. QoL during 6 month treatment with CAP	= D4 D2 E3	= 0.785

We believe great caution is required in using this sort of approach. Even if the approach to estimating the QoL is accepted, the weighting of states 2. and 3. as equivalent must be debatable, as must the differential between 3. & 4. Rating QoL in state 2. (with disease) as static over any period of time where the disease may be deteriorating is problematic, not least, as failure to achieve remission is likely to prompt further courses of treatment. This data is presented not so much a criticism of the approach, which was to some extent addressed in the original report by conducting a sensitivity analysis, but an indication of the difficulty of judging the QoL weights of the health states involved without some direct measures as a guide.

3.3.2 Estimation of net costs

For iv fludarabine, the drug cost to the NHS is £3,900 based on the recommended course of 5 doses of 25mg/m^2 per cycle for a typical patient and for a conventional regimen of 6 cycles of chemotherapy.

Further information on costs was limited. The Schering submission to NICE, as part of its economic analysis presents costing for administration of fludarabine and CHOP, based on a small retrospective case-note audit involving 25 patients. They estimate that the cost of fludarabine, including acquisition, administration, prophylaxis, monitoring and treating adverse events was £6,032. An obvious issue with this costing was that the cost of drug acquisition at £2,665, was considerably less than the £3,900 predicted above. This was explained by the fact that the patients in the audit only received a mean of 4.1 courses. Feed back from clinicians suggests that this is

realistic. Further concerns about the way in which this costing exercise was conducted are raised in section 3.3.4

Beyond this, one further costing for the administration of fludarabine is presented as part of the economic analysis in the Roche submission to NICE on rituximab. In an equally rigorous costing exercise, admittedly concerning administration of fludarabine in a different condition, but with the same treatment regimen, a cost of administration of £11,808 was arrived at. One major reason for the increased cost estimate was a large difference in the cost associated with treating adverse events. In the Schering submission this was £267 per course of fludarabine treatment; in the Roche submission this was £3,540.

The numerical value obtained in the Roche submission should not be used directly, as it is taken out of context. However, the observation does alert to the possibility of high variability in cost estimates depending on just how severe the side effects of fludarabine are in any particular series of patients. In this respect it needs to be appreciated that side-effects of giving iv fludarabine, like any other chemotherapy regimen, can be greatly ameliorated by careful attention to administration and optimal application of simple and cheap prophylactic regimes. Conversely if such care is not exercised the costs associated with adverse events might be unreasonably inflated.

3.3.3 Cost impact of fludarabine

That any savings to the NHS will occur through use of fludarabine is highly debatable. This is based on the consideration that fludarabine is being used in a condition with a prolonged course during which several treatments will be applied, and certainly as many as seem to offer a realistic hope of achieving a clinical response relative to the side-effects that might be suffered. Thus fludarabine probably represents an additional treatment option for previously treated progressive/refractory CLL, rather an option which will completely replace an existing treatment option eg CHOP. Because fludarabine displaces as much as replaces existing treatments, any cost saving may be much smaller than predicted by simply comparing the total administration costs of fludarabine with other second line treatments. We have taken this consideration into account in estimating total budget impact. We assume that most patients currently receiving treatment at some stage of their disease, will receive fludarabine. Further we assume, that use of fludarabine will not reduce their exposure to other widely used treatment regimens. Although this latter assumption is unlikely to be completely fulfilled, we believe that the resulting estimate is of value in indicating an upper limit to what the true budget impact might be. We use annual incidence as a rough proxy of the number of patients who in any year will be entering a defined period of their disease where fludarabine may be considered the most appropriate treatment option. We use 50% as the proportion of patients who receive any treatment for CLL at some point in their disease. The resulting calculation is as follows:

- Approximate annual overall incidence of CLL 3.35/100,000
- Incident cases of NHL in E&W (pop $55x10^6$) 1,840
- Number who will be treated in any year 920
- Cost of administering one course of fludarabine iv [as per Schering submission to NICE] £6,032
- Total cost per annum £5.5 m

One point suggests that the above estimate of budget impact is likely to be an overestimate:

- That fludarabine is already a well established treatment option and that its additional costs have already been largely absorbed into the NHS budget

Three suggest that it may be an underestimate:

- That giving patients two courses of fludarabine may not be uncommon. However, where this does occurs alternative treatments might well be replaced, as opposed to displaced
- That due to an aging population alone the number of cases of CLL requiring treatment will be increasing, because its incidence rises steeply with age
- That the administration cost for fludarabine provided by Schering is unrealistically low, possibly by understating the most likely incidence of adverse events and the costs resulting from their treatment

Clearly it is difficult to take these and other factors into account. However, we believe on balance that £5.5 m represents a realistic upper estimate of budget impact. The Schering submission to NICE predicts very minimal budget impact, and we would suggest that great caution should be exercised in accepting this. Further, it anticipates the impact of introducing an oral preparation, which to reiterate we have not considered in this technology appraisal, as it has only very recently received a licence.

Like impact on the total NHS budget, prediction of the impact for an average HA population of 500,000 is difficult. Based on the same assumptions as used to generate the total NHS budget impact figure, an approximate upper estimate for the additional cost in any year would be £50,000.

3.3.4 Critique of cost-effectiveness studies

The critique below focuses solely on the NICE submission since no other directly relevant published economic analysis was found. Tables 6 to 8 describe some of the key study characteristics and report the results for the base-case cost-effectiveness analyses.

Table 6 Assessment of cost-effectiveness analysis: study characteristics and results

	Schering submission to NICE
Comparators	Three alternative comparators (to iv fludarabine) are used: CHOP, CAP and oral fludarabine*
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
Base-case cost result	▪ Intra-venous fludarabine: *Commercial in confidence* ▪ CHOP: " " " ▪ CAP: " " "
Base-case ICER	Intra-venous fludarabine vs CHOP: £10,588 per year of remission

* Results relating to oral fludarabine not reported further as this was not considered in this technology appraisal as it had not been licenced at the point where the protocol was finalised.

Table 7 Assessment of cost-effectiveness analysis: effectiveness and cost data

	Schering submission to NICE
Source(s) for effectiveness data	Phase III trial (French Cooperative Group on CLL, 1996 [22]) for iv fludarabine vs CAP, and "expert opinion" for CHOP
Analysis of effectiveness data	No further analysis reported in cost-effectiveness section of report
Quality of life data	None reported
Resource use data	Taken from retrospective audit of notes for 25 patients with CLL who received a second line therapy (n=17 for iv fluarabine, 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.
Analysis of cost data	No statistical analysis reported – cost data simply compared.
Price year	2000
Discounting	Not relevant – "data collection was limited to the resource use around the time that chemotherapy was being given - we did not attempt to assess resource use during remission or the long-term consequences of treating these cancers.

Table 8 Assessment of cost-effectiveness analysis: sensitivity analyses

	Schering submission to NICE
Approach	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

The economic analysis reported in the Schering submission considers the use of fludarabine as a second line treatment of CLL. The analysis considers two alternative approaches to administration: iv and oral. We have disregarded the results concerning oral fludarabine for the reasons already stated. The comparators used in the incremental analysis are two alternative forms of chemotherapy: CAP and CHOP. CAP is widely used on mainland Europe and was the comparator in the main clinical trial [22] and CHOP is more commonly used in the UK.

The strengths and weaknesses of the cost analysis have been explored. The clinical trial was not used as a source of data on resource use and costs. All data on resource use have been collected as part of a separate audit or observational study of patients receiving second line treatment of CLL. The report of this study (Appendix 5 of the Schering submission) is described as an Interim Report and it indicates that data collection is continuing. This is

encouraging given that *….[Commercial in confidence: this sentence relates to the small size of the samples taken.]* These resource data were then converted into costs through the use of unit costs taken from a variety of appropriate sources.

One of the principal concerns for the cost analysis relates to the lack of comparability of the resource use data from the patient groups. This is borne out by the data on sample characteristics reported in Table 1 of Appendix 5 of the Schering submission. These data reveal that the three patient groups are not similar, particularly in terms of their mean age, sex distributions, time between diagnosis and second line treatments and percentage with serious co-morbidity.

A further point of concern relates to the comprehensiveness of the resource use data reported in this analysis. The data collection was retrospective and therefore relied on routine data sources. There is also a concern about the consistency of data collection: the submission states that, "Data collection was limited to resource use around the time that chemotherapy was being given - we did not attempt to assess resource use during remission or the long-term consequences of treating these cancers." The implication of this is that there was not a fixed time interval over which data were collected.

A strength of the analysis reported in the Schering submission is the sensitivity analysis which, despite only reporting one-way analyses, indicates the sensitivity of the results to variation in response rates and response duration. Table 9 of the Schering submission reports a range of response data for both fludarabine and CHOP that are taken from the literature. This reveals the great uncertainty surrounding effectiveness; the estimates of disease free days range from 91 to 348 for fludarabine and 38 to 117 or CHOP. For fludarabine, this in keeping with observations made in the effectiveness section of this technology appraisal.

3.4 Summary of economic analysis

- Qualitatively it appears reasonably clear that the balance between beneficial effects and adverse events favours fludarabine over CAP in second line treatment of CLL
- However, the degree to which beneficial effects are outweighed by adverse events is difficult to quantify and there are no direct measures of impact on quality of life to assist in this
- The drug cost of a recommended course of iv fludarabine is £3,900
- The wider cost of administering fludarabine is estimated to be £6,000
- This cost estimate is probably subject to considerable variability depending on what the true incidence, severity and costs of treating adverse events is judged to be
- The total annual budget impact is highly uncertain; we derived an approximate estimate of £5.5 m per annum
- For an average HA of 500,000 persons this is equivalent to an additional £50,000 per annum
- Only one directly relevant published economic analysis was identified, the Schering submission to NICE
- This was a cost-effectiveness analysis generating an incremental cost per year of remission gained for fludarabine compared to CHOP
- Problems were identified with the conduct of the analysis, particularly the way that resource use was ascertained
- The cost-effectiveness of iv fludarabine appears to be favourable relative to CHOP

- A strong feature of the analysis was the sensitivity analysis. However, this showed that ICER was highly sensitive to variation in the effectiveness parameter used
- Given the considerable imprecision surrounding the estimate, it is debatable whether the information provided on incremental cost-effectiveness is in this case helpful in making a policy decision on use fludarabine as second line therapy for relapsed/refractory CLL
- That fludarabine is unlikely to be used as a simple replacement for existing second line treatments, adds to this concern
- Restriction to cost-effectiveness estimates does not give an indication of the value of investing health care resource in fludarabine treatment in CLL as opposed to other areas of health care, especially care of other cancers. An estimation of cost-utility would be required to achieve this.
- Having identified the need for a direct measure of impact on quality of life, and found none, we believe that a robust estimate of cost-utility cannot be obtained with the current information available
- The recent advent of oral fludarabine could impact on the observed ratio of costs to net benefit
- In this technology appraisal, we have considered neither the effectiveness nor the cost-effectiveness of oral fludarabine
- NICE will need to consider separately the potential value of oral fludarabine as second line therapy for progressive relapsed/refractory CLL

4. IMPLICATIONS FOR OTHER PARTIES

The findings of this rapid technology appraisal have wide implications for all parties involved in the health care process particularly patients, their families and their carers. However, no special implications to other parties were identified beyond the general importance to all parties of effectiveness, cost and economic impact already considered.

The advent of an oral preparation of fludarabine could have important consequences on the acceptability of fludarabine treatment for patients and emphasises the need for a proper consideration of the potential impact of oral fludarabine independently of considering the value of the iv preparation addressed by this report.

5. RESEARCH IN PROGRESS

5.1 Method

Early in the course of the appraisal we identified that limitations on the quality of the evidence on effectiveness were likely to be a key issue, suggesting at least the need for further research. Consequently, we felt it was essential to provide as rigorous an inventory as possible of on-going research.

The objective was to identify all randomised trials planned, on-going and completed involving fludarabine, and to indicate key information about nature of these trials (intervention, comparison groups, outcomes and size) and when they were likely to complete recruiting or be published. No restriction was placed on the condition of interest, although the

main studies we focus on in the results in this section are for CLL. The search strategy used incorporated interrogation of bibliographic databases, particularly MEDLINE, EMBASE and the Cochrane library, and a wide range of Internet web-sites of organisations involved in or providing listings of trials in progress. Further details on the search strategy, inclusion criteria and data abstraction processes are provided in Appendices 8 and 9.

5.2 Results

The on-going trials are listed in Table 9 sub-divided by the condition of interest, and whether patients are previously treated or untreated.

Current licensed indications for fludarabine – previously treated CLL
There are no directly relevant randomised trials in progress, which have not already been reported and considered in this technology appraisal. A further trial comparing fludarabine and cladribine appears to have been abandoned owing to problems with drug supply.

On-going randomised trials of fludarabine – previously untreated CLL
There is an enormous amount of high quality randomised controlled trial evidence recently completed and on-going in this area. Pre-eminent amongst these is the Leukaemia Research Fund sponsored MRC-CLL4 trial. 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. It is also, to a small extent, a strategy trial as the protocol extends to the treatment of patients who are resistant or relapsed while in CLL4.

On-going randomised trials of fludarabine in other haematological malignancies
There is clearly also considerable interest in use of fludarabine in other haematological malignancies, particularly NHL and AML, as well as its use as a ‘conditioning’ agent in ‘mini-transplants’.

Table 9 On-going and completed but unpublished trials of fludarabine

(Also includes completed and published trials of fludarabine; shaded cells indicate studies already included in the effectiveness review)

Study (Ref)	Intevention	Comparator	Condition	Population	Outcomes	Design & Size	End
HAEMATOLOGICAL MALIGNANCIES – CHRONIC LYMPHOCYTIC LEULAEMIA (PRIOR TREATMENT)							
French Cooperative Group on CLL[22]	FLUDARABINE	CYCLOPHOSPHAMIDE + DOXORUBICIN + PREDNISOLONE (CAP)	B cell - CLL	Treated with chlorambucil or similar non-anthracycline or anthracinone containing regimes	• Disease response • Progression-free survival • Overall survival • Toxicity	RCT; 48 + 48	Completed & published
Tondini et al [23]	FLUDARABINE	CLADRIBINE	LG-NHL (some IWF A were CLL)	Relapsed/refractory after at least one course of alkylating chemotherapy	• Disease response • Progression-free survival • Toxicity	RCT; 60 total (43% IWF A)	Completed & published
EORTC 06942 [32, 33]	FLUDARABINE	CLADRIBINE	B cell - CLL	Refractory to alkylating agent therapy (but no more than 3 courses)	• Disease response • Time to max response • Progression-free survival • Toxicity • Quality of life	RCT; target total 750	Abandoned as problems with drug supply; no publication expected
HAEMATOLOGICAL MALIGNANCIES – CHRONIC LYMPHOCYTIC LEULAEMIA (NO PRIOR TREATMENT)							
French Cooperative Group on CLL[22]	FLUDARABINE	CYCLOPHOSPHAMIDE + DOXORUBICIN + PREDNISOLONE (CAP)	B cell - CLL	Previously untreated Binet stages B or C	• Disease response • Progression-free survival • Overall survival • Toxicity	RCT; 52 + 48	Completed & published
French Cooperative Group on CLL [34, 35, 36,]	FLUDARABINE	CAP or CYCLOPHOSPHAMIDE + DOXORUBICIN + VINCRISTINE + PREDNISONE (CHOP) (CAP discontinued after interim analysis 9/2/96)	CLL	Previously untreated Binet stage B & C	• Disease response • Progression-free survival • Time to retreatment • Overall survival • Toxicity	RCT; total 983	Completed & published (abstract only)
CLB-9011 [37, 38, 39, 40, 41]	FLUDARABINE (Combined F + C arm stopped 1994)	CHLORAMBUCIL (oral)	B cell - CLL	Previously untreated Intermediate to high risk Rai stages I-IV	• Disease response • Progression-free survival • Overall survival • Toxicity • Quality of life	RCT; target total 538	Completed & published (abstract only)
EORTC 06916 [42, 43, 44, 45]	FLUDARABINE	CHLORAMBUCIL (oral; high dose)	B cell - CLL	Previously untreated	• Disease response • Time to max response • Toxicity • Quality of life	RCT; 82 randomised; 71 analysed (37 + 34)	Completed & published (abstract only)

Spriano et al [46]	FLUDARABINE	CHLORAMBUCIL + PREDNISONE	B cell - CLL	Previously untreated RAI intermediate or high risk	• Disease response • Toxicity	RCT; total 147 (73 + 74); 105 analysed (60 + 55)	Completed & published (abstract only)

Table 9~~Table 9~~ On-going and completed but unpublished trials of fludarabine (continued)

Study (Ref)	Intevention	Comparator	Condition	Population	Outcomes	Design & Size	End
HAEMATOLOGICAL MALIGNANCIES – CHRONIC LYMPHOCYTIC LEULAEMIA (NO PRIOR TREATMENT)							
LRF MRC CLL4 [47]	FLUDARABINE or FLUDARABINE + CYCLO-PHOSHAMIDE	CHLORAMBUCIL	B cell - CLL	Previously untreated Binet stage A progressive, stage B or stage C	• Disease response • Progression-free survival • Overall survival (1^0) • Toxicity • Quality of life	RCT; target total 500	End recruiting 2004
HAEMATOLOGICAL MALIGNANCIES – LOW GRADE NON HODGKIN'S LYMPHOMA (PRIOR TREATMENT)							
Tondini et al [23]	FLUDARABINE	CLADRIBINE	LG-NHL (IWF A –D)	Relapsed/refractory after at least one course of alkylating chemotherapy	• Disease response • Progression-free survival • Toxicity	RCT; total 60	Completed & published
HAEMATOLOGICAL MALIGNANCIES – LOW GRADE NON HODGKIN'S LYMPHOMA (NO PRIOR TREATMENT)							
Coiffer B et al [48]	FLUDARABINE	CHVP + INTERFERON	Follicular NHL (?IWF)	Previously untreated Patients older than 59 y Poor prognosis: presence of large tumour mass; poor performance status; presence of B symptoms; above normal LDH level; ≥ 3 mg/L ß-microglobulin levels	• Disease response • Progression-free survival • Overall survival • Toxicity	RCT; total 131	Completed & published
EORTC 20921 [49, 50, 51]	FLUDARABINE	CYCLOPHOSPHAMIDE+ VINCRISTINE + PREDNISOLONE (CVP)	LG-NHL Classic CLL excluded	Previously untreated Newly diagnosed Stage III/IV	• Disease response • Progression-free survival • Overall survival • Toxicity	RCT; target total 326	Completed; no publication
E-1496 [52]	FLUDARABINE + CYCLO-PHOSPHAMIDE	CYCLOPHOSPHAMIDE + VINCRISTINE + PREDNISONE (CVP)	LG-NHL (SL; Foll SCl; Foll MCl,; Foll Large)	Previously untreated Stage III/IV	• Disease response • Progression-free survival • Overall survival	RCT; target total 400	Temporarily closed
Foussard et al [53]	FLUDARABINE + MITOX-ANTRONE	DOXORUBICIN + CYCLOPHOSPHAMIDE + VINDESINE + PREDNISOLONE (CHEP)	LG-NHL Mantle cell lymphoma excluded	Previously untreated Bulky stage II & stage III/IV One adverse prognostic factor	• Disease response • Toxicity	RCT; total 100	Completed & published (abstract only)
BNLI MCD vs FMD [54]	FLUDARABINE + MITOX-ANTRONE + DEXAMETH-ASONE (FMD)	CHLORAMBUCIL + MITOXANTRONE + DEXAMETH-ASONE (MCD)	LG-NHL REAL FCC lymphoma grades I-III	Previously untreated Newly diagnosed Stage III/IV	• Disease response • Progression-free survival • Overall survival	RCT; target total 500	End recruiting 2004

Table 9~~Table 9~~ On-going and completed but unpublished trials of fludarabine (continued)

Study (Ref)	Intevention	Comparator	Condition	Population	Outcomes	Design & Size	End
HAEMATOLOGICAL MALIGNANCIES – ACUTE MYELOID LEUKAEMIA							
MRC AML- HR [55]	FLUDARABINE + ARABINO-SIDE (high dose) (FLA)	ARABINOSIDE + DAUNORUBICIN + ETOPOSIDE (ADE)	AML	High risk: Resistant after 1 course of remission induction therapy (RIT), or refractory disease after 2 or more RIT, or relapse from first CR, or in CR or PR after 1 RIT but with adverse cytogenetic abnormalities at diagnosis.	• Disease response • Progression-free survival • Overall survival • Toxicity • Supportive care requirements • Quality of life	RCT; target total 600	End recruiting 2003
CCG-2961 [56]	Consolidation FLUDARBINE + CYTARABINE + IDARUBICIN	Consolidation IDARUBICIN + DCTER/ DCTER	AML & myelo-dysplastic syndromes	Previously untreated Children	• Progression-free survival • Event-free survival • Overall survival	RCT; target total 880	Temporarily closed
OTHER MALIGNANCIES & CONDITIONS							
Taylor & Eyre [57]	FLUDARBINE	ACTIVICIN	Malignant gliomas	Recurrent	N/A	Probable RCT	Completed & published
Davis J et al [58]	FLUDARABINE 20mg/m^2 x3d every 4 weeks for 6 months	FLUDARABINE 30mg/m^2 x3d every 4 weeks for 6 months	Rheumatoid arthritis	Severe and refractory to treatment with at least one slow acting anti-rheumatic drug	• Disease response • Toxicity	RCT; 12 + 14	Completed & published

5.3 Key points arising

- There are no other on-going randomised trials that will provide rigorous assessments of effectiveness for the indication of fludarabine considered in this report.
- There is a great deal of on-going and recently completed research investigating the effectiveness of fludarabine as a first line treatment for CLL.
- NICE should anticipate the need for guidance on use of fludarabine in this circumstance
- The on-going Leukaemia Research Fund sponsored MRC CLL4 trial should provide key information for such a future assessment. The opportunity should be taken in guidance now on the use of fludarabine as second line treatment, to encourage recruitment into this study.
- More future RCTs should directly measure impact on quality of life
- The inventory of on-going trials in this report should provide a useful starting point in identifying included trials for such a future NICE report.
- Such a future NICE report should take the opportunity to reassess the place of fludarabine as second line therapy.

6. DISCUSSION

6.1 Main results of report informing conclusions

This rapid technology assessment has generated many important findings. These are highlighted at the end of each of the sections 2, 3, 4 and 5. Here we discuss those results that have been most influential in informing our conclusions

The evidence-base for the use of fludarabine 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, has important limitations. The finding that extensive use of this agent seems to based in the main on a single small RCT was disappointing. Usually researchers would seek to confirm the findings of such a trial with at last one other similarly rigorous piece of research. A detailed search for on-going studies confirms that this has not occurred. It is debatable whether such a trial could now be mounted.

Although there was no conclusive evidence concerning prolongation of overall survival with fludarabine in comparison with CAP, the RCT in question does clearly indicate improved response rate, and in responders, improved time to progression. However, we have identified concerns. These mostly stem from the small size of the trial. An important consequence is an inability to quantify important effects with sufficient precision. The most obvious problem is the width of the confidence intervals around the estimated difference in response between fludarabine and CAP. The RCT indicates that although severe adverse events are common with both fludarabine and CAP, they are markedly less in important respects such as nausea and vomiting, hair loss and alopecia with fludarabine. The excess of death during treatment with fludarabine was of some concern, but is not statistically significant.

Although qualitatively there is evidence of greater net benefit for fludarabine relative to CAP, there is no direct measurement of impact on quality of life to help quantify the degree to which beneficial effects are offset by the adverse events.

The drug costs of fludarabine are high relative to other second line treatments such as CHOP. The total cost associated with administration of fludarabine has been estimated as about £6,000 per treatment course. Uncertainty about incidence of adverse events, their severity and the cost of treating them has led to variability in this estimate. This and other unknowns make the overall budget impact extremely hard to determine. Our upper estimate of impact is £5.5 m. Suggestions that fludarabine will have minimal budget impact need to be considered very carefully.

Published estimates of cost-effectiveness, although at face value suggesting advantage for fludarabine over CHOP need to be interpreted cautiously because of the way the analyses were conducted and the sensitivity of the estimates to the effectiveness parameters. These do vary widely in the existing evidence base. Robust estimates of cost-utility could not be derived, so little assistance can be offered in helping decide whether the ratio of costs to net-benefits is favourable relative to other investments in health which may be under consideration, particularly in the area of cancer care.

The very recent advent of an oral preparation of fludarabine could make a difference to the relationship between costs and net benefit, because of the saved costs of drug administration. This together with improved patient acceptability suggests that guidance by NICE on the use of intravenous fludarabine should be reconsidered soon in the light of full information on effectiveness, costs and health economic impact of the oral preparation. These were outside the scope of this report. The advent of the oral fludarabine preparation is the reason for the early expiry date of this report.

Consideration of research in progress suggests that guidance on the use of fludarabine as a first line therapy will also soon be required. Good randomised trail evidence is in the process of being collected and the recruitment to these trials should be encouraged to ensure that any future decision on the use of fludarabine is underpinned by a more robust evidence base than its use as a second line treatment for CLL.

6.2 Assumptions, limitations and uncertainties

There should be little disagreement about the main findings we report. The systematic review employed an extremely comprehensive search and we employed explicit inclusion/exclusion procedures and defined methods of quality assessment, data abstraction and analysis. This has confirmed that the main evidence-base for fludarabine in 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, is restricted to one small RCT. This was probably never in dispute.

The interpretation of the trial is relatively straight forward, and again its main findings are not in dispute. What its closer scrutiny may raise however, is that in retrospect it did leave certain questions incompletely answered, which should ideally have been the subject of a further confirmatory trial. In consequence we believe there is continuing uncertainty about the size of important effects and the degree to which benefit is offset by adverse effects. Direct measurement of the impact on quality of life is a key outstanding issue.

The main limitation concerning our economic analysis is the poverty of the existing data to predict budget impact and assess cost-utility. More precise answers to questions concerning cost and economic impact would require new data collection, which is not feasible in the time-scale available to conduct rapid technology appraisals.

6.3 Need for further research

There is a need for further research on second line therapy with fludarabine in relapsed/refractory CLL. However, the issue appears to have been overtaken by a focus on good quality recently completed and on-going trials on use of fludarabine as a first line therapy in CLL. Arguably the priority should thus be to support these on-going trials to ensure that the evidence-base for use of fludarabine as a first line therapy is more robust than the evidence-base for second line therapy. Future NICE appraisals on this agent should take the likely time of completion of these trials into account.

7. CONCLUSIONS

- Fludarabine as second line therapy for relapsed/refractory CLL appears to be more effective than CAP, a current alternative
  - Response rates and duration of response are improved
  - The side effects of treatment, although still marked, are less severe
  - There is no evidence for improvement in overall survival
  - There are important uncertainties about the size of benefits and adverse effects
  - There is little certainty about how much the benefits are offset by adverse effects
- If it is used, clinicians should be clear and patients aware of the limits to our knowledge on the effectiveness of this agent
- The drug cost of fludarabine is high at approximately £3,900 per treatment cycle
- The cost of administering fludarabine is estimated to be £6,000, but may be higher
- An approximate upper estimate of the budget impact on the NHS in England and Wales of using fludarabine as second line therapy for relapsed/refractory CLL is £5.5m per annum
- Apparently favourable estimates of cost-effectiveness need to be interpreted cautiously
- The cost-utility of fludarabine cannot be accurately provided and so cannot assist a judgement on whether for a given investment of resources, encouraging use of fludarabine is likely to achieve more net benefit than investing in other areas of health care
- Effectiveness, cost and cost-effectiveness needs to be assessed for the recently licensed oral preparation of fludarabine
- On-going research on the effectiveness of fludarabine as a first line therapy should be supported to ensure that the evidence-base for likely future NICE decisions on use of fludarabine is better.
- Future RCTs must assess impact on quality of life directly.

8. APPENDICES

Appendix 1 Search strategies to identify prospective cohort studies on the natural history of CLL

MEDLINE (Ovid) 1987-Aug 2000

01 leukemia b-cell chronic/
02 prognosis/
03 survival rate/
04 survival analysis/
05 or/2-4
06 1 and 5

Appendix 2 Search strategy to identify effectiveness of any treatments for CLL

This strategy was designed specifically to target published systematic reviews and was based on the ARIF search protocol. The following strategies were executed in the electronic databases.

MEDLINE (Ovid) 1990 – Sept 2000

01 leukemia b cell chronic/th,dt,rt
02 leukemia lymphocytic chronic/dt,th,rt
03 chronic lymphocytic leuk?emia$.ti,ab.
04 or/1-4
05 (meta-analysis or review literature).sh.
06 meta-analy$.tw.
07 metaanal$.tw.
08 meta-analysis.pt.
09 (systematic$ adj4 (review$ or overview$)).tw.
10 review,academic.pt.
11 case report.sh.
12 letter.pt.
13 historical article.pt.
14 review of reported cases.pt.
15 review,multicase.pt.
16 review literature.pt.
17 1 or 2 or 3 or 4 or 5 or 6 or 12
18 7 or 8 or 9 or 10 or 11
19 17 not 18
20 19 and 4

Cochrane Library 2000, Issue 4

01 Exp leukemia b cell chronic:ME
02 chronic lymphocytic leukemia*
03 chronic lymphocytic leukaemia*
04 bcll
05 cll
06 1 or 2 or 3 or 4 or 5

Appendix 3 Details on reviews considered in assessing the effectiveness of treatments other than fludarabine

Review	Type & contents	Treatment options & patients: main conclusions/recommendations
CLL Trialists' CG (1999) [15]	Meta-analysis: Chemotherapeutic options in CLL	1. Immediate vs deferred chemotherapy for early stage CLL: No chemotherapy for most patients with early stage disease. 2. Combination chemotherapy (eg, cyclophosphamide & vincristine plus prednisone/prednisolone – COP or COP plus doxorubicin – CHOP) versus single agent chlorambucil as first line treatment for more advanced disease: Single agent chlorambucil as the first line of treatment for most patients with advanced disease, with no evidence of benefit from early inclusion of an antracycline
Dighiero (1997) [10]	Narrative review:Summary of meeting session, incl. presentation of meta-analysis by CLL TCG.	1. Early vs deferring treatment. 2. Place for chlorambucil for CLL. 3. Purine analogues for 1st line of therapy in CLL.
Kalil & Cheson (2000) [16]	Narrative review (with some quantitative results for fludarabine): Diagnosis; clinical features; staging; therapy; prolymphocytic leukaemia.	1. No treatment for early stage CLL. 2. Single agent chemotherapy: alkylating agents (chlorambucil & cyclophosphamide), the nucleoside analogues fludarabine and cladribine, and the adenosine deamiase inyibitor pentostatin . 3. Initial treatment: for decades, chlorambucil has been the standard agent. Cyclophosphamide is generally used only when chlorambucil has failed or if it is poorly tolerated. Corticosteroids are often reserved for patients with autoimmune complications. 4. Combination chemotherapy: CP, CVP, COP, CHOP. 5. Purine analogues: fludarabine, cladribine, Pentostatin. 6. **Second line therapy** (palliative in intent): the most appropriate treatment for patients with CLL who relapse after, or are refractory to, initial treatment is referral to a clinical research study. Many could be retreated with alkylating agent; fludarabine has become the standard agent for patients initially treated with an alkylating agent based regimen (overall response rate 40-50%). Combination of fludarabine with alkylating agents, antracyclines or related compounds, cytarabine and interferon-alpha are not clearly better than fludarabine alone. 7. New approaches (eg, taxanes, ...); bone marrow transplantation; gene therapy; splenectomy; radiation therapy; supportive care...
Montserrat & Rozman (1995) [17]	Narrative review (with some quantitative results for fludarabine): Epidemiology; etiology; biology; clinical features; complications; diagnosis; prognosis; treatment...	1. Early stage: no treatment. 2. Advanced clinical stage due to high tumor burden and bone marrow failure: chlorambucil, CHOP, local radiotherapy. **Patients failing front-line therapy should be treated with combination chemotherapy or fludarabine**. 3. Patients with cytopenias due to immune mechanism: initially with CCST, cytotoxic agents added where no response after 4-6 weeks. Immunoglobulins. 4. Hypersplenism: splenectomy or radiotherapy. 5. Younger patients (targeting complete response): CHOP, fludarabine, allogeneic bone marrow transplant, ...
Molica et al (1995) [13]	Narrative review: Prognostic features; therapeutic approaces.	1. Radiotherapy; splenectomy 2. Single agent chemotherapy: CLB, cyclophosphamide (CF). 3. Corticosteroids 4. Combination chemotherapy. 5. Fludarabine 6. Deoxycoformycin, 2-chlorodeoxyadenosine, biological agents (alpha-IFN). 7. Bone marrow transplantation
Wilhelm et al (1997) [59]	Narrative with some quantitative data: 1st line therapy of advanced CLL.	1. Corticosteroids: infection is a problem. 2. Alkylating agents: so far, the combination of chlorambucil and prednisone is the mainstay of first line treatment of CLL patients. 3. Polychemotherapy regimens. 4. High-dose chlorambucil therapy. 5. Purin nucleoside analogues 6. Bioimmunotherapy; maintenance therapy; bone marrow transplantation
Pott (1997) [60]	Narrative: purine analogs in CLL	
Bergmann (1997) [61]	Narrative: purine analogs in CLL	
Adkins (1997) [62]	Narrative review: fludarabine.	

Appendix 4 BNF general guidance on use of cytotoxic drugs

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 5 Protocol

West Midlands Development and Evaluation Service

Protocol for the review of:

Rituximab and fludarabine for blood cancers: non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

Full title of research question
Rituximab and fludarabine for blood cancers: non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL).

Clarification of research question and scope
Rituximab and fludarabine are two relatively new agents for the treatment of blood cancers, consequently it is necessary to confirm that the benefits of these new drugs are worth the costs.

Haematological malignancies are a particularly heterogeneous group of cancers. This is particularly true in the case of the NHL for which complex classification systems have been developed. Inevitably some types of blood cancer may be more susceptible to rituximab and fludarabine than others, particularly in the case of the former which targets a particular marker found only on B-lymphocytes.

Therefore the main focus of this report is the effectiveness and cost-effectiveness of rituximab for stage III – IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy and fludarabine for B cell chronic lymphocytic leukaemia (CLL) with sufficient bone marrow reserve and has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen. These are the specific conditions for which the drugs have been licensed.

However we are aware that these drugs are currently being used and investigated in the treatment of other related conditions and earlier in the course of the diseases for which licences have been granted. Therefore we will also provide a formal scoping review to identify research, both complete and ongoing in conditions outside the licensed implications, to indicate where the agents of interest might be applied in the future, and whether there will be rigorous research to support the use in these areas.

Thus the specific objectives of the report will be (in the order in which they will be tackled):

1. To identify trials, published, unpublished and ongoing, examining the use of rituximab and fludarabine in haematological malignancies.

2. To systematically review the evidence of the effectiveness of rituximab for stage III – IV follicular lymphoma that is chemoresistant or is in its second or subsequent relapse after chemotherapy as indicated in the drug licensing information.

3. To systematically review the evidence of the effectiveness of fludarabine for B cell chronic lymphocytic leukaemia (CLL) with sufficient bone marrow reserve and has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen as indicated in the drug licensing information.

4. To systematically review the evidence on costs and health economic impact of rituximab and fludarabine in B-cell NHL and B-cell CLL as described in (2) and (3).

5. To relate the effects identified in (2) and (3) to costs identified in (4) and therefore to consider the validity of any existing estimates of health economic impact, particularly cost-effectiveness.

Report Methods
General: There will be no language restrictions and all searches will stop on 1st September 2000

(1) Formal scoping search to indicate developments in the use of rituximab and fludarabine i.e. RCTs published and on-going.

Searches

Studies will be identified using the following:
- Electronic databases: Cochrane Library, Medline, Embase, Science Citation Index, National Research Register
- Internet Search engines
- Drug company submissions invited by the National Institute for Clinical Excellence
- Citation lists
- Conference abstracts

Inclusion Criteria
Intervention: Rituximab and/or fludarabine
Comparator: Any
Population: Any haematological malignancy
Outcomes: Survival, quality of life, adverse events
Design: RCT

Analysis
As the main purpose will be to indicate the current and future availability of high quality research evidence on rituximab and fludarabine outside of the licensing implications, no attempt to summarize the data will be made. The characteristics or planned characteristics of the trials identified will be presented and sub-divided by the intervention and target condition.

(2 + 3) Systematic review of the effectiveness of rituximab for NHL (2) and fludarabine for CLL (3)

Searches

Studies will be identified using the following;

- Electronic databases: Cochrane Library, Medline, Embase, Science Citation Index, National Research Register
- Internet Search engines
- Drug company submissions invited by the National Institute for Clinical Excellence
- Citation lists
- Conference abstracts

Inclusion Criteria

Intervention :

(2) Rituximab at the dose given on product information sheet.

(3) Fludarabine at the dose given on the product information sheet.

Comparator :

Any, including no treatment

Population :

(2) Stage III/IV follicular B-cell NHL which is chemoresistant or is in its second or subsequent relapse after chemotherapy

(3) B cell CLL with sufficient bone marrow reserve that has not responded to or had progressed during or after treatment with at least one standard alkylating agent containing regime.

Outcomes : Survival, quality of life, adverse events. We will explore the value of tumour response to indicate impact on quality of life if no other data are available.

Design: Ideally RCTs. However we anticipate there will be insufficient numbers to adequately answer the question posed. In this event we will extend the included studies to non-randomized CCTs and if these are not available, before-after studies i.e. with no parallel control arm. In this last instance, quality criteria will be introduced as part of the inclusion/exclusion decisions. These will be designed to protect against the possibility of eligible studies presenting the results of patients unrepresentative of the stated target population.

On this basis included before-after studies will:

- Need to indicate that they were conducted prospectively
- Ideally present the results of a consecutive series
- Give clear indications of the patient characteristics particularly with regard to stage of disease and previous treatments
- That losses to follow-up with respect to particular outcomes of interest are <10%
- Size > 10 subjects

Imputing the effectiveness of rituximab / fludarabine on such studies will inevitably require indirect comparison with information about the natural history of patients in the given condition. A systematic search for prospective cohort studies will be conducted for series giving such information; information provided within studies e.g. from a case-control methodology will not be acceptable.

Application of inclusion/exclusion criteria will be undertaken by two reviewers. Decisions will be made independently of the data extraction and prior to the scrutiny of results.

Quality Assessment
This is partly implicit in the inclusion criteria. If RCTs are present details of relative strengths and weaknesses will be assessed in relation to selection, performance, detection and attrition biases. If non-randomized CCTs are identified established checklists e.g. Jadad will be employed.

Data Extraction
This will be carried out by two reviewers independently.

Analysis
This will be qualitative. It will be amplified by meta-analysis if appropriate. No sub-groups have been identified a priori.

(4+5) Systematic review on the cost effectiveness of rituximab for NHL and fludarabine for CLL
Review question is in relation to the applications of rituximab and fludarabine in (2) and (3) above to assess the costs and relate these to the identified effects and effectiveness of the two agents.

Method
Systematic review of cost assessments and economic evaluations.

Search
Information on cost-effectiveness and quality of life will be sought from Medline, HEED, NEED, DARE, Embase, Science Citation and Internet sites of UK health economics units.

Quality Assessment
Quality of any identified evaluations will be undertaken using a specifically designed checklist based on the BMJ guidelines for economic appraisals.

Analysis
As a minimum a cost-consequence analysis will be conducted. Ideally if quality of life data can be identified, a cost-utility analysis will be undertaken giving cost-per-QALY for each intervention. Where cost data are uncertain a sensitivity analysis will be carries out. The perspective for the health economic analysis will be from the NHS view-point. The main focus of the analyses will be on marginal changes.

Handling the company submissions
Industry submissions will be used to identify effectiveness information, cost data and assessments of health economic impact which meet our inclusion criteria. Any information indicated as being confidential will be marked as such in the final report.

Research in progress
None identified at this stage of the project.

Project Management
(a) Timetable
Deadline for submission of protocol to HTA programme – 22nd September 2000

Deadline for submission of progress report to HTA programme – 7th December 2000
Deadline for submission of draft report to HTA programme – 9th January 2001
[Draft report, without peer reviewers comments to be sent to NICE – 21st December 2000]

(b) Competing Interests
Members of the project management group and advisory panel have been asked to declare any interest they may have (A declaration of competing interests form has already been returned.) None were identified in any of the members of the review team.

(c) Project Management Group
This review will be carried out under the guidance of a project management group, which comprises a lead reviewer (CH), a main author (BW), an information scientist (AFS), a health economist (TR) and an assistant reviewer (CD). A further senior reviewer may be added to this team.

Appendix 6 Search strategies to identify studies on the effectiveness of fludarabine in treating CLL

MEDLINE (Ovid) 1966-Sept 2000

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized 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 randomized controlled trial/
3 clinical trial/
4 prospective study/
5 double blind procedure/
6 randomization/
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 2000, Issue 3
See Appendix 9

Appendix 7 List of experts contacted as part of search

Dr. C. Fegan
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Professor A. Burnett
Chairman of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology on behalf of the British Society of Haematology.
Department of Haematology
University of Wales College of Medicine
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Appendix 8 Search strategy and methods to identify on-going trials of fludarabine

1. The following were searched to specifically identify on-going, or completed but currently unpublished randomised controlled trials, involving fludarabine:
2. Bibliographic database search – see Appendix 9 for details (44 citations scanned)
3. Cochrane Library 2000 Issue 4 – Cochrane Controlled Trials Register (CD-ROM) (30 hits scanned)
4. National Research Register 2000 Issue 4 (via http://www.update-software.com) (159 hits scanned – included on-going & completed studies)
5. British Society for Haematology web-site (http://www.blacksci.co.uk/uk/society/bsh) (no trials listing available)
6. British National Lymphoma Investigation web-site (http://www.bnli.ucl.ac.uk) (14 listed trials scanned)
7. European Organisation for Research and Treatment of Cancer web-site (http://www.eortc.be) (384 "chemotherapy" trial protocols scanned)
8. European Group for Blood and Marrow Transplantation web-site (http://www.ebmt.org) (ongoing studies for each working party scanned)
9. Leukaemia Research Fund (http://dspace.dial.pipex.com/lrf-//research/director.pdf) (2 hits in research directory scanned)
10. Medical Research Council & Current Controlled Trials web-site (http://www.controlled-trials.com) (26 hits scanned)
11. National Institutes of Health/CancerNet web-site (http://www.cancertrials.nci.nih.gov) (121 hits scanned – includes open and closed studies)
12. Schering company web-site (http://www.schering-plough.com & http://www.sp-research.com) (no trials listing available)
13. General web-search using Google search engine (142 hits scanned)
14. Schering Industry submission (all reference lists scanned; does not include anything marked "commercial in confidence" unless already identified by one of other elements of search strategy above)

In general, where search terms could be used, the text word "FLUDARABINE" was employed. For the general web search the phrase "(RANDOMISED OR RANDOMIZED) AND "CONTROLLED TRIAL") was used.in addition. Potentially relevant hits were scanned, and a judgement made on whether it was likely that the study was an RCT, and that it was likely that the effectiveness of fludarabine was being tested. Where search terms could not be used, details of all identifiable trial entries were scanned using the same criteria.If an entry appeared to relate to a trial, and information was brief, further details were sought either from the organisation co-ordinating the trial or the lead investigator. Wherever possible full copies of the trial protocols were obtained. All searches were conducted during the period 1/11/2000 to 10/12/2000.

Appendix 9 Details of bibliographic database search employed to identify on-going trials involving fludarabine

MEDLINE (Ovid) 1966 to August 2000

01 fludara$.ti,ab.
02 exp hematologic neoplasms/
03 exp leukemia/
04 exp lymphoma/
05 or/2-4
06 randomized controlled trial.pt.
07 controlled clinical trial.pt.
08 randomized controlled trials/
09 random allocation/
10 double blind method/
11 single blind method/
12 or/6-11
13 animal/ not human/
14 12 not 13
15 clinical trial.pt.
16 exp clinical trials/
17 (clin$ adj25 trials$).ti,ab.
18 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mas k$)).ti,ab.
19 placebos/
20 placebo$.ti,ab.
21 random$.ti,ab.
22 research design/
23 or/15-22
24 23 not 13
25 24 not 14
26 14 or 25
27 1 and 5 and 26

EMBASE (Ovid) 1980 – May 2000

1 fludara$.mp.
2 fludara$.ti,ab.
3 exp hematologic disease/
4 exp leukemia/
5 exp lymphoma/
6 malignanc$.ti,ab.
7 cancer$.ti,ab.
8 leuk?emia.ti,ab.
9 or/3-8
10 controlled trial/
11 randomized controlled trial/
12 clinical trial/
13 controlled study/
14 clinical study/
15 prospective study/
16 double blind procedure/
17 randomization/
18 major clinical study/
19 trial$.ti,ab.
20 study.ti,ab.
21 studies.ti,ab.
22 or/10-21
23 1 and 9 and 22
24 limit 23 to human

Science Citation Index (BIDS) 1981-2000

1 Fludara*
2 (Lymphoma* or malignan* or cancer* or leukaemia* or leukemia*)
3 1 and 2

Cochrane Library 2000 Issue 3

Fludara*

Appendix 10 Details of excluded studies and reasons for exclusion

Angelopoulou MA, Poziopoulos C, Boussiotis VA, Kontopidou F, Pangalis GA.
Fludarabine monophosphate in refractory B-chronic lymphocytic leukemia: maintenance may be significant to sustain response.
Leukemia & Lymphoma 1996;**21**:321-4.
Reason for exclusion; less than 50 patients

Briones J, Montserrat E, Urbano-Ispizua A, Esteve J, Colomer D, Lopez-Guillermo A et al.
[Treatment with fludarabine of lymphoid neoplasms with low grade malignity resistant to treatment or in relapse]. [Spanish]
Medicina Clinica 1996;**107**:86-9.
Reason for exclusion; less than 50 patients

Cheson BD.
New prospects in the treatment of indolent lymphomas with purine analogues.
Cancer Journal From Scientific American 1998;**4** (Suppl 2):S27-36.
Reason for exclusion; review

French Cooperative Group on CLL.
Comparison of fludarabine, cyclophosphamide/doxorubicin/prednisone, and cyclophosphamide/doxorubicin/vincristine/prednisone in advanced forms of chronic lymphocytic leukemia: Preliminary results of a controlled clinical trial.
Seminars in Oncology 1993;**20**(Suppl 7):21-23.
Reason for exclusion; patients all untreated

Gillis S, Dann EJ, Cass Y, Rochlemer RR, Polliack A.
Activity of fludarabine in refractory chronic lymphocytic leukemia and low grade non-Hodgkin's lymphoma--the Jerusalem experience.
Leukemia & Lymphoma 1994;**15**:173-5.
Reason for exclusion; less than 50 patients

Giraldo P, Palomera L, Mayayo P, Moneva JJ, Diego P, Pardo M et al.
Fludarabine as single therapy for advanced stage of refractory chronic lymphocytic leukemia.
Blood 1998;**92**:4192.
Reason for exclusion; less than 50 patients

Gjedde SB, Hansen MM.
Salvage therapy with fludarabine in patients with progressive B-chronic lymphocytic leukemia.
Leukemia & Lymphoma 1996;**21**:317-20.
Reason for exclusion; less than 50 patients

Grever MR, Kopecky KJ, Coltman CA, Files JC, Greenberg BR, Hutton JJ et al.
Fludarabine monophosphate: a potentially useful agent in chronic lymphocytic leukemia.
Nouvelle Revue Francaise d Hematologie 1988;**30**:457-9.
Reason for exclusion; less than 50 patients

Grever M. Leiby J. Kraut E. Metz E. Neidhart J. Balcerzak S. Malspeis L.
A comprehensive phase I and II clinical investigation of fludarabine phosphate.
Seminars in Oncology 1990;**17**(Suppl 8):39-48.
Reason for exclusion; less than 50 eligible patients

Hiddemann W, Rottmann R, Wormann B, Thiel A, Essink M, Ottensmeier C et al.
Treatment of advanced chronic lymphocytic leukemia by fludarabine. Results of a clinical phase-II study.
Annals of Hematology 1991;**63**:1-4.
Reason for exclusion; less than 50 patients

Hocepied AM. Falkson CI. Falkson G.
A phase II trial of fludarabine in patients with previously treated chronic lymphocytic leukaemia.
South African Medical Journal 1996;**86**:549-50.
Reason for exclusion; less than 50 patients

Keating MJ, Kantarjian H, O'Brien S, Robertson L, Huh Y.
New agents and strategies in CLL treatment.
Leukemia & Lymphoma 1991;**5**(Suppl):139-142.
Reason for exclusion; suspicion of duplication Keating 1989 [30]

Keating MJ, Kantarjian H, Talpaz M, Redman J, McCredie KB.
Fludarabine therapy in chronic lymphocytic leukemia (CLL).
Nouvelle Revue Francaise d Hematologie 1988;**30**:461-6.
Reason for exclusion; suspicion of duplication Keating 1989 [30]

Keating MJ, O'Brien S, Kantarjian H, Plunkett W, Estey E, Koller C et al.
Department of Hematology, M.D. Anderson Cancer Center, Houston, TX 77030.
Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent.
Blood 1993;**81**:2878-84.
Reason for exclusion; suspicion of duplication Keating 1989 [30]

Keating MJ, O'Brien S, Robertson L, Huh Y, Kantarjian H, Plunkett W.
Chronic lymphocytic leukemia--correlation of response and survival.
Leukemia & Lymphoma 1993;**11** (Suppl 2):167-75.
Reason for exclusion; suspicion of duplication Keating 1989 [30]

Keating MJ. Smith TL. Lerner S. O'Brien S. Robertson LE. Kantarjian H. Freireich EJ.
Prediction of prognosis following fludarabine used as secondary therapy for chronic lymphocytic leukemia.
Leukemia & Lymphoma 2000;**37**:71-85.
Reason for exclusion; less than 50 eligible patients

Kemena A, O'Brien S, Kantarjian H, Robertson L, Koller C, Beran M et al.
Phase II clinical trial of fludarabine in chronic lymphocytic leukemia on a weekly low-dose schedule.
Leukemia & Lymphoma 1993;**10**:187-93.
Reason for exclusion; less than 50 patients

Laplante S, Grenier JF.
Cost-efficacy evaluation of fludarabine phosphate in the treatment of chronic lymphocytic leukemia refractory to other therapies
European Journal of Cancer 1997;**33**:42.
Reason for exclusion; cost-effectiveness

Leporrier M, Chevret S, Cazin B, Boudjerra N, Maloum K, Feugier P et al.
Randomized clinical trial comparing two anthracyclin-containing regimens (CHOP and CAP) and fludarabine (FDR) in advanced chronic lymphocytic leukemia (CLL).
Blood 1999;**94**:2682.
Reason for exclusion; patients were untreated

Levy V, Porcher R, Leporrier M, Delabarre F, Cazin B, Chevret S.
Patients with advanced chronic lymphocytic leukemia (CLL) randomly treated by chop, cap or fludarabine - Usefulness in determining the optimal treatment.
Blood 1999;**94**:810.
Reason for exclusion; patients were untreated

Montillo M, Tedeschi A, Delfini C, Olivieri A, D'Adamo F, Leoni P.
Effectiveness of fludarabine in advanced B-cell chronic lymphocytic leukemia.
Tumori 1995;**81**:419-423.
Reason for exclusion; less than 50 patients

OBrien S, Kantarjian H, Beran M, Freireich E, Komblau S, Koller C et al.
Fludarabine (FAMP) and cyclophosphamide (CTX) therapy in chronic lymphocytic leukemia (CLL).
Blood 1996;**88**:1910.
Reason for exclusion; previously untreated patients

O'Brien MER, Matutes E, Cunningham D, Hill M, Emmett E, Ellis PA et al.
Fludarabine in lymphoproliferative disorders: The Royal Marsden Hospital Experience.
Leukemia & Lymphoma 1994;**14**(Suppl 2):17-23.
Reason for exclusion; less than 50 eligible patients

Puccio CA, Mittelman A, Lichtman SM, Silver RT, Budman DR, Ahmed T et al.
A loading dose/continuous infusion schedule of fludarabine phosphate in chronic lymphocytic leukemia.
Journal of Clinical Oncology 1991;**9**:1562-9.
Reason for exclusion; less than 50 eligible patients

Rummel MJ, Kafer G, Pfreundschuh M, Jager E, Reinhardt U, Mitrou PS et al.
Fludarabine and epirubicin in the treatment of chronic lymphocytic leukaemia: a German multicenter phase II study.
Annals of Oncology 1999;**10**:183-8.
Reason for exclusion; less than 50 patients

Spriano M, Clavio M, Carrara P, Canepa L, Miglino M, Pierri I et al.
Fludarabine in untreated and previously treated B-CLL patients: a report on efficacy and toxicity.

Haematologica 1994;**79**:218-24.
Reason for exclusion; less than 50 patients

Stelitano C, Morabito F, Kropp MG, Callea V, Iuliano F, Oriana V et al.
Fludarabine treatment in B-cell chronic lymphocytic leukemia: response, toxicity and survival analysis in 47 cases.
Haematologica 1999;**84**:317-23.
Reason for exclusion; less than 50 patients

Thomas D, O'Brien S, Kantarjian H, Giles FJ, Lerner S, Keating MJ.
Outcome in 203 patients (PTS) with relapsed or refractory B-cell chronic lymphocytic leukemia (CLL) with salvage therapy (RX): Retreatment with fludarabine (FLU).
Blood 1998;**92**:419.
Reason for exclusion; less than 50 eligible patients

Zittoun R, De Witte T.
A randomized phase ii trial of high-dose chlorambucil vs. fludarabine in patients with advanced B-chronic lymphocytic leukemia.
Hematology and Cell Therapy 1999;41;127-136.
Reason for exclusion; previously untreated patients

Appendix 11 Population characteristics of total cohorts in included case series

	Bezares 1998[24]	**Fenchel 1995**[25]	**Keating 1989**[30]	**Liso 1998**[26]	**Monserrat 1996**[27]	**Sorensen 1997**[28]	**Zinzani 1997**[29]
Type of study	Case series	Case series	Case Series	Case series	Case series	Case series	Case series
Aim of study	To evaluate the efficacy of Fludarabine in CLL patients with and without prior therapy (interim analysis after 2 year period)	Report fludarabine clinical results in refractory CLL and LG-NHLs, and severe infectious complications and immunosuppressive effects.	Summarize experience with fludarabine in 68 previously treated patients with CLL and analyse the association of prognostic factors with response and survivial.	To address the topic of fludarabine activity after the failure of either chlorambucil or CHOP-like regimen using a retrospective series.	Analyse results of fludarabine in unselected popn. patients with previously treated and advanced CLL from different Spanish institutions.	Describe fludarabine toxicity and activity in refractory CLL in a 'setting that more closely resembles clinical practice than most published trials'.	Fludarabine and αIFN in Rx of B-CLL and LG-NHL advanced refractory /relapsed patients.Reports on initial Fludarabine before randomisation to receive/not receive αIFN.
Total number of patients	92 (84 evaluated)	77	68	57	75	791 (724 treated)	137
% relapsed	N/S	N/S	N/S	N/S	76%	N/S	N/S
% resistant	N/S	N/S	N/S	N/S	24%	N/S	N/S
Demographics Age:	Median 66 (range 38-80)	Median 59 (range 26-81)	Median 60 (range 32-79)	N/S	Mean 62 (range 32-83)	Median 65 (n=724)	N/S overall
Sex:	54% male 46% female	65% male 35% female	74% male 26% female	N/S	71% male 29% female	72% male 28% female	N/S overall
Inclusion/exclusion criteria given in published paper:							
Condition	Yes – CLL	Yes - advanced CLL or LG- NHL	Yes – CLL	Yes – B cell CLL	Yes – CLL	Yes-CLL	Yes – B-CLL or LG-NHL
Stage	No	No	Yes – Stage III/IV (Stage 0-II only if had progressive disease)	No	No	Yes - Intermediate or high grade Rai stage	Yes – stage III/IV CLL
Prior Rx	No	No	Yes – previously treated patients only	Yes – must have had chlorambucil & CHOP	No	Yes – failed to respond to chlorambucil or cycloph-osphamide +/- prednisone	Yes – advanced relapsed or refractory to previous Rx
Age	No	No	No	No	No	Yes - ≥18 years only	No
Sex	No – m & f included	No – m & f included	No – m & f included	No	No – m & f included	No – m & f included	No – m & f included
Performance status	No	No	No	No	No	Yes – ECOG PS 0-3	No
Pregnancy/lactation	No	No	No	No	No	Yes – excluded	No
Other serious disease/infection	No	No	No	No	No	Yes – excluded	No
HIV/Hepatitis	No	No	No	No	No	No- N/S	No
CNS involvement	No	No	No	No	No	Yes – excluded	No
Other anti-cancer therapy	No	No	No	No	No	Yes – excluded	No
Other	N/S	N/S	N/S	N/S	N/S	N/S	N/S

Appendix 12 Population characteristics of most relevant subset of patients in included case series

	Bezares 1998[24]	**Fenchel 1995**[25]	**Keating 1989**[30]	**Liso 1998**[26]	**Monserrat 1996**[27]	**Sorensen 1997**[28]	**Zinzani 1997**[29]
Total number in study	92 (84 evaluated)	77	68	57	75	791 (724 treated)	137
% patients relevant to review i.e. meeting current licensing indications	Not known	Not known	87%	100%	Not known	100%	56%
Reasons for uncertainty	Although 63 patients relapsed or refractory we do not know if they have received alkylating agent	Of the 59 patients with CLL we do not know how many have been treated with an alkylating agent	n/a	n/a	100% are previously treated but we cannot assume with an alkylating agent also not all patients received correct dose - % unknown	n/a	n/a
Nearest relevant subset of cohort for which results are given	None available for clinical response or toxicity but survival and progression free interval given separately for previously treated patients (n=63)	59 CLL patients (only 56 evaluated)	Patients with previous alkylating agent Rx	n/a	None available	n/a	77 patients meet the licensing indications
Information not known about this subset	% who had relapsed after treatment with alkylating agent	% who have relapsed after treatment with an alkylating agent	n/a	n/a	n/a	n/a	n/a
Demographics of this subset Age: Sex:	 None given None given	 Not given No given	 None given None given	 n/a n/a	 n/a n/a	 n/a n/a	 Median 61 (range 40-77) 65% male 35% female

Appendix 13 Details of interventions and outcomes for total cohorts in included case series

	Bezares 1998[24]	**Fenchel 1995**[25]	**Keating 1989**[30]	**Liso 1998**[26]	**Monserrat 1996**[27]	**Sorensen 1997**[28]	**Zinzani 1997**[29]
Intervention	25mg/sm/day iv x 5 days every 28 days x 6 cycles	25mg/m^2 iv over 30-mins for 5 days,repeated every 5th week.	25-30mg/m^2 iv x 5 days at 30 min infusion repeated every 3-4 week (88% every 4 weeks)	N/S	20-30mg/m^2 iv for 3-5 days every 5 days. Most common25mg/m^2 IV for 5 days	25mg/m2 ≤ 30 min iv daily for 5 consecutive days with repetition every 28 days	25mg/m^2 daily by 30 min iv for 5 consecutive days, repeated every 28 days
Concomitant Rx:							
Corticosteroids banned	N/S	N/S	N/S	N/S	N/S	Yes	No
Other Rx allowed	N/S	N/S	N/S	N/S	Antibiotics prophylactically in 36 patients	Allopurinal, hydration, alkalisation urine(high risk patients), prednisone - 27%	Antibiotics and cortico-steroids permitted for Rx of side effects
Pre-treatment tests stated:							
Serum chemistries	N/S	Yes	Yes	N/S	N/S	Yes	No
Blood counts	N/S	Yes	Yes	N/S	N/S	Yes	No
Physical examination	N/S	Yes	Yes	N/S	N/S	Yes	No
Pathology specimen	N/S	Yes	No	N/S	N/S	No	No
Bone Marrow tests	N/S	Yes	Yes	N/S	N/S	Yes	Yes
Outcome Measures:							
Clinical Response	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adverse Events	Yes	Yes	Yes	No	Yes	Yes	Yes
Survival analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes (For other outcomes
Quality of Life	No	No	No	No	No	No	No some patients had
Time to progression	Yes	No	Yes	No	No	No	Yes received the second
Duration of response	No	No	No	No	No	Yes	No Rx i.e. α-IFN)
Other	None	Mortality	None	None	None	None	None

Appendix 13~~Appendix 13~~ Details of interventions and outcomes for total cohorts of included case series (continued)

Clincial Response definitions	**Bezares 1998**[24]	**Fenchel 1995**[25]	**Keating 1989**[30]	**Liso 1998**[26]	**Monserrat 1996**[27]	**Sorensen 1997**[28]	**Zinzani 1997**[29]
Complete response	N/S	Lymphocytes <4x109/L; granulocytes> 1.5x10^9/L,thromb>100^x10^9/L , Hb >11g/dL, BM infiltration <30%, no palpable nodes or hepato/splenomegaly.	<4000 lymphocytes/ µL in blood, < 30% lymphocytes and no nodules in BM, impalpable liver and spleen, no pathological nodes.	N/S	Total disappearance symptoms and signs of disease; normalisation blood parameters: < 30% lymphocytes in BM aspirate and/or normal BM biopsy.	(>2 months duration) No liver/spleen/lymph node symptoms, neutrophils≥1,500/µL, platelets > 100,000/µL, Hb > 11g/dL, lymph - ocytes≤4000/µL, BM 30% lymphocytes	No palpable masses, recovery blood parameters (neutrophils to ≥ 1500/µL, platelets to ≥ 100,000/µL, Hb to ≥ 11g/dL, lymphocytes ≤ 4000/µL), BM lymph infiltration to below 30%.
Partial response	N/S	↓lymphocytes>50% and ↓ node size>50%. ≥1: granulocytes.>1500 µL/50% ↑ ; platelets>100 000/µL50, %↑; HB>11g/ dL /50%↑; 50% ↓ hepato/ splenomegaly, BM infil < 30% for at least 2 months.	>4000 lymphocytes/ µL in blood and > 1 log ↓, ≥ 50% ↓ BM infiltrate with > 30% lymphocytes or nodules, ≥ 50% ↓ in span below costal margin, , ≥ 50% ↓ in node size	N/S	Switch of disease to a less advanced clinical stage.	(>2 months duration)≥ 50% ↓ liver/spleen/lymph node symptoms, neutrophils ≥1,500/µL or ≥ 50% baseline, platelets >100,000/µL or ≥ 50% base, Hb 11g/dL or ≥ 50% base, lymph ≥ 50% baseline	≥ 50% decrease in palpable masses and peripheral lymphocytosis, recovery or at least 50% improvement of 1 or more of above mentioned parameters.
Stable disease	N/S	No PR,CR or PD	N/S	N/S	Failure	N/S	N/S
Progressive disease	N/S	≥1 : >50% ↑ node size, >50% ↑ hepato/ splenomegaly, >50% ↑number lymphocytes.	> 25% ↑ nodes, liver, spleen size or white cell count. (Patients were considered to be resistant if achieved < PR after 3 or more courses or had progressive disease)	N/S	Failure	liver/spleen/lymph node ≥ 50% ↑, new nodes, lymph ≥ 50% baseline.	N/S

Appendix 14 Quality assessment, threats to validity and relevance in included case series

	Bezares 1998[24]	Fenchel 1995[25]	Keating 1989[30]	Liso 1998[26]	Monserrat 1996[27]	Sorensen 1997[28]	Zinzani 1997[29]
Number in study	92 (84 evaluated)	77	68	57	75	791 (724 treated)	137
Source of case series	N/S	N/S	N/S	Retrospective series of 57 patients from 7 institutions who had Fludarabine as 3rd line Rx after Chlorambucil and CHOP-like regimen	75 patients treated at 13 Spanish institutions from 7/89 – 3/95 – represents 90% all patients treated in Spain	Participating physicians phoned National Cancer Institute with eligible patients which NCI confirmed and entered into the trial.	N/S
Characteristics well defined: Whole cohort Parent population	 No – PS and prev. Rx not given No	 No – PS not given No	 No – PS not given No	 None given No	 No –PS not given No	 No – Prev. Rx not given No	 No – PS not given No
% of cohort relevant to review	Not known	Not known	87%	100%	Not known	100%	56%
Adequate follow-up (<10% unreported) Length of follow-up	 2 years	 N/S but > 1 year	 Median 15m (4 to 37)	 Median 13m (1 to 65)	 N/S ≤ 5 months for some	 Median 59 months	 Median 32 months
Analysis done according to possible prognostic factors?: Stage Performance status Age Sex N[o/] previous Rx / relapses Resistance Blood Counts Other	 No No No No No No No None	 Yes No No No Yes No No Duration of disease until Rx with fludarabine, histological subtype	 Yes No Yes No Yes No Yes Serum Chemistries	 Yes No Yes No No Yes No Tumour response	 No No Yes No Yes Yes No None	 Yes Yes Yes Yes No No Yes Prednisone use, hepatosplenomegaly, lymphadenopathy.	 Yes No No No Yes Yes No None
Threats to validity	No comparator Small cohort Not enough information on prognostic factors Non-blinded assessment of outcomes Selection bias?	No comparator Small cohort Inadequate follow-up time Not enough information on prognostic factors Non-blinded assessment of outcomes Selection bias?	No comparator Small cohort Inadequate follow-up time Not enough information on prognostic factors Non-blinded assessment of outcomes Selection bias?	No comparator Small cohort Inadequate follow-up time No information on prognostic factors Non-blinded assessment of outcomes Selection bias?	No comparator Small cohort Not enough information on prognostic factors Non-blinded assessment of outcomes	No comparator Not enough information on prognostic factors Non-blinded assessment of outcomes Selection bias?	No comparator Not enough information on prognostic factors Non-blinded assessment of outcomes Selection bias?
Threats to relevance	Although 63 patients relapsed or refractory we do not know if they have received alkylating agent	Of the 59 patients with CLL we do not know how many have been treated with an alkylating agent	13% patients had not had prior Rx with alkylating agent, 5 patients had previously had diffuse, small lymphocytic lymphoma and developed CLL.	None	100% are previously treated but we cannot assume with an alkylating agent also not all patients received correct dose - % unknown	None	None

Appendix 15 Results in included case series

	Bezares 1998[24]	Fenchel 1995[25]	Keating 1989[30]	Liso 1998[26]	Monserrat 1996[27]	Sorensen[28]	Zinzani 1997[29]
Total number in study	92 (84 evaluated)	77	68	57	75	791 (724 treated)	137
Follow-up period	2 years	N/S but > 1 year	Median 15 m (range 4 to 37)	Median 13 m (range 1 to 65)	N/S ≤ 5 months for some	Median 59 months	Median 32 months
Losses to follow-up and reasons	N/S	N/S	None	n/a	None	4 early , further 11 lost to follow-up after 5 y	N/S
Drop-outs/Exclusions before assessment and reasons	N/S	7, 3 too early for evaluation, 4 died during Rx (1 ruptured liver, 1 anaphylactic shock, 2 septicaemia)	Of 29 non-responders: 19 excluded during Rx due to refractory disease. 10 died during Rx	n/a	7 patients still under therapy - at assessment, 1 other person missing – no reason given	67 no Rx (35 deteriorated or died, 19 refused, 4 improved, 4 ineligible, 5 not known) 21 non-assessable (incl. 1 death and 4 lost to follow-up)	4 deaths due to infection during Rx
Deaths	N/S	4 during Rx 15 further deaths (3 due to thrombocytopenic bleeding, 12 to infection)	10 during Rx Overall 36/68 had died at follow-up	At follow-up 22/57 died	26/75 died at follow up (3 of responders and 23 of the non-responders)	655/724 died at follow-up (482 disease, 79 infection, 26 cardiac, 20 other cancer, 12 pulmonary, 36 other)	4 during Rx Others N/S
Patients evaluated for response	84	70	68	57	68	703	137
Evaluated as intention-to-treat	No	No	n/a	n/a (100% relevant)	n/a	No	n/a
Clinical response rates	18% CR, 43% PR 61% RR	6% CR, 67% PR 73% RR	13% CR, 28% PR, 16% nodular PR , 57% RR	5% CR, 53% PR 56% RR	4% CR, 24% PR 28% RR	3% CR, 29% PR 32% RR	3% CR, 44% PR 47% RR
Patients evaluated for toxicity	84	77	68	n/a	N/S	705	137
Other outcomes : Time to progression Duration of response Quality of life Survival analysis	 Not given Not given Not given Not given	 Median 7m (2 to 20+) Not given Not given Overall survival probability at 18 m = 42%, event-free survival at 18 m = 22%	 13m in PR patients, 21 m in CR and nPR Not given Not given Median overall survival was 16 m	 Not given Not given Not given Median survival 30 months	 Not given Not given Not given Median survival 11 months (non-responders) and not reached in responders	Of 724 treated patients: Median 7.5 months Median 13 months (responders only) Not given Not given	 Not given Not given Not given Not given Not given
Nearest subset relevant patients i.e.meeting licensing indications	Prev. Rx patients (n=63)	Patients with CLL (n=56)	Patients prev. Rx with alkylating agent (n=59)	n/a	None available	n/a	B cell CLL (n=77)
Response rates for subset	Not given	5% CR, 68% PR, 73% RR	51% RR	n/a	n/a	n/a	4% CR, 41%PR, 45% RR
Other outcomes for subset	Progression free interval 8 months, estimated survival at 20 months = 52% (95%CI 28% to 71%)	None	None	n/a	n/a	n/a	Progression free survival median - 20 months (responders). Overall survival median 24 months.

Appendix 16 Further detail on adverse events in included case series (toxicity is given overall – for all patients in study)

		Bezares 1998[24]	Fenchel 1995[25]	Keating 1989[30]	Liso 1998[26]	Monserrat 1996[27]	Sorensen 1997[28]	Zinzani 1997[29]
Total number in study		92	77	68	57	75	791(724 treated)	137
Evaluated for toxicity		84	77	68	N/S	75	705	137
Deaths suspected to be related to fludarabine Rx		None	N/S	10 died during study but not known if these are due to Rx	N/S	N/S	2 from neutropenic sepsis, 3 from TLS.	4 deaths from infection
Haematological events:		Overall 72 events	N/S		N/S			
Anaemia	Mild/mod	N/S		N/S		Autoimmune	54% patients	9% patients
	Severe	N/S		N/S		haemolytic – 4 cases	37% patients	None
Leucopenia	Mild/mod	N/S		N/S		N/S	13% patients	N/S
	Severe	N/S		N/S		N/S	46% patients	N/S
Neutropenia	Mild/mod	N/S		Overall courses 100		Overall 10	N/S	33% patients
	Severe	N/S		cases		cases	N/S	11% patients
Thrombocytopenia	Mild/mod	N/S		Overall courses 46		Overall 15	25% patients	17% patients
	Severe	N/S		cases		cases	46% patients	5% patients
Non-haematological events:		N/S			N/S			
Pain	Mild/mod		N/S	N/S		N/S	N/S	N/S
	Severe		N/S	N/S		N/S	N/S	N/S
Fever	Mild/mod		N/S	Overall 23 cases of		N/S	N/S	4% patients
	Severe		N/S	FUO		N/S	N/S	None
Nausea and vomiting	Mild/mod		11% patients	Overall courses 9		N/S	26% patients	1% patients
	Severe		N/S	cases		N/S	0.6% patients	None
Diarrhoea	Mild/mod		N/S	Overall courses 6		N/S	12% patients	N/S
	Severe		N/S	cases		N/S	2.4% patients	N/S
Neurological	Mild/mod		N/S	Overall course 7		N/S	23% patients	N/S
	Severe		N/S	events		N/S	6% patients	N/S
Infections	Mild/mod	N/S		24% patients	N/S	Overall 33 cases of	26% patients	11% patients
	Severe	18 cases	29% patients	3 cases		fever/infection	22% patients	4% patients
Tumour Lysis Syndrome		N/S	1 event	N/S	N/S	1 case	1% patients	N/S
* Additional information obtained from commercial in confidence data submitted								
Mild/moderate adverse events are taken to be WHO scale grades 1-2; severe events are grades 3-5								

Appendix 17 Search strategies to identify cost and quality of life studies

- The NHS Economic Evaluation Database was searched using the following terms: Fludara$, rituximab, mabthera, idec-c2b8$, rituxan.

- 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

MEDLINE (Ovid) 1966-Sept 2000

01 economics/
02 exp “costs and cost analysis”/
03 cost of illness/
04 exp health care costs/
05 economic value of life/
06 exp economics medical/
07 exp economics hospital/
08 economics pharmaceutical/
09 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$.mp.
14 12 and 13
15 rituximab$.mp.
16 mabthera$.mp.
17 idec-c2b8$.ti,ab.
18 rituxan$.mp.
19 or/15-18
20 12 and 19
21 quality of life/
22 life style/
23 health status/
24 health status indicators/
25 treatment outcome/
26 “outcome assessment (health care)”/
27 or/21-26
28 exp lymphoma non-hodgkin/
29 non hodgkin$ lymphoma$.ti,ab.
30 b cell lymphocytic.ti,ab.
31 follicular lymphoma$.ti,ab.
32 or/28-31
33 27 and 32
34 exp leukemia b cell chronic/
35 cll.ti,ab.
36 b-cll.ti,ab.
37 chronic lymphocytic leuk?emia.ti,ab.
38 or/34-37
39 38 and 27

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