

# **Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment**

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**Health Technology Assessment  
NHS R&D HTA Programme**





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# Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment

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## Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

### Glossary\*

**Chemoresistant** Generally synonymous with refractory (see below)

**Conditioning agent** In this instance, fludarabine is used to prepare bone marrow for transplant by depletion of T cells

**First-line therapy** 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–I and Binet stage A

**Mini-transplant** Partial replacement of bone marrow from matched donor

**Recurrence** Resurgence of chronic lymphocytic leukaemia 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

**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 when there is only evidence of disease in lymphoid nodules in bone marrow without evidence of a diffuse or infiltrative pattern

**Second-line therapy** 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 the most commonly used are the Rai and Binet systems based on factors, such as lymphocytosis, anaemia, thrombocytopenia and areas of lymphoid involvement

**Third-line therapy** Treatment options applied when patients have relapsed/ recurred following, or proved refractory/ chemoresistant to, both first- and then second-line treatment options (see above)

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

## List of abbreviations

AML	acute myeloid leukaemia	IWF	International Working Formulation
CAP	cyclophosphamide plus doxorubicin plus prednisolone	LRF	Leukaemia Research Fund
CHOP	cyclophosphamide plus doxorubicin plus vincristine plus prednisolone	MRC	Medical Research Council
CI	confidence interval	NA	not applicable*
CLL	chronic lymphocytic leukaemia	NHL	non-Hodgkin's lymphoma
CR	complete response/remission	NICE	National Institute for Clinical Excellence
CVP	cyclophosphamide plus vincristine plus prednisolone	PR	partial response/remission
DEC	Development and Evaluation Committee	QoL	quality of life
EORTC	European Organisation for Research on the Treatment of Cancer*	RCT	randomised controlled trial
HA	health authority	RR	response/remission rate (overall – including partial and complete responses)

\* Used only in tables and appendices





## Executive summary

### Background

Launched in 1994, intravenous fludarabine is a relatively new chemotherapeutic agent. It is currently licenced for use in patients with B cell chronic lymphocytic leukaemia (CLL) with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent-containing regimen (i.e. as a second-line treatment).

CLL is a cancer of the lymphocytes, which 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 health authority of 500,000 may have approximately 16 new patients presenting each year, most of whom will be aged > 60 years and asymptomatic. Only about 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 (QoL) by inducing remission and abolishing symptoms associated with relapse with minimal 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 cyclophosphamide plus doxorubicin plus vincristine plus prednisolone (CHOP) or fludarabine.

### Objective

Although the use of intravenous fludarabine is already well established in its current licensed indication, this review considers whether this should be supported and further encouraged.

### Methods

A systematic review of effectiveness was undertaken using a predefined protocol. Databases, including

MEDLINE, EMBASE and the Cochrane Library, were searched until September 2000. Ascertainment of relevant literature was augmented by citation checking of the studies and reviews obtained and the reference list of the single industry submission, contact with experts in the field and Internet searches. Randomised controlled trials (RCTs) and case-series with  $\geq 50$  patients assessing any effects of fludarabine as a second-line treatment were focused on. Inclusion decisions, quality assessment and data abstraction were performed independently by two reviewers. Synthesis was qualitative and meta-analysis was not employed. The economic analysis comprised in the main a systematic review of past economic evaluations.

### Results

#### 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 cyclophosphamide plus doxorubicin plus prednisolone (CAP). Overall response rates (RRs) were 48% with fludarabine versus 27% with CAP – a difference of 21% (95% confidence interval, 2 to 40). Improvements in RR were seen for both complete and partial response. 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 entire trial, which included a further 100 previously untreated patients (total  $n = 196$  – 100 given fludarabine and 96 given CAP), adverse events were common in both arms, but nausea and vomiting, and alopecia and hair loss were markedly less with fludarabine. Deaths during treatment were greater with fludarabine than with CAP (nine versus three), but this difference was not statistically significant.

Seven case-series were also considered. The variability of the results for RRs and times to

progression suggested that 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 favoured fludarabine over CAP. However, the degree to which beneficial effects outweighed adverse events was difficult to quantify, particularly in the absence of any direct measures of the impact of fludarabine on QoL.

### **Costs**

The drug cost of a recommended course of intravenous fludarabine is £3900. The wider cost of administration is estimated to be £6000, but this could be subject to variation depending on the true incidence, severity and costs of treating adverse events. The total annual budget impact is highly uncertain – we derived an approximate upper estimate of £5.5 million per annum for the NHS in England and Wales, which equates to a cost of £50,000 per annum for an average health authority 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 thus cannot assist a judgement on whether, for a given investment of resources, encouraging the use of fludarabine is likely to achieve more net benefit than investing in other areas of healthcare.

## **Conclusions**

### **Implications for healthcare**

Based on the limited evidence available, intravenous fludarabine seems to be an effective second-line treatment for CLL. Whether fludarabine used in this way is an efficient use of healthcare resources is uncertain. 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.

### **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 to support and amplify ongoing RCTs to ensure an adequate evidence base for future decisions on the use of fludarabine. Future RCTs should assess impact on QoL directly.

# Chapter I

## Background and objectives

### Description of the underlying health problem

#### Nature of the condition

Chronic lymphocytic leukaemia (CLL) is a malignant disorder of circulating blood cells. There are several types of blood cells, but those that proliferate in CLL are lymphocytes – a type of white blood cell. Lymphocytes are of two main types – B 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 proliferation of the abnormal lymphocytes impairs the production and function of normal red blood cells, which causes anaemia, platelets, which predisposes to bleeding (thrombocytopenia), and white cells, which gives 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, which is lymphocytosis. The severity of the disease is gauged by the number of main symptoms present in a patient. This is the basis of staging systems, the most commonly used of which are the Binet<sup>1</sup> system and the Rai<sup>2</sup> system (see *Tables 1* and *2*). The International Workshop on CLL has recommended integrating the Rai and Binet

systems based on the following equivalence: Binet stage A = Rai stages 0–I, Binet stage B = Rai stages I–II and Binet stage C = Rai stages III–IV.<sup>3</sup>

#### Epidemiology

CLL is the most common leukaemia in adults.<sup>4</sup> In 1998, there were 824 deaths from CLL in England and Wales,<sup>5</sup> and there were approximately 1700 new cases of CLL in the UK in 1989. It is most common in older persons,<sup>6</sup> with the average age of diagnosis being 64 years.<sup>4</sup> It is also more common in men than women, with an overall incidence rate in England and Wales in 1992 of 3.8 and 2.7 per 100,000 of the population, 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, there will be approximately 16 new cases each year. There is, however, some uncertainty about precise levels of incidence. The prevalence is considerably in excess of incidence due to the long median survival times of patients, which is approximately 10 years overall (and > 10 years in two-thirds of patients).<sup>4</sup> Thus, there are likely to be about 160 patients with CLL in the average HA at any one time.<sup>7</sup> However, it should be noted that at any one time, only half of these will be being actively treated (see below).

**TABLE 1** Binet staging system for CLL<sup>1</sup>

Stage	Diagnostic specification
A	No anaemia, no thrombocytopenia, < three lymphoid areas enlarged
B	No anaemia, no thrombocytopenia, ≥ three lymphoid areas enlarged
C	Anaemia (haemoglobin < 10 g/dl) and/or platelets < 100 × 10 <sup>9</sup> /l

**TABLE 2** Rai staging system for CLL<sup>2</sup>

Stage	Risk	Diagnostic specification
0	Low	Lymphocytosis > 5 × 10 <sup>9</sup> /l in blood and > 30% in bone marrow
I	Intermediate	Lymphocytosis in blood and bone marrow with enlarged lymph nodes
II		Lymphocytosis in blood and bone marrow with enlarged spleen and/or liver (with or without enlargement of nodes)
III	High	Lymphocytosis in blood and bone marrow with anaemia (haemoglobin < 110 g/l)
IV		Lymphocytosis in blood and bone marrow with thrombocytopenia (platelets < 100 × 10 <sup>9</sup> /l)

## Aetiology and prognosis

The causes of CLL are largely unknown. Risk factors may include genetic abnormalities, for example, 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.<sup>6</sup> Migrant studies of Japanese moving to the USA<sup>8</sup> demonstrate that the Japanese retain their low rates of CLL, which 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 (QoL). Survival may be as long as 10 years from diagnosis. Indeed, many patients die of unrelated diseases.<sup>4</sup> However, at the present time, CLL remains incurable because 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 at least 5 years.<sup>9</sup> Low-risk (indolent) disease, corresponding to Rai stage 0 and Binet stage A, has an expected survival of 10 years, intermediate-risk disease (Rai stages I–II and Binet stage B) has a median survival of 7–9 years and high-risk disease (Rai stages III–IV and Binet stage C) has a median survival of 5 years.<sup>4</sup> More than 25% of patients with low-risk disease die of unrelated causes, whilst the disease progresses to a more advanced stage in 40%. Ultimately, 50% of patients require treatment.<sup>10</sup>

## 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 on prognostic factors in CLL: three reviews and two by the same authors about laboratory factors.

Tefferi and colleagues suggested that the major prognostic factor in B cell CLL is the clinical stage of the disease.<sup>11</sup> Molica and co-workers listed other prognostic parameters, including age and gender, peripheral blood lymphocyte count and lymphocyte doubling time, pattern of bone marrow

involvement, cytogenetics and immunophenotype.<sup>12</sup> They cited results from the French Cooperative Group for CLL Study in which the 5-year survival rate was 89% for Binet stage A (Rai stage 0) and 77% for Binet stage A (Rai stages I–III) using the International Workshop on CLL system.

In a different study by Molica and co-workers, 93 patients with CLL were followed up for a median time of 49 months.<sup>13</sup> It was found that patients with low CD20 antigen expression had a better survival outcome than those with high CD20 antigen expression (relative risk = 0.51, 95% confidence interval (CI), 0.24 to 1.04). Multivariate analysis indicated that only absolute peripheral blood lymphocytosis and Binet clinical stages remained independent prognostic factors. The authors 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-haematological features in the prognostic assessment of B-CLL patients”.

In another paper, Molica and colleagues found that  $\beta_2$ -microglobulin and soluble CD23 contribute individually to prognosis of B cell CLL.<sup>14</sup> In addition, a combination of  $\beta_2$ -microglobulin and soluble CD23 was to be 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.

## Significance in terms of ill health (burden of disease)

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

## Current service provision

### Objectives of treatment and important health outcomes

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

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\* A peer reviewer notes that use of soluble CD23 levels in the UK is rare and that much greater emphasis is placed on the mutational status of the IgV genes and the expression of CD38.

- 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, and thus improving QoL
- helping patients come to terms with their condition and thus, again, improving QoL
- managing the terminal stages of the disease and, therefore, 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
- QoL
- patient and carer satisfaction.

However, because the prospect of cure with current treatments is acknowledged to be rare in CLL (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 and thus maximising QoL 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:

- the number of episodes of symptomatic progression
- the duration of these episodes
- the severity of associated symptoms
- the ability to bring about a remission
- the speed of induction of remission
- the reduction of symptoms associated with the remission
- adverse events associated with induction of the remission
- the duration of remission.

### 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 treatment

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 also increasingly being considered as a first-line therapy.

### Second-line treatment

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

### 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 eight narrative reviews were considered. Further details on these are provided in appendix 3. The key points arising were as follows:

- In the meta-analysis,<sup>15</sup> immediate chemotherapy was compared with deferred chemotherapy (six randomised controlled trials (RCTs)), and combination chemotherapy was compared with the single agent chlorambucil as first-line treatment for more advanced CLL (ten trials).
- The conclusion concerning early versus deferred chemotherapy for early disease, was that early treatment offers no advantage in terms of overall survival.
- Concerning first-line treatment, the value of the 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.
- Five narrative reviews considered treatment options in CLL, but only two mentioned second-line therapy<sup>16</sup> or treatment for “patients failing front-line therapy”.<sup>17</sup>
- Kalil and Cheson,<sup>16</sup> writing in the context of USA 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, anthracyclines or related compounds, cytarabine and interferon- $\alpha$  are not clearly better than fludarabine alone”.

- Similarly, Montserrat and Rozman<sup>17</sup> suggested that “patients failing front-line therapy should be treated with combination chemotherapy or fludarabine”.
- Three of the eight narrative reviews focused on purine analogues (mainly fludarabine) for CLL.

### Current service cost

As 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 within the NHS. However, consideration of the long duration of the disease and the variety of treatments to which an individual might be exposed to over the course of their illness suggest that the costs of caring for patients with CLL are likely to be considerable.

### Variation in services

There seems to be remarkable consensus about the treatment of CLL, which predicts that variation in treatment, although constituting only one part of the 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 this treatment may no longer be considered new in most clinicians’ minds.

### Description of fludarabine

Fludarabine (Fludara<sup>®</sup>) is manufactured by Schering Health Care Limited, UK. It is a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine (9- $\beta$ -D-arabinofuranosyladenine) that is relatively resistant to deamination by adenosine deaminase. It is an antimetabolite that prevents 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” (i.e. as second-line therapy). It had been previously licensed in the USA by the Food and Drug Administration in April 1991 under the trade name Fludara from Berlex Laboratories Inc., USA, 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 British National Formulary<sup>18</sup> 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 [(central nervous system)] 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 < 30 ml/minute. Specific interacting drugs are given as dipyridamole, which may possibly reduce the efficacy of fludarabine, and pentostatin, which increases pulmonary toxicity with an unacceptably high incidence of fatalities.

The recommended dose is 25 mg/m<sup>2</sup> daily for 5 days consecutively in every 28 days by the intravenous route. It should be administered up to the achievement of a maximal response (usually six cycles) and then discontinued. The quoted cost per 50 mg vial is £130.<sup>18</sup> This suggests a net drug cost for a six-cycle treatment will be approximately £3900 (5  $\times$  6  $\times$  £130). This would be sufficient to treat a person with a surface area of up to 2 m<sup>2</sup> (the average surface area for a UK adult being approximately 1.7 m<sup>2</sup>).

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

The Schering submission to the National Institute for Clinical Excellence (NICE) refers to an oral version of fludarabine, which “has recently been approved and will be available by the end of the year”.<sup>19</sup> It should be noted that this technology appraisal has not formally considered the oral preparation.

### Summary of the key points from the background

#### Disease

- CLL is a cancer of lymphocytes, the vast majority of which 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 one time.
- Only a maximum of 50% of these will require treatment.
- Prognosis varies by clinical stage. Using the Binet classification, median survival is > 10 years for stage A, 7–9 years for stage B and 5 years for stage C.
- Most patients are asymptomatic and stage A at presentation.
- 25% of low-risk patients die of unrelated causes.
- It is currently licensed for treatment of patients with B cell CLL with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent-containing regimen (i.e. as second-line therapy).
- It is administered as a course of five injections over 5 days, repeated every 28 days for six cycles.
- The cost of the drug is approximately £3900 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, but this has not been considered in this technology appraisal.

### 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 QoL by inducing remission and abolishing symptoms associated with relapse with minimal 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 previous RCTs.

### New treatment

- Fludarabine is a cytotoxic agent of the antimetabolite class.

### Objectives of the review

Despite undoubted improvements in the treatment of haematological malignancies, a number of conditions remain difficult to treat. 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 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?” – these being the circumstances for which fludarabine is currently licensed.





## Chapter 2

# Clinical effectiveness of fludarabine

### Objective

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

### Methods for reviewing the effectiveness of fludarabine

#### Protocol

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

#### Search strategy

A broad comprehensive search for studies assessing the effectiveness of fludarabine was undertaken. Electronic bibliographic databases, including MEDLINE (Ovid) 1966–September 2000, EMBASE (Ovid) 1980–September 2000, Science Citation Index (Web of Science) 1981–October 2000 and the Cochrane Library 2000, issue 3, were searched (see appendix 6 for details of the search terms used). The studies and reviews obtained and the reference list of the single industry submission were citation checked. Experts in the field were also contacted (see appendix 7). Finally, Internet search engines were browsed for suitable trials.

This search strategy was amplified by the 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) and the identification of ongoing and unpublished trials involving fludarabine (see appendices 8 and 9 for further details). This included extensive interrogation of relevant Internet websites, 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.

### Inclusion and exclusion criteria

#### Intervention

Fludarabine at the dose given on the product information sheet, i.e. 25 mg/m<sup>2</sup> intravenously daily for 5 days consecutively in every 28 days for approximately six cycles.

#### Population

Patients with B cell CLL with sufficient bone marrow reserve and who had not responded to or whose disease had progressed during or after treatment with at least one standard alkylating agent-containing regimen, as indicated in the UK licensing information.

#### Comparator

Any comparator, which also included no treatment and any of the current recommended treatments.

#### Outcomes

No restriction was made according to the outcomes measured. However, survival, QoL and adverse events were the outcomes designated beforehand as those of greatest interest.

#### Design

The initial inclusion criteria specified RCTs. In our protocol, in the absence of RCTs, we indicated an intention to extend our inclusion criteria to include non-randomised clinical controlled trials and studies with no parallel control arm, i.e. 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. In a pragmatic amendment to our protocol (see appendix 5), only case-series with 50 patients or more were considered; originally we had intended to consider all case-series with more than ten patients, but this could not be achieved in the time available. Where case-series were included, the inclusion criterion relating to presence of a comparator was inevitably dropped.

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

### Data extraction strategy

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

### 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.<sup>20</sup> The RCTs were also assessed using the Jadad checklist.<sup>21</sup>

For case-series, the strengths and weaknesses of the included studies were assessed using a pre-specified framework developed by two of the authors in a previous systematic review on a different topic.<sup>22</sup> The studies had 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) and have a rate of losses to follow-up with respect to particular outcomes of interest of < 10%.

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

### Analysis

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

## Results

### 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

Nine studies were finally included. Two studies were RCTs<sup>23,24</sup> and seven were case-series (six prospective and one retrospective).<sup>25-31</sup>

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

Of the potentially included 38 studies, 29 were excluded. Most were excluded either because the

patient population was < 50 or because the study was restricted to untreated patients. See appendix 10 for the full details of the excluded studies and the reasons for their exclusion.

### Effectiveness evidence from the RCT Included study characteristics (see Table 3)

The study by the French Cooperative Group on CLL<sup>23</sup> compared fludarabine using a standard regimen with CAP in patients with Binet stages B and 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 and 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 QoL.

In the study by Tondini and colleagues,<sup>24</sup> it was noted that although the stated population was patients with indolent non-Hodgkin's lymphoma (NHL), it included International Working Formulation (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 patients with IWF type A did indeed have CLL. However, it also seems very likely that the number was small, and the results for this subgroup were not readily available. For this reason, the results of this study are not presented further, despite the fact that they are potentially of great interest because it was the only study identified that compared fludarabine with another new antimetabolite cytotoxic agent, cladribine.

### Included study quality (see Table 4)

Quality assessment of the main included RCT in its entirety (not just the subgroups of most relevance to this review) suggested it was well conducted with respect to randomisation. Its main shortcoming related to avoidance of detection bias. Clearly, it is difficult to devise a double-blind 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, that is, those relying directly or indirectly on assessment of clinical response. Arguably, this shortcoming would have least impact on assessment of outcome based on death, particularly overall survival.

TABLE 3 Characteristics of identified fludarabine RCTs

	French Cooperative Group on CLL, 1996 <sup>23</sup>	Tondini et al., 2000 <sup>24</sup>
<b>Aim of study</b>	To conduct a two-arm comparison of fludarabine with CAP for patients with B cell CLL	To evaluate tolerability and crossover activity of fludarabine and cladribine in NHL
<b>Number randomised</b>	100 to fludarabine (52 untreated and 48 previously treated); 96 to CAP (48 untreated and 48 previously treated)	Originally 60 (two excluded before treatment) – 26 to fludarabine; 32 to cladribine
<b>Demographics</b>		
<b>Age</b>	Median = 63 (range 39–70) in fludarabine arm; median = 62 (range 43–78) in CAP arm	Not stated
<b>Sex</b>	74% male in fludarabine arm; 66% male in CAP arm	Not stated
<b>Inclusion/exclusion criteria given</b>		
<b>Condition</b>	Yes: B cell CLL	Yes: relapsed indolent lymphoma (but included International Working Formulation (IWF) type A, some of which could have been CLL)
<b>Stage</b>	Yes: Binet stage B or C in untreated patients	No
<b>Prior treatment</b>	No: untreated and previously treated with chlorambucil or similar treatment eligible	Yes: must have received at least one previous treatment and be relapsed or refractory
<b>Age</b>	Yes: ≥ 18 years	Yes: 17–75 years
<b>Sex</b>	No: male and female included	No: demographics not given
<b>Performance status</b>	Yes: WHO scale 4 excluded	Yes: had to have Karnofsky performance status of ≥ 60
<b>Pregnancy/lactation</b>	No: not stated	No
<b>Other serious disease/infection</b>	Yes: abnormal liver or renal function, haemolytic anaemia and thrombocytopenia excluded	No
<b>HIV/hepatitis</b>	Yes: HIV-related disease excluded	No
<b>Central nervous system involvement</b>	No: not stated	No
<b>Other anti-cancer therapy</b>	No: not stated	Yes: must not have been receiving other anti-cancer treatment, including corticosteroids
<b>Other</b>	Yes: Must have been 'in need of therapy'	Yes: had to have active disease, and a life expectancy of > 3 months
<b>% of cohort relevant to review</b>	49% of evaluated patients were previously treated with an alkylating agent	43% had IWF A (not known how many of these had CLL, but all had probably previously received an alkylating agent)
<b>Demographics</b>	Not given for subset of cohort most relevant	Not given for subset of cohort most relevant
<b>Follow-up</b>		
<b>Adequate (target &lt; 10% unreported)</b>	Yes: 12/208 (6%)	Not stated
<b>Length</b>	Median = 36 months (range 1–61)	Not stated
<b>Intervention</b>	Fludarabine 25 mg/m <sup>2</sup> per day for 5 days consecutively by a 30-minute infusion repeated every 28 days for six cycles	Fludarabine 25 mg/m <sup>2</sup> by a 30-minute i.v. infusion for 5 days consecutively every 4 weeks
<b>Comparator</b>	CAP (cyclophosphamide 750 mg/m <sup>2</sup> per day on day 1, doxorubicin 50 mg/m <sup>2</sup> per day i.v. on day 1 and oral prednisolone 40 mg/m <sup>2</sup> per day on days 1–5) repeated every 28 days for six cycles	Cladribine 0.14 mg/kg by a 2-hour i.v. infusion for 5 days consecutively every 4 weeks

continued

TABLE 3 contd Characteristics of identified fludarabine RCTs

	<b>French Cooperative Group on CLL, 1996<sup>23</sup></b>	<b>Tondini et al., 2000<sup>24</sup></b>
<b>Concomitant treatment</b>		
<b>Corticosteroids</b>	Banning of use not stated	Stated as being banned
<b>Other treatment allowed</b>	Not stated	Prophylactic cotrimoxazole and itraconazole
<b>Pre-treatment tests</b>	Serum chemistries, blood counts, physical examination, pathology specimen, bone marrow tests	Serum chemistries, blood counts, physical examination, pathology specimen, bone marrow tests
<b>Outcome measures</b> All outcome measures presented by untreated and previously treated subgroups (note: randomisation stratified by prior treatment)		
<b>Clinical response</b>	Yes (primary)	Yes
<b>Adverse events</b>	Yes	Yes
<b>Survival analysis</b>	Yes	No
<b>QoL</b>	No	No
<b>Time to progression</b>	Yes	Yes
<b>Duration of response</b>	Yes	No
<b>Other</b>	None	None
<b>Clinical response definitions</b>		
<b>Complete response (CR)</b>	Disappearance of all palpable disease and a return to normal blood counts, granulocytes > 1500/ $\mu$ l, platelets > 100,000/ $\mu$ l, haemoglobin > 11 g/dl, bone marrow lymphocytes < 30%	Disappearance of all clinical evidence of tumour for a period of $\geq$ 2 months. No lymphadenopathy, hepato/splenomegaly, constitutional symptoms, granulocytes > $1.5 \times 10^9$ /l, platelets > $100 \times 10^9$ /l, haemoglobin > 11 g/dl, lymphocytes $\leq 4 \times 10^9$ /l. Bone marrow normocellular for age with < 30% of mature lymphocytes for $\geq$ 2 months after clinical complete remission
<b>Partial response (PR)</b>	> 50% reduction in measurable disease and > 50% improvement in all abnormal blood counts	> 50% decrease in lymphocytes from baseline and > 50% reduction in lymphadenopathy, > 50% reduction in the size of the liver and/or spleen, and one or more of: granulocytes $\geq 1.5 \times 10^9$ /l or 50% improvement, platelets > $100 \times 10^9$ /l or 50% improvement, haemoglobin > 11 g/dl or 50% improvement
<b>Stable disease</b>	No change in parameters	Patients with no response/not progressive
<b>Progressive disease</b>	Lymphocytes > 10,000/ $\mu$ l, > 25% increase above remission values or > 50% increase in bone marrow infiltration or corresponding enlargement of lymph nodes, liver or spleen	Not stated
IWF, International Working Formulation		

**TABLE 4** Quality assessment of the included RCT for fludarabine<sup>23</sup>

<b>Generation of allocation schedule</b>	
A1. Was the trial described as randomised?	Yes
A2. Was allocation truly random? or Was allocation quasi-random? or Was allocation systematic? or Was the method of randomisation not stated or unclear?	Yes No No No
Note: randomisation was stratified by prior treatment	
<b>Concealment of treatment allocation</b>	
B1. Was concealment adequate? or Was concealment inadequate? or Was concealment unclear?	Yes No No
<b>Implementation of masking</b>	
C1. Was the trial described 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
<b>Completeness of the trial</b>	
D1. Were the numbers of withdrawals in each group stated?	Yes
D2. Was an intention-to-treat analysis performed?	Yes
D3. What were the dropout rates in each group of the trial for each of the main outcomes?	Generally: fludarabine 6/106 (6%); CAP 6/102 (6%) (response duration assessment restricted to responders)
D4. Are there substantial differences in completeness between the groups?	No
<b>Jadad score</b>	3

**Results (see Table 5)****Clinical response – overall response rates**

Overall, the response rate (RR) 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% with fludarabine and 27% with CAP. The difference in response was thus 21% (95% CI, 2 to 40).

**Clinical response – complete response**

The rates of complete response (CR) 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**

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

**Time to progression**

Overall, the median time to progression was 817 days with fludarabine and 270 days with

CAP, and the difference was statistically significant ( $p = 0.0001$ ). For previously treated patients, the time to progression was a median of 324 days with fludarabine and 179 days with CAP. This difference was consistent in magnitude with the difference observed in the overall group, but was not statistically significant ( $p = 0.22$ ). However, the study was not powered to detect a difference in this outcome.

It should be noted that these figures are not mean or median durations of response for all patients exposed to either fludarabine or CAP, but 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 patients, the median overall survival was 728 days (95% CI, 392 to 939) with

TABLE 5 Results from the included RCT for fludarabine<sup>23</sup>

	Fludarabine	CAP
<b>Number entered into study</b>	106	102
<b>Follow-up period</b>	Median = 36 months (range 1–61)	
<b>Losses to follow-up</b>	Not stated	Not stated
<b>Dropouts/exclusions before assessment</b>	Six excluded for protocol violation (33 patients did not complete treatment, but were included in assessment – nine of these were deaths during treatment)	Six excluded for protocol violation (35 patients did not complete treatment, but were included in assessment – three of these were deaths during treatment)
<b>Number randomised</b>	100 (52 untreated and 48 previously treated)	96 (48 untreated and 48 previously treated)
<b>Patients evaluated for response</b>	100	96
<b>Evaluated as intention-to-treat</b>	Yes	Yes
<b>Clinical response rates (overall RR = CR + PR)</b>	60% (95% CI, 50 to 70)	44% (95% CI, 34 to 54; $p = 0.023$ )
<b>Patients evaluated for adverse events</b>	100	96
<b>Deaths during treatment</b>	Nine	Three
<b>Adverse events</b>		
<b>Total adverse events</b>	Not stated	Not stated
<b>Mild/moderate adverse events</b>	Haematological = 357; non-haematological = 143; infections = 98	Haematological = 332; non-haematological = 369; infections = 98
<b>Severe and fatal adverse events</b>	Haematological = 194; non-haematological = 12; infections = 21	Haematological = 191; non-haematological = 105; infections = 12
<b>Differences</b>	Significantly greater numbers of nausea and vomiting, and hair loss in CAP arm	
<b>Other outcomes</b>		
<b>Time to progression (in responders)</b>	Median = 817 days (95% CI, 453 to 996)	270 days (95% CI, 136 to 445; $p = 0.0001$ )
<b>QoL</b>	Not assessed	Not assessed
<b>Survival analysis (in responders)</b>	Median overall survival = 1348 days (95% CI, 936 to > 1661)	Median overall survival = 999 days (95% CI, 774 to 1537; $p = 0.27$ )
<b>Nearest subset of relevant patients</b>	Previously treated ( $n = 48$ )	Previously treated ( $n = 48$ )
<b>Response rates for relevant subset</b>	CR = 13%; PR = 35%; overall RR = 48%	CR = 6%; PR = 21%; overall RR = 27% ( $p = 0.036$ )
<b>Other outcomes for relevant subset</b>		
<b>Time to progression (in responders)</b>	Median = 324 days (95% CI, 272 to 459)	Median = 179 days (95% CI, 56 to 567; $p = 0.22$ )
<b>QoL</b>	Not assessed	Not assessed
<b>Survival analysis (in responders)</b>	Median overall survival = 728 days (95% CI, 392 to 939)	Median overall survival = 731 days (95% CI, 409 to 999, $p =$ not significant)

fludarabine and 731 days (95% CI, 409 to 999) with CAP. The survival curves were virtually identical and, inevitably, any differences were not statistically significant.

### QoL

No direct measure of impact on QoL was provided. It should be noted, however, that the definition of CR, in particular, does capture features of the disease that are likely to impinge on QoL, such as 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 (nine patients), intercurrent illness (15 patients) and death (nine patients). Four patients died from infection, two from progression, one from myocardial infarction and one from a cerebrovascular accident related to severe thrombocytopenia. The reasons for failure to complete treatment in the CAP group were progressive disease (21 patients), intercurrent illness (ten patients) and death (three patients). All three patients died due to infection during treatment in the CAP group. The difference in deaths during treatment (nine with fludarabine versus three with CAP) was not statistically significant.

Adverse events other than death were extremely common in both treatment arms. However, the way in which adverse events are defined must be taken into account, and this may mean that even severe adverse events do not necessarily lead to clinical symptoms or require treatment. Furthermore, once it is known that they are likely to occur, adverse events can often be ameliorated with simple prophylactic treatment, such as antibiotics for infection. This given, there were 598 mild/moderate adverse events in the fludarabine group and 799 in the CAP group, and 227 and 308 severe adverse events, respectively. 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 also at least one severe adverse event. The majority of adverse events, whether severe or mild/moderate, were haematological, of which granulocytopenia was the most common problem, but this was not greatly different in incidence than other haematological adverse events, such as anaemia, thrombocytopenia and infection.

However, there were some important differences between the level and profiles of adverse events

between the fludarabine and CAP arms. They were less common in the fludarabine arm, and the CAP arm, in particular, had statistically significantly higher rates of non-haematological adverse events, such as nausea and vomiting, and alopecia and hair loss.

### Discussion of results

The study by the French Cooperative Group on CLL<sup>23</sup> is critical to the assessment of effectiveness of fludarabine in 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. 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 was a small trial. Considering the population of interest, there were only 96 patients (48 per arm).
- The comparison of fludarabine to CAP is relevant, although CAP is not the anthracycline-containing regimen most used, which is, in fact, probably CHOP.
- This was a generally well-conducted RCT, particularly with respect to quality of randomisation and allocation concealment.
- There was a clear 21% difference in the overall RRs in favour of fludarabine, which was statistically significant ( $p = 0.036$ ). 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 versus 179 days. However, this impressive result does have to take into account the fact 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 (nine deaths during treatment with fludarabine versus three deaths with CAP), although this difference was not statistically significant. 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 crossover from CAP to fludarabine and vice versa occurs during the period of follow-up, as is the case in this trial.
- The incidence of adverse events in 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. The way in which adverse events are defined must be taken into account, which may mean that even severe adverse events do not necessarily lead to clinical symptoms or require treatment. Furthermore, once it is known that they are likely to occur, adverse events can often be ameliorated with simple prophylactic treatment, such as antibiotics for infection.
- Deaths during the treatment period (again for the entire trial) were higher in the fludarabine arm than the CAP arm (nine versus three), but this difference was 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 QoL, and it is, therefore, 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 a direct measure of impact on QoL 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 replicated in other RCTs.

In summary, concerning the evidence on effectiveness, the results from the study by the French Cooperative Group on CLL<sup>23</sup> provide good evidence, at face value, 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 that some notes of caution need 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 RRs.

## Effectiveness evidence from the 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. Consequently, 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 and 13)

The seven case-series with > 50 patients varied in size, but most considered between 50 and 100 patients. However, one was larger than this<sup>30</sup> with 137 patients and another was considerably larger than this<sup>29</sup> 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.<sup>27,29</sup> All studies collected information on clinical response and all but one<sup>27</sup> collected some information on adverse events. However, no studies collected information on impact on QoL.

### 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 entire population meeting the inclusion criteria at the institutions involved in the studies also lays them open to the possibility of selection bias.

## Results (see appendices 15 and 16)

### Overall RRs

The overall RRs varied markedly across the seven case-series, and ranged from 28<sup>28</sup> to 73%.<sup>26</sup>

### Time to progression (in responders)

This was available for four studies<sup>25,26,29,31</sup> that reported median times of 8 months (about 240 days),<sup>25</sup> 7 months (about 210 days),<sup>26</sup> 7.5 months (about 225 days)<sup>29</sup> and 13 or 21 months (about 390 or 630 days).<sup>31</sup> In the last study,<sup>31</sup> the two figures given are time to progression in PR and CR plus 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.<sup>30,31</sup> An exception was the largest study,<sup>29</sup> which indicated that many of the patients suffered severe haematological adverse events, such as anaemia (37%), leucopenia (46%) and 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. Although to be expected given the variable patient populations of the included studies, especially with respect to prior treatment and whether the patients were relapsed or refractory, the variability of the results is the key observation. With this in mind, the results do confirm that caution is appropriate in the interpretation of the results of the evidence on effectiveness provided by the single small RCT identified.<sup>23</sup>

The case-series identified provided no further information on a key outcome absent from the RCT – impact on QoL.

**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 QoL. 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. The fact that QoL has not been measured directly must, therefore, be considered a handicap to assessing the effectiveness of fludarabine. The fact that RRs, in general, incorporate direct measurement of haemoglobin, platelets and white blood cells offsets this criticism to some degree, but not completely.

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

The results, which, at face value, are favourable with regard to the effects of fludarabine relative

to CAP on RRs 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 CIs around the difference in RR
- 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, despite the fact that the difference in fatal adverse events was not statistically significant
- the variability of the results observed in the case-series reviewed, although predictable on the basis of variation in study populations.

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.

With respect to 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 the absence of conclusive evidence that overall survival is improved with fludarabine compared with 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, a difference in the emphasis placed on some aspects of the RCT. The high levels of side-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.

## Summary of effectiveness

- A systematic review of effectiveness was undertaken.
  - The review question was “what is the effectiveness of fludarabine in 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”.
  - 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 the review question.
  - The RCT included in the analysis included 96 directly relevant patients (48 treated with fludarabine and 48 with CAP).
  - In most clinical conditions, the size of the trial alone would suggest that confirmation of results would be prudent.
  - Seven case-series were also considered to corroborate key findings from the RCT; these included in excess of 1000 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 QoL from any of the studies considered.
  - The main findings were based on the results of the single small RCT.
- Overall RRs were 48 versus 27% for fludarabine and CAP, respectively.
  - The 95% CI for the difference was 2 to 40%.
  - The improvements in RR were seen in both CR and PR categories.
  - The time to progression in responders was markedly increased from a median of 179 days with CAP to 324 days with fludarabine, but this difference was not statistically significant ( $p = 0.22$ ).
  - The survival times were identical: 728 versus 731 days with fludarabine and CAP, respectively.
  - Adverse events appeared to be common. Severe adverse events are probably universal with both fludarabine and CAP. However, the way in which adverse events are defined must be taken into account, which may mean that even severe adverse events do not necessarily lead to clinical symptoms or require treatment. Furthermore, once it is known that they are likely to occur, adverse events can often be ameliorated with simple prophylactic treatment, such as antibiotics for infection.
  - Deaths during the treatment period were greater for fludarabine (nine) than for CAP (three), but this difference was not statistically significant.
  - The non-haematological adverse events of nausea and vomiting, and alopecia and hair loss were markedly and statistically significantly less with fludarabine.
  - 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 outweigh adverse events is difficult to quantify.
  - Although we have probably placed greater emphasis on some of the limitations, our conclusions on effectiveness appear to be consistent with others summarising research in this area.

## Chapter 3

# Economic analysis of fludarabine

### Objectives

The original objectives defined in the protocol were re-stated slightly and are as follows.

- To systematically review the evidence on costs and health economic impact of fludarabine in 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.
- 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.

### 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, and the pre-specified method was, therefore, designed on this basis. Following confirmation from the systematic review of effectiveness that the prior assumption about quality of evidence on effectiveness was correct, no amendments to the protocol concerning economic analysis were made.

### Search strategy

A specific search strategy for information on costs, cost-effectiveness and QoL involved searches of bibliographic databases, such as MEDLINE (Ovid) 1966–September 2000 and the NHS EED, and 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 the economic evaluation, all studies encountered in the searches for effectiveness referring in any way to cost were also considered.

### Handling the information identified

The inclusion criteria allowed all information on costs, QoL 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 *British Medical Journal* 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.

### Results

#### Estimation of the net benefits (i.e. taking into account disbenefits)

The results and conclusions of the systematic review of effectiveness contain our assessment of net benefit (see Summary of effectiveness section). It is important to reiterate that no directly collected information on impact on 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 are balanced against adverse events still stands.

In the Wessex Development and Evaluation Committee (DEC) report 44,<sup>32</sup> 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 Index of Health-related Quality of Life 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 P2 E3 = 0.79 |

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) and (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 because failure to achieve remission is likely to prompt further courses of treatment. This data is presented not so much as a criticism of the approach, which was to some extent addressed in the original report by conducting a sensitivity analysis, but as an indication of the difficulty of judging the QoL weights of the health states involved without some direct measures as a guide.

### Estimation of net costs

For intravenous fludarabine, the drug cost to the NHS is about £3900 based on the recommended course of five doses of 25 mg/m<sup>2</sup> per cycle for a typical patient and for a conventional regimen of six cycles of chemotherapy.

Further information on costs was limited. The Schering submission to NICE,<sup>19</sup> 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 estimated that the cost of fludarabine, including acquisition, administration, prophylaxis, monitoring and treating adverse events, is £6032. An obvious issue with this costing is that the cost of drug acquisition at £2665 was considerably less than the £3900 predicted above. This was explained by the fact that the patients in the audit only received a mean of 4.1 courses. Feedback from clinicians suggests that this is realistic. Further concerns about the way in which this costing exercise was conducted are raised in the Critique of cost-effectiveness studies section.

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.<sup>33</sup> 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 calculated. 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;<sup>19</sup> in the Roche submission, this was £3540.<sup>33</sup>

The numerical value obtained in the Roche submission should not be used directly because it is taken out of context and may clearly be subject to bias arising from Roche's position as a commercial competitor with Schering. However, the observation does alert to the possibility of

high variability in cost estimates depending on the severity of the side-effects of fludarabine in any particular series of patients. In this respect, it needs to be appreciated that side-effects of intravenous fludarabine, like any other chemotherapy regimen, can be greatly ameliorated by careful attention to administration and optimal application of simple and cheap prophylactic regimens. Conversely, if such care is not exercised the costs associated with adverse events might be unreasonably inflated.

### 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 than an option that will completely replace an existing treatment, such as CHOP. As 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. Furthermore, 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 one year will be entering a defined period of their disease where fludarabine may be considered the most appropriate treatment option, and 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 CLL in England and Wales (population of 55 million)	1840
Number who will be treated in any 1 year	920

Cost of administering one course of fludarabine intravenously (as per the Schering submission to NICE <sup>19</sup> )	£6032
Total cost per annum	£5.5 million

However, the fact that fludarabine is already a well-established treatment option and its additional costs have already been largely absorbed into the NHS budget suggests that the above estimate of budget impact is likely to be an overestimate.

The fact that giving patients two courses of fludarabine may not be uncommon is suggestive that the above may be an underestimate. However, where this does occur, alternative treatments might well be replaced, as opposed to displaced. Due to an aging population alone, the number of cases of CLL requiring treatment will be increasing, because its incidence rises steeply with age, which also suggests that the above estimate might be an underestimate. Finally, 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 million represents a realistic upper estimate of budget impact. The Schering submission to NICE predicts very minimal budget impact,<sup>19</sup> and we would suggest that great caution be exercised in accepting this. Furthermore, 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 one year would be £50,000.

### 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 6–8* describe some of the key study characteristics and report the results for the base-case cost-effectiveness analyses.

The economic analysis reported in the Schering submission considers the use of fludarabine as a second-line treatment of CLL.<sup>19</sup> The analysis considers two alternative approaches to administration: intravenous 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 found for the evaluation of clinical effectiveness<sup>23</sup> and CHOP is more commonly used in the UK.

The strengths and weaknesses of the cost analysis have been explored. The RCT was not used as a

**TABLE 6** Assessment of cost-effectiveness analysis: study characteristics and results<sup>19</sup>

<b>Comparators</b>	Three alternative comparators (to i.v. fludarabine) were used: CHOP, CAP and oral fludarabine
<b>Perspective</b>	Health sector
<b>Type of economic evaluation</b>	Main analysis: cost-effectiveness analysis (i.e. incremental cost per year of remission gained)
<b>Base-case effectiveness result</b>	
<b>Overall RR</b>	Significantly more pre-treated patients responded to fludarabine than to CAP
<b>Response duration</b>	Fludarabine median duration = 324 days; CAP median duration = 179 ( $p = 0.22$ )
<b>Expected disease-free days</b>	i.v. fludarabine = 155 days; CHOP and CAP = 48 days
<b>Base-case cost result</b>	
<b>i.v. fludarabine</b>	Details not included as data was commercial in confidence
<b>CHOP</b>	Details not included as data was commercial in confidence
<b>CAP</b>	Details not included as data was commercial in confidence
<b>Base-case incremental cost-effectiveness ratio</b>	i.v. fludarabine versus CHOP = £10,588 per year of remission

**TABLE 7** Assessment of cost-effectiveness analysis: effectiveness and cost data<sup>19</sup>

<b>Source(s) for effectiveness data</b>	Phase III trial (French Cooperative Group on CLL <sup>23</sup> ) for i.v. fludarabine versus CAP, and 'expert opinion' for CHOP
<b>Analysis of effectiveness data</b>	No further analysis reported in cost-effectiveness section of report
<b>QoL data</b>	None reported
<b>Resource use data</b>	Taken from a retrospective audit of notes for 25 patients with CLL who received a second-line therapy ( <i>n</i> = 17 for i.v. fludarabine; <i>n</i> = 5 for CHOP; <i>n</i> = 3 for fludarabine-containing combination regimens)
<b>Source(s) for cost data</b>	Taken from a range of national and local sources, e.g. the British National Formulary and local hospital trusts
<b>Analysis of cost data</b>	No statistical analysis reported – cost data simply compared
<b>Price year</b>	2000
<b>Discounting</b>	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 analysis<sup>19</sup>

<b>Approach</b>	One-way sensitivity analysis only
<b>Parameters</b>	RR (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. six courses of therapy) Costs per patient (+/- 1 standard deviation)
<b>Results</b>	Incremental cost-effectiveness ratio ranges from dominance to £10,264 per year of remission

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 for CLL. The report of this study (appendix 5 of the Schering submission<sup>19</sup>) is described as an interim report and it indicates that data collection is continuing. (Further details have been excluded due to commercial in confidence data.) 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 to NICE.<sup>19</sup> These data reveal that the three patient groups are not similar, particularly in terms of their

mean age, sex distribution, 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”.<sup>19</sup> The implication of this is that there was not a fixed time interval over which data were collected.<sup>†</sup>

A strength of the analysis reported in the Schering submission is the sensitivity analysis which, despite only reporting one-way analysis, indicates the sensitivity of the results to variations in the

<sup>†</sup> Schering Health Care in commenting on the technology appraisal, after it was considered by the NICE appraisal committee, noted that “data were collected for the costs of giving one full course of therapy with each of the combinations included. This was estimated consistently for all patients included. We have not included costs of healthcare resources not directly related to the chemotherapy in question.”

effectiveness parameters RRs 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.<sup>19</sup> This reveals the great uncertainty surrounding effectiveness: the estimates of disease-free days range from 91 to 348 for fludarabine treatment and 38 to 117 for CHOP treatment. For fludarabine, this is in keeping with observations made in the effectiveness section of this technology appraisal.

### Summary of the 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 QoL to assist in this.
- The drug cost of a recommended course of intravenous fludarabine is £3900.
- The wider cost of administering fludarabine is estimated to be £6032.
- 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 million 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 with fludarabine compared with CHOP.
- Problems were identified with the conduct of the analysis, particularly the way that resource use was ascertained.
- The cost-effectiveness of intravenous fludarabine appears to be favourable relative to CHOP.
- A strong feature of the analysis was the sensitivity analysis. However, this showed that the incremental cost-effectiveness ratio was highly sensitive to variations 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 of 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 healthcare resources into fludarabine treatment for CLL as opposed to other areas of healthcare, 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 QoL, 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 costs:net benefit ratio.
- 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.





# Chapter 4

## Research in progress

### Methods

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 ongoing research.

The objective was to identify all RCTs planned, ongoing and completed involving fludarabine, and to indicate key information about the 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 of this chapter are for CLL. The search strategy used incorporated interrogation of bibliographical databases, particularly MEDLINE, EMBASE and the Cochrane Library, and a wide range of Internet websites 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.

### Results

The ongoing trials<sup>23,24,34-60</sup> are listed in appendix 18, and are subdivided by the condition of interest and whether patients have been previously treated or untreated.

#### Current licensed indications for fludarabine – previously treated CLL

There are no directly relevant RCTs in progress that 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.

#### Ongoing RCTs of fludarabine – previously untreated CLL

There is an enormous amount of high-quality RCT evidence recently completed and ongoing in this

area. Pre-eminent amongst these is the Leukaemia Research Fund (LRF) sponsored Medical Research Council (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 QoL. It is also, to a small extent, a strategy trial because the protocol extends to the treatment of patients who are resistant or relapsed whilst participating in the trial.

#### Ongoing RCTs of fludarabine in other haematological malignancies

There is clearly also considerable interest in the use of fludarabine in other haematological malignancies, particularly NHL and acute myeloid leukaemia (AML), as well as as a ‘conditioning’ agent in ‘mini-transplants’.

### Key points arising

- There are no other ongoing RCTs that will provide rigorous assessments of effectiveness for the indication of fludarabine considered in this report.
- There is a great deal of ongoing and recently completed research investigating the effectiveness of fludarabine as a first-line treatment for CLL.
- NICE should anticipate the need for guidance on the use of fludarabine in this circumstance.
- The ongoing LRF sponsored MRC CLL4 trial should provide key information for such a future assessment. The opportunity should be taken now for guidance on the use of fludarabine as second-line treatment to encourage recruitment into this study.
- More future RCTs should directly measure impact on QoL.
- The inventory of ongoing 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.



## Chapter 5

# Discussion and conclusions

### Main results of the report that informed the conclusions

This rapid technology assessment has generated many important findings. Here, we discuss those results that have been most influential in informing our conclusions.

The evidence base for the use of fludarabine in 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 has important limitations. The finding that extensive use of this agent seems to be 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 least one other similarly rigorous piece of research. A detailed search for ongoing 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 compared with CAP, the RCT in question does clearly indicate an improved RR 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 CIs around the estimated difference in response between fludarabine and CAP. The RCT also indicates that severe adverse events are common with both fludarabine and CAP, however, they are markedly less in important respects, such as nausea and vomiting, and hair loss and alopecia, with fludarabine. The excess of deaths during treatment with fludarabine was of some concern, but it was not statistically significant. Although, qualitatively, there is evidence of a greater net benefit with fludarabine than with CAP, there is no direct measurement of impact on QoL to help quantify the degree to which beneficial effects are offset by 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 at about £6000 per treatment course. Uncertainty about the 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 was £5.5 million. Suggestions that fludarabine will have minimal budget impact need to be considered very carefully.

Published estimates of cost-effectiveness, although, at face value, suggest advantages with 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, and thus little assistance can be offered in helping decide whether the costs:net benefits ratio is favourable relative to other investments in healthcare that may be under consideration, particularly in the area of cancer care.

### Implications for healthcare

The findings of this rapid technology appraisal have wide implications for all parties involved in the healthcare 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 very recent 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 intravenous preparation addressed by this report. The oral preparation of fludarabine could make a difference to the relationship between costs and net benefit, due to 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 RCT 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.

## 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 and exclusion procedures and defined methods of quality assessment, data abstraction and analysis. This has confirmed that the main evidence base for fludarabine in 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 is restricted to one small RCT. This was probably never in dispute.

The interpretation of the trial is relatively straightforward, 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. Consequently, we believe there is continuing uncertainty about the size of important effects and the degree to which benefit is offset by adverse events. Direct measurement of the impact on QoL 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.

## 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 ongoing trials on the use of fludarabine as a first-line therapy in CLL. Arguably, the priority should thus be to support these ongoing trials to ensure that the evidence base for the use of fludarabine as a first-line therapy is more robust than the evidence base for second-line therapy, and includes information on the impact on QoL. Future NICE appraisals on this agent should take the likely time of completion of these trials into account.

## Conclusions

- Fludarabine as second-line therapy for relapsed/refractory CLL appears to be more effective than a current alternative CAP with improved RRs and duration of response and less severe, although still marked, side-effects of treatment. However, there is no evidence for improvement in overall survival, there are important uncertainties about the size of benefits and adverse effects and there is little certainty about how much the benefits are offset by adverse effects.
- The drug cost of fludarabine is high at approximately £3900 per treatment cycle.
- The cost of administering fludarabine is estimated at £6000, 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 £5.5 million per annum.
- Apparently favourable estimates of cost-effectiveness need to be interpreted cautiously.
- The cost–utility of fludarabine cannot be accurately calculated, and thus cannot assist a judgement on whether, for a given investment of resources, encouraging the use of fludarabine is likely to achieve more net benefit than investing in other areas of healthcare.
- Effectiveness, cost and cost-effectiveness need to be assessed for the recently licensed oral preparation of fludarabine.
- Ongoing 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 the use of fludarabine is better.
- Future RCTs must assess impact on QoL directly.



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## Appendix I

### Search strategy to identify prospective cohort studies on the natural history of CLL

#### **MEDLINE (Ovid) 1987– August 2000**

#1 leukemia b cell chronic/

#2 prognosis/

#3 survival rate/

#4 survival analysis/

#5 or/#2–#4

#6 #1 and #5



## Appendix 2

### Search strategies to identify studies of the effectiveness of any treatments for CLL

These strategies were designed specifically to target published systematic reviews and were based on the Aggressive Research Intelligence Facility search protocol. The following strategies were executed in the electronic databases.

#### MEDLINE (Ovid) 1990–September 2000

#1 leukemia b cell chronic/th,dt,rt  
 #2 leukemia lymphocytic chronic/dt,th,rt  
 #3 chronic lymphocytic leuk?emia\$.ti,ab  
 #4 or/#1–#4  
 #5 (meta-analysis or review literature).sh  
 #6 meta-analy\$.tw  
 #7 metaanal\$.tw  
 #8 meta-analysis.pt  
 #9 (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

#1 exp leukemia b cell chronic:me  
 #2 chronic lymphocytic leukemia\*  
 #3 chronic lymphocytic leukaemia\*  
 #4 bcll  
 #5 cll  
 #6 #1 or #2 or #3 or #4 or #5



## Appendix 3

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

Review	Type and contents	Treatment options and patients: main conclusions/recommendations
CLL Trialists' Collaborative Group, 1999 <sup>15</sup>	Meta-analysis: chemotherapeutic options in CLL	<ol style="list-style-type: none"> <li>1. Immediate versus deferred chemotherapy for early stage CLL: no chemotherapy recommended for most patients with early stage disease</li> <li>2. Combination chemotherapy (e.g. CVP or CHOP) versus single agent chlorambucil as first-line treatment for more advanced disease: single agent chlorambucil was the first line of treatment for most patients with advanced disease, with no evidence of benefit from early inclusion of an anthracycline</li> </ol>
Dighiero <i>et al.</i> , 1997 <sup>10</sup>	Narrative review: summary of meeting session, including presentation of meta-analysis by CLL Trialists' Collaborative Group	<ol style="list-style-type: none"> <li>1. Early versus deferred treatment</li> <li>2. Place for chlorambucil for CLL</li> <li>3. Purine analogues for first-line therapy in CLL</li> </ol>
Kalil and Cheson, 2000 <sup>16</sup>	Narrative review (with some quantitative results for fludarabine): diagnosis, clinical features, staging, therapy, prolymphocytic leukaemia	<ol style="list-style-type: none"> <li>1. No treatment for early stage CLL</li> <li>2. Single agent chemotherapy: alkylating agents (chlorambucil and cyclophosphamide), the nucleoside analogues fludarabine and cladribine and the adenosine deaminase inhibitor pentostatin</li> <li>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</li> <li>4. Combination chemotherapy: cyclophosphamide plus prednisolone, CVP, CAP, CHOP</li> <li>5. Purine analogues: fludarabine, cladribine, pentostatin</li> <li>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 an alkylating agent, however, fludarabine has become the standard agent for patients initially treated with an alkylating agent-based regimen (overall RR = 40–50%). Combination of fludarabine with alkylating agents, anthracyclines or related compounds, cytarabine and interferon-<math>\alpha</math> are not clearly better than fludarabine alone</li> <li>7. New approaches (e.g. taxanes), bone marrow transplantation, gene therapy, splenectomy, radiation therapy, supportive care</li> </ol>

continued

Review	Type and contents	Treatment options and patients: main conclusions/recommendations
Montserrat and Rozman, 1995 <sup>17</sup>	Narrative review (with some quantitative results for fludarabine): epidemiology, aetiology, biology, clinical features, complications, diagnosis, prognosis, treatment	<ol style="list-style-type: none"> <li>1. Early stage: no treatment</li> <li>2. Advanced clinical stage due to high tumour burden and bone marrow failure: chlorambucil, CHOP, local radiotherapy. Patients failing first-line therapy should be treated with combination chemotherapy or fludarabine</li> <li>3. Patients with cytopenias due to immune mechanism: initially with corticosteroids, and cytotoxic agents added where there is no response after 4–6 weeks; immunoglobulins</li> <li>4. Hypersplenism: splenectomy or radiotherapy</li> <li>5. Younger patients (targeting CR): CHOP, fludarabine, allogeneic bone marrow transplant</li> </ol>
Molica <i>et al.</i> , 1995 <sup>13</sup>	Narrative review: prognostic features, therapeutic approaches	<ol style="list-style-type: none"> <li>1. Radiotherapy, splenectomy</li> <li>2. Single agent chemotherapy: chlorambucil, cyclophosphamide</li> <li>3. Corticosteroids</li> <li>4. Combination chemotherapy</li> <li>5. Fludarabine</li> <li>6. Deoxycoformycin, 2-chlorodeoxyadenosine, biological agents (interferon-<math>\alpha</math>)</li> <li>7. Bone marrow transplantation</li> </ol>
Wilhelm <i>et al.</i> , 1997 <sup>61</sup>	Narrative with some quantitative data: first-line therapy of advanced CLL	<ol style="list-style-type: none"> <li>1. Corticosteroids: infection is a problem</li> <li>2. Alkylating agents: so far, the combination of chlorambucil and prednisolone is the mainstay of first-line treatment of CLL</li> <li>3. Polychemotherapy regimens</li> <li>4. High-dose chlorambucil therapy</li> <li>5. Purine nucleoside analogues</li> <li>6. Bioimmunotherapy, maintenance therapy, bone marrow transplantation</li> </ol>
Pott and Hiddemann, 1997 <sup>62</sup>	Narrative: purine analogues in CLL	
Bergmann, 1997 <sup>63</sup>	Narrative: purine analogues in CLL	
Adkins <i>et al.</i> , 1997 <sup>64</sup>	Narrative review: fludarabine	



## Appendix 4

# British National Formulary general guidance on the 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 subclinical 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.

### Committee on the Review of Medicines guidelines on handling cytotoxic drugs

1. Trained personnel only 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 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

# West Midlands Development and Evaluation Service protocol for the review of fludarabine for blood cancers: NHL and CLL

### Full title of research question

Rituximab and fludarabine for blood cancers:  
NHL and 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 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 the former, which targets a particular marker found only on B lymphocytes.

Thus, the main focus of this report is the effectiveness and cost-effectiveness of rituximab for stage III or IV follicular lymphoma that is chemo-resistant or is in its second or subsequent relapse after chemotherapy, and fludarabine for patients with B cell CLL with sufficient bone marrow reserve and who have not responded to or have progressed during or after treatment with at least one standard alkylating agent-containing regimen. These are the specific conditions for which these 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 as follows (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 review systematically the evidence of the effectiveness of rituximab for stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy, as indicated in the drug licensing information.
- (3) To review systematically the evidence of the effectiveness of fludarabine for patients with B cell CLL with sufficient bone marrow reserve and who have not responded to or have progressed during or after treatment with at least one standard alkylating agent-containing regimen, as indicated in the drug licensing information.
- (4) To review systematically 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 1 September 2000.

#### Formal scoping search to indicate developments in the use of rituximab and fludarabine (i.e. RCTs published and ongoing)

##### Searches

Studies will be identified using electronic databases, such as the Cochrane Library, MEDLINE, EMBASE, Science Citation Index and the National Research Register, Internet search engines,

pharmaceutical company submissions invited by NICE, citation lists and conference abstracts.

### **Inclusion criteria**

#### **Intervention**

Rituximab and/or fludarabine.

#### **Comparator**

Any.

#### **Population**

Any haematological malignancy.

#### **Outcomes**

Survival, QoL and 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 summarise the data will be made. The characteristics or planned characteristics of the trials identified will be presented and subdivided by the intervention and target condition.

### **Systematic review of the effectiveness of rituximab for NHL and fludarabine for CLL**

#### **Searches**

Studies will be identified using electronic databases, such as the Cochrane Library, MEDLINE, EMBASE, Science Citation Index and the National Research Register, Internet search engines, pharmaceutical company submissions invited by NICE citation lists and conference abstracts.

### **Inclusion criteria**

#### **Intervention**

Rituximab at the dose given on the product information sheet and fludarabine at the dose given on the product information sheet.

#### **Comparator**

Any, including no treatment.

#### **Population**

For rituximab, stage III/IV follicular B cell NHL that is chemoresistant or is in its second or subsequent relapse after chemotherapy. For fludarabine, patients with B cell CLL with sufficient bone marrow reserve that have not responded to or have progressed during or after treatment with at least one standard alkylating agent-containing regimen.

### **Outcomes**

Survival, QoL and adverse events. The value of tumour response will be explored to indicate impact on QoL if no other data are available.

### **Design**

Ideally, RCTs. However, it is anticipated that there will be insufficient numbers to adequately answer the question posed. In this event, the included studies will be extended to non-randomised controlled clinical trials, and, if these are not available, before/after studies, that is, 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
- have losses to follow-up, with respect to particular outcomes of interest, of < 10%
- include > ten patients.

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, for example, from a case-control methodology, will not be acceptable.

The 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-randomised controlled clinical trials are identified, established checklists, for example, Jadad will be employed.

### **Data extraction**

This will be carried out by two reviewers independently.

**Analysis**

This will be qualitative and will be amplified by meta-analysis if appropriate. No subgroups have been identified *a priori*.

**Systematic review of the cost-effectiveness of rituximab for NHL and fludarabine for CLL**

The review question is in relation to the applications of rituximab and fludarabine in objectives (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 QoL will be sought from MEDLINE, HEED, NHS EED, DARE, EMBASE, Science Citation Index and Internet sites of UK health economics units.

**Quality assessment**

The quality of any identified evaluations will be undertaken using a specifically designed checklist based on the *British Medical Journal* guidelines for economic appraisals.

**Analysis**

As a minimum, a cost–consequence analysis will be conducted. Ideally, if QoL data can be identified, a cost–utility analysis will be undertaken giving cost per quality-adjusted life-year for each intervention. Where cost data are uncertain, a sensitivity analysis will be carried out. The health economic analysis will be from the NHS perspective. 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 that 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****Timetable**

Deadline for submission of the protocol to the NHS R&D HTA Programme: 22 September 2000.

Deadline for submission of the progress report to the NHS R&D HTA Programme: 7 December 2000.

Deadline for submission of the draft report to the NHS R&D HTA Programme: 9 January 2001.

[The draft report, without reviewers' comments, to be sent to NICE: 21 December 2000]

**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 for any of the members of the review team.

**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–September 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–September 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–October 2000

#1 fludara\*  
 #2 (leukemia\* or leukaemia\* or cll or bcll)  
 #3 #1 and #2

### Cochrane Library 2000, issue 3

See appendix 9.





## Appendix 7

### List of experts contacted as part of the search

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  
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Consultant Haematologist  
Department of Haematology  
South Warwickshire General Hospital  
Lakin Road  
Warwick  
Warwickshire  
CV34 5BW



## Appendix 8

### Search strategy and methods to identify ongoing trials of fludarabine

The following were searched to specifically identify ongoing or completed but currently unpublished RCTs involving fludarabine.

1. Bibliographic database search (see appendix 9 for details (44 citations scanned)).
2. Cochrane Library 2000, issue 4 via the Cochrane Controlled Trials Register CD-ROM (30 hits scanned).
3. National Research Register 2000, issue 4 via <<http://www.update-software.com>> (159 hits scanned, which included ongoing and completed studies).
4. British Society for Haematology website <<http://www.blacksci.co.uk/uk/society/bsh>> (no trial listing available).
5. British National Lymphoma Investigation website <<http://www.bnli.ucl.ac.uk>> (14 listed trials scanned).
6. European Organisation for Research and Treatment of Cancer (EORTC) website <<http://www.eortc.be>> (384 'chemotherapy' trial protocols scanned).
7. European Group for Blood and Marrow Transplantation website <<http://www.ebmt.org>> (ongoing studies for each working party scanned).
8. LRF <<http://dSPACE.dial.pipex.com/lrf//research/director.pdf>> (two hits in research directory scanned).
9. MRC and Current Controlled Trials website <<http://www.controlled-trials.com>> (26 hits scanned).
10. National Institutes of Health/CancerNet website <<http://www.cancertrials.nci.nih.gov>> (121 hits scanned, which included open and closed studies).
11. Schering-Plough website <<http://www.schering-plough.com>> and <<http://www.sp-research.com>> (no trial listing available).
12. General Internet search using the Google search engine (142 hits scanned).
13. Schering Health Care industry submission (all reference lists were scanned, but did not include anything marked as commercial in confidence unless already identified by one of the other elements of the search strategy above).

In general, where search terms could be used, the text word "FLUDARABINE" was employed. For the general Internet search, the phrase "(RANDOMISED OR RANDOMIZED) AND CONTROLLED TRIAL" was also used. Potentially relevant hits were scanned, and a judgement made on whether it was likely that the study was an RCT and whether 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 coordinating the trial or the lead investigator. Wherever possible, full copies of the trial protocols were obtained. All searches were conducted during the period 1 November 2000 to 10 December 2000.



## Appendix 9

### Details of the bibliographical database search employed to identify ongoing trials involving fludarabine

#### MEDLINE (Ovid) 1966–August 2000

#1 fludara\$.ti,ab  
 #2 exp hematologic neoplasms/  
 #3 exp leukemia/  
 #4 exp lymphoma/  
 #5 or/#2–#4  
 #6 randomized controlled trial.pt  
 #7 controlled clinical trial.pt  
 #8 randomized controlled trials/  
 #9 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 mask\$)).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 leukaemia/  
 #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

#1 fludara\*



## Appendix 10

### Details of excluded studies and reasons for exclusion

Reference	Reason 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. <i>Leuk Lymphoma</i> 1996; <b>21</b> :321–4.	< 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]. <i>Med Clin</i> 1996; <b>107</b> :86–9.	< 50 patients
Cheson BD. New prospects in the treatment of indolent lymphomas with purine analogues. <i>Cancer J Sci Am</i> 1998; <b>4</b> Suppl 2:S27–36.	A 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. <i>Semin Oncol</i> 1993; <b>20</b> Suppl 7:21–3.	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. <i>Leuk Lymphoma</i> 1994; <b>15</b> :173–5.	< 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. <i>Blood</i> 1998; <b>92</b> :4192.	< 50 patients
Gjedde SB, Hansen MM. Salvage therapy with fludarabine in patients with progressive B-chronic lymphocytic leukemia. <i>Leuk Lymphoma</i> 1996; <b>21</b> :317–20.	< 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. <i>Nouv Rev Fr Hematol</i> 1988; <b>30</b> :457–9.	< 50 patients
Grever M, Leiby J, Kraut E, Metz E, Neidhart J, Balcerzak S, et al. A comprehensive phase I and II clinical investigation of fludarabine phosphate. <i>Semin Oncol</i> 1990; <b>17</b> Suppl 8:39–48.	< 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. <i>Ann Hematol</i> 1991; <b>63</b> :1–4.	< 50 patients
Hocepied AM, Falkson CI, Falkson G. A phase II trial of fludarabine in patients with previously treated chronic lymphocytic leukaemia. <i>S Afr Med J</i> 1996; <b>86</b> :549–50.	< 50 patients
Keating MJ, Kantarjian H, O'Brien S, Robertson L, Huh Y. New agents and strategies in CLL treatment. <i>Leuk Lymphoma</i> 1991; <b>5</b> Suppl:139–42.	Suspicion of being a duplication of Keating et al. <sup>31</sup>
Keating MJ, Kantarjian H, Talpaz M, Redman J, McCredie KB. Fludarabine therapy in chronic lymphocytic leukemia (CLL). <i>Nouv Rev Fr Hematol</i> 1988; <b>30</b> :461–6.	Suspicion of being a duplication of Keating et al. <sup>31</sup>
Keating MJ, O'Brien S, Kantarjian H, Plunkett W, Estey E, Koller C, et al. Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent. <i>Blood</i> 1993; <b>81</b> :2878–84.	Suspicion of being a duplication of Keating et al. <sup>31</sup>
Keating MJ, O'Brien S, Robertson L, Huh Y, Kantarjian H, Plunkett W. Chronic lymphocytic leukaemia – correlation of response and survival. <i>Leuk Lymphoma</i> 1993; <b>11</b> Suppl 2:167–75.	Suspicion of being a duplication of Keating et al. <sup>31</sup>

continued

Reference	Reason for exclusion
Keating MJ, Smith TL, Lerner S, O'Brien S, Robertson LE, Kantarjian H, et al. Prediction of prognosis following fludarabine used as secondary therapy for chronic lymphocytic leukemia. <i>Leuk Lymphoma</i> 2000; <b>37</b> :71–85.	< 50 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. <i>Leuk Lymphoma</i> 1993; <b>10</b> :187–93.	< 50 patients
Laplante S, Grenier JF. Cost-efficacy evaluation of fludarabine phosphate in the treatment of chronic lymphocytic leukemia refractory to other therapies. <i>Eur J Cancer</i> 1997; <b>33</b> :42.	Cost-effectiveness study
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). <i>Blood</i> 1999; <b>94</b> :2682.	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. <i>Blood</i> 1999; <b>94</b> :810.	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. <i>Tumori</i> 1995; <b>81</b> :419–23.	< 50 patients
O'Brien S, Kantarjian H, Beran M, Freireich E, Komblau S, Koller C, et al. Fludarabine (FAMP) and cyclophosphamide (CTX) therapy in chronic lymphocytic leukemia (CLL). <i>Blood</i> 1996; <b>88</b> :1910.	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. <i>Leuk Lymphoma</i> 1994; <b>14</b> Suppl 2:17–23.	< 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. <i>J Clin Oncol</i> 1991; <b>9</b> :1562–9.	< 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. <i>Ann Oncol</i> 1999; <b>10</b> :183–8.	< 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. <i>Haematologica</i> 1994; <b>79</b> :218–24.	< 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. <i>Haematologica</i> 1999; <b>84</b> :317–23.	< 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). <i>Blood</i> 1998; <b>92</b> :419.	< 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. <i>Hematol Cell Ther</i> 1999; <b>41</b> :127–36.	Previously untreated patients



## **Appendix II**

Population characteristics of the total cohorts of the included case-series

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1998<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Type of study</b>	Case-series	Case-series	Case-series	Case-series	Case-series	Case-series	Case-series
<b>Aim of study</b>	To evaluate the efficacy of fludarabine in CLL patients with and without prior therapy (interim analysis after 2 years)	To report the clinical results of fludarabine in refractory CLL and low-grade NHL, and severe infectious complications and immunosuppressive effects	To summarise the experience with fludarabine in 68 previously treated patients with CLL and to analyse the association of prognostic factors with response and survival	To address fludarabine activity after the failure of a chlorambucil or CHOP-like regimen using a retrospective series	To analyse the results of fludarabine in an unselected population of patients with previously treated and advanced CLL from different Spanish institutions	To describe fludarabine toxicity and activity in refractory CLL in a 'setting that more closely resembles clinical practice than most published trials'	To report on initial fludarabine before randomisation to receive/not receive interferon- $\alpha$ in the treatment of B cell CLL and low-grade NHL in advanced refractory/relapsed patients
<b>Total number of patients</b>	92 (84 evaluated)	77	68	57	75	791 (724 treated)	137
<b>% relapsed</b>	Not stated	Not stated	Not stated	Not stated	76%	Not stated	Not stated
<b>% resistant</b>	Not stated	Not stated	Not stated	Not stated	24%	Not stated	Not stated
<b>Demographics</b>							
<b>Age</b>	Median = 66 (range 38–80)	Median = 59 (range 26–81)	Median = 60 (range 32–79)	Not stated	Mean = 62 (range 32–83)	Median = 65 (n = 724)	Not stated overall
<b>Sex</b>	54% male, 46% female	65% male, 35% female	74% male, 26% female	Not stated	71% male, 29% female	72% male, 28% female	Not stated overall
<b>Inclusion/exclusion criteria given in published paper</b>	CLL	Advanced CLL or low-grade NHL	CLL	B cell CLL	CLL	CLL	B cell CLL or low-grade NHL
<b>Stage</b>	No specific requirement	No specific requirement	Stage III/IV (stage 0–II only if progressive disease)	No specific requirement	No specific requirement	Intermediate or high-grade Rai stage	Stage III/IV CLL
<b>Prior treatment</b>	No specific requirement	No specific requirement	Previously treated patients only	Must have had chlorambucil or CHOP	No specific requirement	Failed to respond to chlorambucil or cyclophosphamide +/- prednisolone	Advanced relapsed or refractory to previous treatment
<b>Age</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	$\geq$ 18 years only	No specific requirement
<b>Sex</b>	Males and females included	Males and females included	Males and females included	No specific requirement	Males and females included	Males and females included	Males and females included
<b>Performance status</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	Eastern Cooperative Oncology Group performance status 0–3	No specific requirement

continued

	Bezares et al., 1998 <sup>25</sup>	Fenchel et al., 1995 <sup>26</sup>	Keating et al., 1989 <sup>31</sup>	Liso et al., 1998 <sup>27</sup>	Montserrat et al., 1996 <sup>28</sup>	Sorensen et al., 1997 <sup>29</sup>	Zinzani et al., 1997 <sup>30</sup>
<i>Inclusion/exclusion criteria given in published paper contd</i>							
<b>Pregnancy/lactation</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	Such patients excluded	No specific requirement
<b>Other serious disease/infection</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	Such patients excluded	No specific requirement
<b>HIV/hepatitis</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	Not stated	No specific requirement
<b>Central nervous system involvement</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	Such patients excluded	No specific requirement
<b>Other anti-cancer therapy</b>	No specific requirement	No specific requirement	No specific requirement	No specific requirement	No specific requirement	Such patients excluded	No specific requirement
<b>Other</b>	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated



## **Appendix 12**

Population characteristics of the most relevant subset of patients of the included case-series

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1988<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Patients relevant to review, i.e. meeting current licensing indications</b>	Not known	Not known	87%	100%	Not known	100%	56%
<b>Reasons for uncertainty</b>	Although 63 patients were relapsed or refractory, it is not known if they had previously received an alkylating agent	Of the 59 patients with CLL, it is not known how many had previously been treated with an alkylating agent	NA	NA	100% were previously treated, but it cannot be assumed that this was with an alkylating agent. Also, not all patients received the correct dose	NA	NA
<b>Nearest relevant subset of cohort for which results are given</b>	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 who had alkylating agent treatment	NA	None available	NA	77 patients met the licensing indications
<b>Information not known about this subset</b>	% who had relapsed after treatment with an alkylating agent	% who had relapsed after treatment with an alkylating agent	NA	NA	NA	NA	NA
<b>Demographics</b>							
<b>Age</b>	Not given	Not given	Not given	NA	NA	NA	Median = 61 (range 40–77)
<b>Sex</b>	Not given	Not given	Not given	NA	NA	NA	65% male, 35% female
NA, not applicable							

## **Appendix 13**

Details of the interventions and  
outcomes for the total cohorts of the  
included case-series

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1988<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Intervention</b>	25 mg/m <sup>2</sup> /day i.v. for 5 days every 28 days for six cycles	25 mg/m <sup>2</sup> i.v. over 30 minutes for 5 days repeated every fifth week	25–30 mg/m <sup>2</sup> i.v. for 5 days as a 30-minute infusion repeated every 3–4 weeks (88% every 4 weeks)	Not stated	20–30 mg/m <sup>2</sup> i.v. for 3–5 days every 5 weeks (most common = 25 mg/m <sup>2</sup> i.v. for 5 days)	25 mg/m <sup>2</sup> for ≤ 30 minutes i.v. daily for 5 days consecutively with repetition every 28 days	25 mg/m <sup>2</sup> daily by a 30-minute i.v. infusion for 5 days consecutively, repeated every 28 days
<b>Concomitant treatment</b>							
<b>Corticosteroids banned</b>	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	No
<b>Other treatment allowed</b>	Not stated	Not stated	Not stated	Not stated	Antibiotics prophylactically in 36 patients	Allopurinal, hydration, alkalisation urine (high-risk patients), prednisolone (27%)	Antibiotics and corticosteroids permitted for treatment of side-effects
<b>Pre-treatment tests</b>							
<b>Serum chemistries</b>	Not stated	Yes	Yes	Not stated	Not stated	Yes	No
<b>Blood counts</b>	Not stated	Yes	Yes	Not stated	Not stated	Yes	No
<b>Physical examination</b>	Not stated	Yes	Yes	Not stated	Not stated	Yes	No
<b>Pathology specimen</b>	Not stated	Yes	No	Not stated	Not stated	No	No
<b>Bone marrow tests</b>	Not stated	Yes	Yes	Not stated	Not stated	Yes	Yes
<b>Outcome measures</b>							
<b>Clinical response</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>Adverse events</b>	Yes	Yes	Yes	No	Yes	Yes	Yes
<b>Survival analysis</b>	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>QoL</b>	No	No	No	No	No	No	No
<b>Time to progression</b>	Yes	No	Yes	No	No	No	Yes
<b>Duration of response</b>	No	No	No	No	No	Yes	No
<b>Other</b>	None	Mortality	None	None	None	None	None

continued



	Bezares et al., 1998 <sup>25</sup>	Fenchel et al., 1995 <sup>26</sup>	Keating et al., 1989 <sup>31</sup>	Liso et al., 1998 <sup>27</sup>	Montserrat et al., 1996 <sup>28</sup>	Sorensen et al., 1997 <sup>29</sup>	Zinzani et al., 1997 <sup>30</sup>
<b>Clinical response definitions</b>							
<b>CR</b>	Not stated	Lymphocytes < $4 \times 10^9/l$ ; granulocytes > $1.5 \times 10^9/l$ , thrombocytes > $100 \times 10^9/l$ , haemoglobin > 11 g/dl, bone marrow infiltration < 30%, no palpable nodes or hepato/splenomegaly	< 4000 lymphocytes/ $\mu$ l in blood, < 30% lymphocytes and no nodules in bone marrow, impalpable liver and spleen, no pathological nodes	Not stated	Total disappearance of symptoms and signs of disease; normalisation of blood parameters: < 30% lymphocytes in bone marrow aspirate and/or normal bone marrow biopsy	No liver/spleen/lymph node symptoms, neutrophils $\geq 1500/\mu$ l, platelets $\geq 100,000/\mu$ l, haemoglobin to $\geq 11$ g/dl, lymphocytes to $\leq 4000/\mu$ l, bone marrow lymph infiltration to < 30%	No palpable masses, recovery of blood parameters (neutrophils to $\geq 1500/\mu$ l, platelets to $\geq 100,000/\mu$ l, haemoglobin to $\geq 11$ g/dl, lymphocytes to $\leq 4000/\mu$ l), bone marrow lymph infiltration to < 30%
<b>PR</b>	Not stated	Decrease in lymphocytes of > 50%, decrease in node size of > 50%, $\geq$ one of the following: granulocytes > $1500/\mu$ l or 50% rise, platelets > $100,000/\mu$ l or 50% rise, haemoglobin > 11 g/dl or 50% rise, 50% decrease in hepato/splenomegaly, bone marrow infiltration < 30% for at least 2 months	> 4000 lymphocytes/ $\mu$ l in blood with > 1 log decrease, $\geq$ 50% decrease in bone marrow infiltrate with > 30% lymphocytes or nodules, $\geq$ 50% decrease in span below costal margin, $\geq$ 50% decrease in node size	Not stated	Switch of disease to a less advanced clinical stage	$\geq$ 50% decrease in liver/spleen/lymph node symptoms, neutrophils $\geq 1500/\mu$ l or $\geq$ 50% of baseline, platelets > $100,000/\mu$ l or $\geq$ 50% of baseline, haemoglobin > 11 g/dl or $\geq$ 50% of baseline, lymphocytes $\geq$ 50% of baseline for a duration of > 2 months	$\geq$ 50% decrease in palpable masses and peripheral lymphocytosis, recovery or $\geq$ 50% improvement of one or more of the above mentioned parameters
<b>Stable disease</b>	Not stated	No PR, CR or progressive disease	Not stated	Not stated	Failure	Not stated	Not stated
							<i>continued</i>

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1998<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Clinical response definitions contd</b>	Not stated	≥ one of the following: > 50% rise in node size, > 50% rise in hepato/splenomegaly, > 50% rise in lymphocytes	> 25% rise in nodes, liver, spleen size or white cell count. (Patients were considered to be resistant if they achieved < PR after ≥ three courses or had progressive disease)	Not stated	Failure	Liver/spleen/lymph node ≥ 50% rise, new nodes, lymphocytes ≥ 50% of baseline	Not stated
<b>Progressive disease</b>							

## **Appendix 14**

Quality assessment, threats to validity and  
relevance of the included case-series

	Bezares et al., 1998 <sup>25</sup>	Fenchel et al., 1995 <sup>26</sup>	Keating et al., 1989 <sup>31</sup>	Liso et al., 1998 <sup>27</sup>	Montserrat et al., 1996 <sup>28</sup>	Sorensen et al., 1997 <sup>29</sup>	Zinzani et al., 1997 <sup>30</sup>
<b>Source of case-series</b>	Not stated	Not stated	Not stated	Retrospective series of 57 patients from seven institutions who had fludarabine as third-line treatment after chlorambucil and CHOP-like regimen	75 patients treated at 13 Spanish institutions from July 1989–March 1995 (represents 90% of all patients treated in Spain)	Participating physicians telephoned the National Cancer Institute with eligible patients, which were confirmed and entered into the trial	Not stated
<b>Were the population characteristics well defined?</b>							
<b>Entire cohort</b>	No (performance status and previous treatment not given)	No (performance status not given)	No (performance status not given)	None given	No (performance status not given)	No (previous treatment not given)	No (performance status not given)
<b>Parent population</b>	No	No	No	No	No	No	No
<b>% of cohort relevant to review</b>	Not known	Not known	87	100	Not known	100	56
<b>Length of follow-up</b>	2 years	Not stated, but > 1 year	Median = 15 months (range 4–37)	Median = 13 months (range 1–65)	Not stated, but ≤ 5 months for some	Median = 59 months	Median = 32 months
<b>Was analysis done according to possible prognostic factors?</b>							
<b>Stage</b>	No	Yes	Yes	Yes	No	Yes	Yes
<b>Performance status</b>	No	No	No	No	No	Yes	No
<b>Age</b>	No	No	Yes	Yes	Yes	Yes	No
<b>Sex</b>	No	No	No	No	No	Yes	No
<b>Number with previous treatment/relapses</b>	No	Yes	Yes	No	Yes	No	Yes
<b>Resistance</b>	No	No	No	Yes	Yes	No	Yes
<b>Blood counts</b>	No	No	Yes	No	No	Yes	No
<b>Other</b>	None	Duration of disease until treatment with fludarabine, histological subtype	Serum chemistries	Tumour response	None	Prednisolone use, hepato/splenomegaly, lymphadenopathy	None

continued

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1998<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Threats to validity</b>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Small cohort</li> <li>- Inadequate follow-up time</li> <li>- Not enough information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> <li>- Selection bias?</li> </ul> <p>Although 63 patients were relapsed or refractory, it is not known if they had previously received an alkylating agent</p>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Small cohort</li> <li>- Inadequate follow-up time</li> <li>- Not enough information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> <li>- Selection bias?</li> </ul> <p>Of the 59 patients with CLL, it is not known how many had been previously treated with an alkylating agent</p>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Small cohort</li> <li>- Inadequate follow-up time</li> <li>- Not enough information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> <li>- Selection bias?</li> </ul> <p>13% of patients had not had prior treatment with an alkylating agent. Five patients had previously had diffuse small lymphocytic lymphoma and had developed CLL</p>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Small cohort</li> <li>- Inadequate follow-up time</li> <li>- No information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> <li>- Selection bias?</li> </ul> <p>None</p>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Small cohort</li> <li>- Not enough information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> </ul> <p>100% were previously treated, but it cannot be assumed that this was with an alkylating agent. Also, not all patients received the correct dose (% unknown)</p>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Not enough information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> <li>- Selection bias?</li> </ul> <p>None</p>	<ul style="list-style-type: none"> <li>- No comparator</li> <li>- Not enough information on prognostic factors</li> <li>- Non-blinded assessment of outcomes</li> <li>- Selection bias?</li> </ul> <p>None</p>
<b>Threats to relevance</b>							



## **Appendix 15**

### **Results of the included case-series**

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1988<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Follow-up period</b>	2 years	Not stated, but > 1 year	Median = 15 months (range 4–37)	Median = 13 months (range 1–65)	Not stated, but ≤ 5 months for some	Median = 59 months	Median = 32 months
<b>Losses to follow-up</b>	Not stated	Not stated	None	NA	None	Four early losses, 11 more lost to follow-up after 5 years	Not stated
<b>Dropouts/exclusions before assessment and reasons</b>	Not stated	Seven – three too early for evaluation and four died during treatment (one had a ruptured liver; one had anaphylactic shock and two had septicemia)	Of 29 non- responders, 19 were excluded during treatment due to refractory disease and ten died during treatment	NA	Seven patients still under therapy at assessment and one other missing, but no reason given	67 had no treatment (35 deteriorated or died, 19 refused treatment, four improved, four were ineligible and five were not known- and 21 were non- assessable (including one death and four lost to follow-up)	Four deaths due to infection during treatment
<b>Deaths</b>	Not stated	Four during treatment and 15 more deaths (three due to thrombo- cytopenic bleeding, 12 due to infection)	Ten during treatment. Overall, 36/68 had died at follow-up	At follow-up, 22/57 had died	26/75 had died at follow-up (three responders and 23 non- responders)	655/724 had died at follow-up (482 from disease, 79 from infection, 26 from cardiac causes, 20 from other cancers, 12 from pulmonary causes and 36 from other causes)	Four during treatment. Others were not stated
<b>Patients evaluated for response</b>	84	70	68	57	68	703	137
<b>Evaluated as intention-to-treat</b>	No	No	NA	NA (100% relevant)	NA	No	NA
<b>Clinical RRs (% of patients with CR and PR (overall RR = CR + PR))</b>	18% CR, 43% PR 61% overall RR	6% CR, 67% PR 73% overall RR	13% CR, 28% PR, 16% nodular PR, 57% overall RR	5% CR, 53% PR 58% overall RR	4% CR, 24% PR 28% overall RR	3% CR, 29% PR 32% overall RR	3% CR, 44% PR 47% overall RR
<b>Patients evaluated for toxicity</b>	84	77	68	NA	Not stated	705	137

continued



	Bezares et al., 1998 <sup>25</sup>	Fenchel et al., 1995 <sup>26</sup>	Keating et al., 1989 <sup>31</sup>	Liso et al., 1998 <sup>27</sup>	Montserrat et al., 1996 <sup>28</sup>	Sorensen et al., 1997 <sup>29</sup>	Zinzani et al., 1997 <sup>30</sup>
<b>Other outcomes</b>							
<b>Time to progression</b>	Not given	Median = 7 months (range 2→20)	13 months in PR patients, 21 months in CR and nodular PR	Not given	Not given	Of 724 treated patients: Median = 7.5 months	Not given
<b>Duration of response</b>	Not given	Not given	Not given	Not given	Not given	Median = 13 months (responders only)	Not given
<b>QoL</b>	Not given	Not given	Not given	Not given	Not given	Not given	Not given
<b>Survival analysis</b>	Not given	42% overall survival probability and 22% event-free survival at 18 months	Median overall survival = 16 months	Median survival = 30 months	Median survival = 11 months (non-responders) and not reached in responders	Median = 12.6 months	Not given
<b>Nearest subset of relevant patients, i.e. meeting licensing indications</b>	63 previously treated patients	56 patients with CLL	59 patients previously treated with alkylating agent	NA	None available	NA	77 with B cell CLL
<b>RRs for subset</b>	Not given	5% CR, 68% PR, 73% overall RR	51% overall RR	NA	NA	NA	4% CR, 41% PR, 45% overall RR
<b>Other outcomes for subset</b>	Progression-free interval = 8 months, estimated survival at 20 months = 52% (95% CI, 28 to 71)	None	None	NA	NA	NA	Progression-free survival median = 20 months (responders). Overall survival median = 24 months



## **Appendix 16**

Further details on the adverse events of the included case-series\*

	<b>Bezares et al., 1998<sup>25</sup></b>	<b>Fenchel et al., 1995<sup>26</sup></b>	<b>Keating et al., 1989<sup>31</sup></b>	<b>Liso et al., 1998<sup>27</sup></b>	<b>Montserrat et al., 1996<sup>28</sup></b>	<b>Sorensen et al., 1997<sup>29</sup></b>	<b>Zinzani et al., 1997<sup>30</sup></b>
<b>Evaluated for toxicity</b>	84	77	68	Not stated	75	705	137
<b>Deaths suspected to be related to fludarabine treatment</b>	None	Not stated	Ten died during the study, but not known if these were due to treatment	Not stated	Not stated	Two from neutropenic sepsis, three from tumour lysis syndrome	Four deaths from infection
<b>Haematological events<sup>†</sup></b>	72 events overall	Not stated	Not stated	Not stated	Four cases of autoimmune haemolytic		
<b>Anaemia</b>							
<b>Mild/moderate</b>	Not stated		Not stated			54%	9%
<b>Severe</b>	Not stated		Not stated			37%	None
<b>Leucopenia</b>							
<b>Mild/moderate</b>	Not stated		Not stated		Not stated	13%	Not stated
<b>Severe</b>	Not stated		Not stated		Not stated	46%	Not stated
<b>Neutropenia</b>			100 cases over all courses		Ten cases overall		
<b>Mild/moderate</b>	Not stated					Not stated	33%
<b>Severe</b>	Not stated					Not stated	11%
<b>Thrombocytopenia</b>			46 case over all courses		15 cases overall		
<b>Mild/moderate</b>	Not stated					25%	17%
<b>Severe</b>	Not stated					46%	5%
<b>Non-haematological events<sup>†</sup></b>	Not stated			Not stated			
<b>Pain</b>							
<b>Mild/moderate</b>		Not stated	Not stated		Not stated	Not stated	Not stated
<b>Severe</b>		Not stated	Not stated		Not stated	Not stated	Not stated
<b>Fever</b>			Overall, 23 of fever of unknown origin				
<b>Mild/moderate</b>		Not stated			Not stated	Not stated	4%
<b>Severe</b>		Not stated			Not stated	Not stated	None
<b>Nausea and vomiting</b>			Nine cases over all courses				
<b>Mild/moderate</b>		11%			Not stated	26%	1%
<b>Severe</b>		Not stated			Not stated	0.6%	None
<b>Diarrhoea</b>			Six cases over all courses				
<b>Mild/moderate</b>		Not stated			Not stated	12%	Not stated
<b>Severe</b>		Not stated			Not stated	2.4%	Not stated

continued

	Bezares et al., 1998 <sup>25</sup>	Fenchel et al., 1995 <sup>26</sup>	Keating et al., 1989 <sup>31</sup>	Liso et al., 1998 <sup>27</sup>	Montserrat et al., 1996 <sup>28</sup>	Sorensen et al., 1997 <sup>29</sup>	Zinzani et al., 1997 <sup>30</sup>
<b>Non-haematological events<sup>†</sup></b>	Not stated	Not stated	Seven events over all courses	Not stated	Not stated	Not stated	Not stated
<b>Neurological</b>							
<b>Mild/moderate</b>		Not stated			Not stated	23%	Not stated
<b>Severe</b>		Not stated			Not stated	6%	Not stated
<b>Infections</b>					33 cases of fever/infection overall	26%	11%
<b>Mild/moderate</b>	Not stated		24%	Not stated		22%	4%
<b>Severe</b>	18 cases	29%	Three cases				
<b>Tumour lysis syndrome</b>	Not stated	One case	Not stated	Not stated	One case	1%	Not stated

\* Toxicity is given overall for all patients in the study

† 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 QoL studies

The NHS EED was searched using the following terms: fludara\$, rituximab, mabthera, idec-c2b8\$ and rituxan. Internet sites of the University of York Centre for Health Economics, the Health Economics Research Unit and the Health Economics Research Group were also searched. Finally, MEDLINE (Ovid) was searched from 1966–September 2000 using the following strategy.

#1 economics/  
 #2 exp costs and cost analysis/  
 #3 cost of illness/  
 #4 exp health care costs/  
 #5 economic value of life/  
 #6 exp economics medical/  
 #7 exp economics hospital/  
 #8 economics pharmaceutical/  
 #9 exp fees and charges/  
 #10 (costs or cost or costed or costly or costing).tw  
 #11 (economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw  
 #12 or/#1–#11  
 #13 fludara\$.mp  
 #14 #12 and #13

#15 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-ll.ti,ab  
 #37 chronic lymphocytic leuk?emia.ti,ab  
 #38 or/#34–#37  
 #39 #38 and #27





## **Appendix 18**

Ongoing and completed but unpublished  
trials of fludarabine\*

Study	Intervention	Comparator	Condition	Population	Outcomes	Design and size	End
<b>Haematological malignancies – CLL (prior treatment)</b>							
French Cooperative Group on CLL <sup>23</sup>	Fludarabine	CAP	B cell CLL	Treated with chlorambucil or similar non-anthracycline- or anthracinone-containing regimens	Disease response, progression-free survival, overall survival, toxicity	RCT; 48 + 48	Completed and published
Tondini <i>et al.</i> <sup>24</sup>	Fludarabine	Cladribine	Low-grade NHL (some IWFA were CLL)	Relapsed/refractory after ≥ one course of alkylating chemotherapy	Disease response, progression-free survival, toxicity	RCT; 60 total (43% IWFA)	Completed and published
EORTC 06942 <sup>33,35</sup>	Fludarabine	Cladribine	B cell CLL	Refractory to alkylating agent therapy (but no more than three courses)	Disease response, time to maximum response, progression-free survival, toxicity, QoL	RCT; target total 750	Abandoned due to problems with drug supply; no publication expected
<b>Haematological malignancies - CLL (no prior treatment)</b>							
French Cooperative Group on CLL <sup>23</sup>	Fludarabine	CAP	B cell CLL	Previously untreated Binet stages B or C	Disease response, progression-free survival, overall survival, toxicity	RCT; 52 + 48	Completed and published
French Cooperative Group on CLL <sup>36-38</sup>	Fludarabine	CAP or CHOP (CAP discontinued after interim analysis on 9 February 1996)	CLL	Previously untreated Binet stages B and C	Disease response, progression-free survival, time to retreatment, overall survival, toxicity	RCT; total 983	Completed and published (abstract only)
CLB-901 <sup>39-43</sup>	Fludarabine (combined fludarabine + chlorambucil arm stopped in 1994)	Chlorambucil (oral)	B cell CLL	Previously untreated intermediate- to high-risk Rai stages I-IV	Disease response, progression-free survival, overall survival, toxicity, QoL	RCT; target total 538	Completed and published (abstract only)
EORTC 06916 <sup>44-47</sup>	Fludarabine	Chlorambucil (oral; high dose)	B cell CLL	Previously untreated	Disease response, time to maximum response, toxicity, QoL	RCT; 82 randomised, 71 analysed (37 + 34)	Completed and published (abstract only)
Spriano <i>et al.</i> <sup>48</sup>	Fludarabine	Chlorambucil + prednisolone	B cell CLL	Previously untreated Rai intermediate- or high-risk stages	Disease response, toxicity	RCT; total 147 (73 + 74), 105 analysed (60 + 55)	Completed and published (abstract only)

continued

Study	Intervention	Comparator	Condition	Population	Outcomes	Design and size	End
<b>Haematological malignancies – CLL (no prior treatment) contd</b> LRF MRC CLL <sup>49</sup>	Fludarabine or fludarabine + cyclophosphamide	Chlorambucil	B cell CLL	Previously untreated Binet stage A progressive, stage B or stage C	Disease response, progression-free survival, overall survival (primary), toxicity, QoL	RCT; target total 500	End of recruiting in 2004
<b>Haematological malignancies – low-grade NHL (prior treatment)</b> Tondini et al. <sup>4</sup>	Fludarabine	Cladribine	Low-grade NHL (IWFA–D)	Relapsed/refractory after ≥ one course of alkylating chemotherapy	Disease response, progression-free survival, toxicity	RCT; total 60	Completed and published
<b>Haematological malignancies – low-grade NHL (no prior treatment)</b> Coiffer et al. <sup>50</sup>	Fludarabine	Cyclophosphamide + doxorubicin + teniposide (VM 26) + prednisolone + interferon α	Follicular NHL (IWFi?)	Previously untreated patients > 59 years with a poor prognosis (presence of large tumour mass, poor performance status, presence of B symptoms, above normal lactate dehydrogenase level; ≥ 3 mg/l β <sub>2</sub> -microglobulin levels)	Disease response, progression-free survival, overall survival, toxicity	RCT; total 131	Completed and published
EORTC 2092 <sup>51–53</sup>	Fludarabine	CVP	Low-grade NHL – classic CLL excluded	Previously untreated newly diagnosed Rai stage III/IV	Disease response, progression-free survival, overall survival, toxicity	RCT; target total 326	Completed; no publication
E-1496 <sup>54</sup>	Fludarabine + cyclophosphamide	CVP	Low-grade NHL	Previously untreated Rai stage III/IV	Disease response, progression-free survival, overall survival	RCT; target total 400	Temporarily closed
Foussard et al. <sup>55</sup>	Fludarabine + mitoxantrone	CHOP	Low-grade NHL (mantle-cell lymphoma excluded)	Previously untreated bulky Rai stage II and stage III/IV with one adverse prognostic factor	Disease response, toxicity	RCT; total 100	Completed and published (abstract only)
British National Lymphoma Investigation <sup>56</sup>	Fludarabine + mitoxantrone + dexamethasone	Chlorambucil + mitoxantrone + dexamethasone	Low-grade NHL	Previously untreated newly diagnosed Rai stage III/IV	Disease response, progression-free survival, overall survival	RCT; target total 500	End of recruiting in 2004

continued

Study	Intervention	Comparator	Condition	Population	Outcomes	Design and size	End
<b>Haematological malignancies – AML</b> MRC AML-HR <sup>57</sup>	Fludarabine + arabinoside (high dose)	Arabinoside + daunorubicin + etoposide	AML	High-risk disease (resistant after one course of remission induction therapy, refractory disease after ≥ two remission induction therapies, relapse from first CR or in CR or PR after one remission induction therapy, but with adverse cytogenetic abnormalities at diagnosis)	Disease response, progression-free survival, overall survival, toxicity, supportive care requirements, QoL	RCT; target total 600	End of recruiting in 2003
CCG-2961 <sup>58</sup>	Consolidation fludarabine + cytarabine + idarubicin	Consolidation idarubicin + dexamethasone + cytarabine + thioguanine + etoposide + daunorubicin	AML and myelodysplastic syndromes	Previously untreated children	Progression-free survival, event-free survival, overall survival	RCT; target total 880	Temporarily closed
<b>Other malignancies and conditions</b> Taylor and Eyre <sup>59</sup>	Fludarabine	Activicin	Malignant gliomas	Recurrent	NA	Probable RCT	Completed and published
Davis et al. <sup>60</sup>	Fludarabine 20 mg/m <sup>2</sup> for 3 days every 4 weeks for 6 months	Fludarabine 30 mg/m <sup>2</sup> for 3 days every 4 weeks for 6 months	Rheumatoid arthritis	Severe and refractory to treatment with ≥ one slow-acting anti-rheumatic drug	Disease response, toxicity	RCT; 12 + 14	Completed and published

\* Also includes completed and published trials of fludarabine. Shaded cells indicate studies already included in the effectiveness review



# Health Technology Assessment Programme

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### Feedback

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***We look forward to hearing from you.***

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