

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

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CONTRIBUTIONS OF AUTHORS

Chris Hyde: Responsible for all aspects of this annexe. The report builds on comprehensive searches done by other researchers. These were performed as part of the original report and another on-going systematic review in the Dept of Public Health & Epidemiology at the University of Birmingham.

CONFLICTS OF INTEREST

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1 Introduction

In January 2001, the University of Birmingham submitted a rapid and systematic review to NICE on the effectiveness of fludarabine as second line therapy for chronic lymphocytic leukaemia (CLL) ¹. Comments were received on this report from several sources, some of which have been responded to with minor changes to the original report. These changes did not alter the original report's conclusions. The executive summary from the original report is reproduced in the Appendix.

A number of comments however could not be dealt with by amendments to the original report as they related to alleged failure to consider particular pieces of evidence on effectiveness. In all cases these pieces of evidence could not have been considered according to the protocol for the original systematic review finalised in August 2000. This protocol was open to scrutiny and agreed as reasonable before the original report was embarked on. Specifically, one item of "new" evidence only became available after the pre-specified completion date for searches of September 2000. Other items related to a preparation or application of fludarabine that fell outside the licensed indication when the protocol was finalised, the licensed indications being the main basis for the pre-specified inclusion criteria to the systematic review.

The NICE appraisals committee, recognising that the additional sources of effectiveness evidence indicated in responses could be relevant to their decision on the clinical and cost-effectiveness asked the University of Birmingham to compile and comment on the additional evidence on effectiveness. This was to be in relation to the effectiveness element of the original question:

"What is the clinical effectiveness of fludarabine in B-cell CLL with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen?"

This task was commenced in early April 2001. The timescale for this report was hence a little over 1 month, and it must be considered with this constraint in mind.

The following three chapters deal in turn with each group of additional evidence on effectiveness suggested as being important:

- Randomised controlled trials (RCT) involving use of fludarabine, other than as second line therapy
- CLL3NR study
- Evidence on effectiveness of oral fludarabine

2 RCTs of fludarabine, other than on its use second line

2.1 Method

The main purpose was to identify any published RCTs assessing the effectiveness of fludarabine not considered in the original report and to evaluate their results. In particular, the report attempts to assess whether fludarabine has greater effects on patients with CLL than other commonly used treatments, especially chlorambucil. This assumes that the effects in say first line therapy are similar to those that might be achieved in second line therapy. This seems reasonable for direction of effect, provided the agents being compared have not been used previously in the same patients. However, it seems less reasonable to generalise size of effect from say RCTs using fludarabine first line, to its use second line, and less emphasis is placed on this aspect of the results accordingly.

The search to identify RCTs was the same as that used in the original report, particularly those detailed in Appendices 6, 8 and 9. The strategies did not specify use at a particular stage of CLL and thus should have captured all RCTs assessing the impact of fludarabine up to the original end-date, September 2000. The outputs of the original searches of MEDLINE (Ovid) 1996-Sept 2000, EMBASE (Ovid) 1980-Sept 2000, Science Citation Index (Web of Science) 1981-Oct 2000 and the Cochrane Library 2000 (Issue 3) from the original report were double-checked as part of this report to ensure that no RCTs were overlooked. In addition the searches of MEDLINE, EMBASE and the Cochrane Library were updated to the end of March 2001. These additional searches were undertaken by Sarah Hancock, with advice from Anne Fry-Smith.

Potentially relevant material was assessed for relevance by the report author alone. Relevant material was appraised and summarised by the same. The corresponding authors of included RCTs have been contacted to ensure they agree with data abstracted; for clarification of data items on which there was ambiguity in the original reports; and to ask whether certain items of additional information were available. These requests were dispatched by airmail 19/4/2001; at the time of writing this report no replies have been received.

2.2 Overall quantity of material identified

Five RCTs were identified and included^{2 3 4 5 6}. These RCTs contributed information the effectiveness of fludarabine relative to chlorambucil (normal dosage)², chlorambucil (intermediate dosage) + prednisone³, chlorambucil (high dose continuous)⁴, CAP^{5 6} and CHOP⁶. The characteristics, quality and results of the included studies are presented for each of these comparisons. Important supplementary information on the

potentially dangerous effect of adding fludarabine to chlorambucil, as evidenced by an RCT which provides a comparison between fludarabine + chlorambucil and chlorambucil alone ² is also discussed.

2.3 Results – fludarabine vs chlorambucil (normal dosage)

2.3.1 Included study characteristics

One RCT contributed information on this comparison. The results have been fully published ². Further information was derived from the published protocol for this study ⁷.

As part of a larger trial, iv fludarabine was compared to oral chlorambucil in previously untreated CLL patients, Rai stages I-II (provided participants were symptomatic or had specific risk factors) or III-IV. 195 were allocated to fludarabine, which was given in standard dosage (25mg/m²/d for 5 days repeated every 28 days) for a maximum of 12 cycles. 200 were allocated to chlorambucil, also given at standard dosage (40mg/m² once every 28 days) for a maximum of 12 cycles. In both cases the drug was stopped if there was disease progression, complete remission or a response which plateaued over two months of treatment. The only specified prophylaxis in each case was allopurinol. Switching from fludarabine to chlorambucil or vice versa was allowed if there was no partial response or disease progression, or if the patient relapsed within 6 months of stopping the initially allocated drug.

Specified outcomes were disease response, progression-free survival, overall survival, toxicity and quality of life. The latter consisted of assessment of need for transfusion, incidence of infection and performance status. The primary outcome was progression-free survival. A power calculation was done; the target number of patients for the trial as a whole (544) including an additional combined fludarabine + chlorambucil arm was exceeded.

2.3.2 Included study quality

The study was generally well conducted. Allocation was likely to have been concealed and there was minimal loss to follow-up for the outcomes reported. The study was open to detection bias through lack of blinding, but this was off-set somewhat by central review being required for specimens from patients who had a complete remission.

2.3.3 Included study results

These are summarised in Table 1.

Table 1 Included study results of RCT comparing iv fludarabine with oral chlorambucil (normal dose)

Study	Outcome		Fludarabine	Chlorambucil	Difference (FI – ChI)	Comment
Rai 2000 ²	Response rates (complete + partial responses)		107/195 55%	67/200 34%	21% (95% CI 12% to 31%)	Favours FI
	Progression-free survival - median (all participants)		Approx 600 days ^I	Approx 420 days ^I	Approx 180 days ^I (p [log rank] <0.001)	Favours FI
	Overall survival - median		Approx 1980 days ^I	Approx 1680 days ^I	Approx 300 days ^I (p [log rank] =0.1)	Favours FI; results could have occurred by chance alone
	Toxicity - deaths		1/195 0.5%	0/200 0%	0.5% ^{II}	Favours ChI; results could have occurred by chance alone
	Toxicity - severe adverse events ^{III}	Thrombocytopenia	22/170 13%	25/178 14%	-1% (95% CI -8% to 7%)	Generally favours ChI; results could have occurred by chance alone
		Neutropenia	46/170 27%	34/178 19%	8% (95% CI -1% to 17%)	
Infections		27/170 16%	16/178 9%	7% (95% CI 0% to 14%)		
Impact on quality of life ^{IV}			Measured but not yet reported			
Notes:						
I - Results expressed in paper in months; results converted to days by multiplying by 30 to facilitate ease of comparison with the results from other RCTs						
II - Statistical significance of difference not formally tested						
III - Proportion of patients with severe (grade III) or life-threatening (grade IV) side-effects						
IV - Need for transfusion, incidence of infection and performance status						

Relative to chlorambucil at normal dosage, the results show a pattern of benefit in favour of fludarabine, particularly in terms of response rate and progression-free survival, off-set by increased incidence of severe adverse events, particularly infection. That any excess of infections observed with fludarabine treatment is clinically important has been confirmed⁸. Indeed the rates of infection reported in the table above, derived from the paper by Rai et al², seem to understate the number of patients with “major” infections. Using the criteria of hospitalisation for treatment of infection or need for parenteral antibiotics, assessed on retrospective review of case-notes, 29% of 189 patients in the fludarabine group had major infections, compared to 17% of 188 patients in the chlorambucil group (difference 12%; 95% CI 4% to 20%)⁸. The degree to which adverse events off-set the clinical benefits cannot be quantified from the available data.

2.4 Results – fludarabine vs chlorambucil (intermediate dosage) + prednisone

2.4.1 Included study characteristics

One RCT contributed information on this comparison. The results, described as a “first interim report”, have only been published in limited form as a conference abstract ³.

Iv fludarabine was compared to oral chlorambucil plus im prednisone in previously untreated CLL patients, Rai stages intermediate and high risk. 73 were allocated to fludarabine, which was given in standard dosage (25mg/m²/d for 5 days repeated every 28 days) for 6 cycles in the first instance. 74 were allocated to chlorambucil, which was given at a slightly higher than normal dosage (30mg/m² twice every 28 days) combined with im prednisone (40mg/m²/day for 5 days, repeated twice every 28 days). The chlorambucil + prednisone regime was again given for 6 cycles in the first instance. In both cases the regimes were stopped if there was disease progression or stable disease after 3 or 6 cycles. Two additional cycles were allowed if a complete remission was achieved; 3 if a partial response was obtained. There was no information on any prophylactic regime, or on switching in the event of failure of the initially allocated treatment.

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

2.4.2 Included study quality

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

2.4.3 Included study results

The conference abstract reports that the overall response rate was 70% for fludarabine and 66% for chlorambucil + prednisone. It should be emphasised that these results are only based on 60/73 evaluable participants in the fludarabine arm and 55/74 in the chlorambucil + prednisone arm. The reporting of results on toxicity is limited to the statement, “Toxicity was acceptable and comparable in the two treatment arms”.

Great circumspection is required in taking the study results as currently reported at face value. Firmer conclusions on the effectiveness of fludarabine relative to chlorambucil + prednisone should await full

publication of the results of this trial. Nonetheless, provided this trial is fully published, it should provide useful information on the relative effectiveness of fludarabine in CLL in the future.

2.5 Results – fludarabine vs chlorambucil (high dosage)

2.5.1 Included study characteristics

One RCT contributed information on this comparison. The results are currently only available as conference abstracts and posters ⁴. Further information was derived from the published protocol for this study ⁹.

Iv fludarabine was compared to oral chlorambucil in previously untreated CLL patients with advanced disease defined on the basis of Total Tumour Mass (TTM) scores or bone marrow failure. Approximately 40 participants were allocated to fludarabine ^{*}. The regime was slightly different to that employed in other RCTs; 25mg/m²/d for 4 days repeated every 21 days for 6 cycles. Approximately 36 participants were allocated to chlorambucil ^{*}. This regime is markedly different from that normally employed; 10mg/m²/d continuously for 18 weeks. Dose modification was specified for each regimen. A prophylactic regime was also specified allowing use of gammaglobulin infusions and corticosteroids. Switching from fludarabine to chlorambucil or vice versa was allowed if there was no response or disease progression at 9 or 18 weeks, or if there was a minor response at 18 weeks. It was stated that treatment with the crossover regime should not exceed 18 weeks.

Specified outcomes were disease response, overall survival, toxicity and quality of life. The latter consisted of number of nights in hospital and frequency of admission; frequency and nature of infectious episodes; and number of red blood cell and platelet transfusions. The primary outcome was stated to be response rates. A power calculation was done; the target number of patients for the trial was stated to be 260. With 80 participants the “feasibility” study reported is hence under-powered, and this needs to be taken into account in its interpretation.

2.5.2 Included study quality

Within the limits of the reporting, the study was reasonably well conducted. Allocation in particular was likely to have been concealed. Loss to follow-up was probably minimal, as 76 participants are accounted for in the results and the maximum number said to have been randomised was 82. The study was open to detection bias through lack of blinding. There were no features off-setting this apart from clear definition of

^{*} There is some ambiguity about the precise number of patients allocated to each arm; one report suggests a total of 82 patients have been randomised between the two treatment arms

most outcomes. As mentioned in the preceding section, the fact that the study is under-powered also needs to be taken into account in its interpretation

2.5.3 Included study results

These are summarised in Table 2.

Table 2 Included study results of RCT comparing iv fludarabine with oral chlorambucil (high dose continuous)

Study	Outcome	Fludarabine	Chlorambucil	Difference (FI – ChI)	Comment	
Jaksic 2000 ⁴	Response rates (complete + partial responses)	30/40 75%	31/36 86%	-11% (95% CI -29% to 6%)	Favours ChI-HD; results could have occurred by chance alone	
	Progression-free survival - median (? responders alone)	No detail available from reports ^I		No detail bar (p [log rank] = 0.92)	Unable to assess direction of effect	
	Overall survival - median (? all participants)	No detail available from reports ^I		No detail bar (p [log rank] = 0.207)	Unable to assess direction of effect	
	Toxicity - deaths	?0/40 ^{II}	?0/36 ^{II}	No difference	No difference	
	Toxicity - severe adverse events ^{III}	Anaemia	11/40 28%	13/36 36%	-9% (95% CI -29% to 12%)	Generally favours FI; all results bar thrombocytopenia could have occurred by chance alone
		Thrombocytopenia	3/40 8%	13/36 36%	-29% (95% CI -46% to -11%)	
		Neutropenia	14/40 35%	16/36 44%	-9% (95% CI -31% to 13%)	
Infections		2/40 5%	2/36 6%	-1% (95% CI -11% to 10%)		
Impact on quality of life ^{IV}		Measured but not yet reported				

Notes:

I - Unable to read off detailed results from Kaplan-Meier curve because of poor quality of reproduction in published abstract

II - No mention made of any deaths despite relatively full reporting on other toxicity events

III - Proportion of patients with WHO grade III or IV adverse events; information on other events also reported

IV - Number of nights in hospital and frequency of admission; frequency and nature of infectious episodes; and number of red blood cell and platelet transfusions.

The meaning of the superficially obvious pattern of benefit in favour high dose continuous chlorambucil relative to fludarabine, at the expense of higher levels of adverse needs to be interpreted very cautiously in the light of the knowledge that the study is under-powered. Full assessment of the potential of high dose continuous chlorambucil to deliver similar or improved response rates relative to fludarabine should await the results of larger trials with fully reported data on impact on quality of life.

2.6 Results – fludarabine vs CAP

2.6.1 Included study characteristics

Two RCTs contributed information on this comparison^{5 6}. The study by the French Cooperative Group on CLL et al has been fully published⁵. The study by Leporrier et al (also under the auspices of the French Cooperative Group on CLL) has effectively only been reported in conference abstracts⁶. One reference does relate to a full journal article from 1993, but this reports very preliminary results.

- French Cooperative Group on CLL et al 1996⁵

Iv fludarabine was compared to CAP in a mixture of previously treated and untreated CLL patients, Binet stages B and C. The results for the previously treated sub-group were included in our original report. Here we consider the trial as a whole[†]. 106 were allocated to fludarabine, which was given in standard dosage (25mg/m²/d for 5 days repeated every 28 days) for 6 cycles. 102 were allocated to CAP for 6 cycles. This consisted of cyclophosphamide iv 750mg/m² on day 1; doxorubicin iv 50mg/m² on day 1; oral prednisolone 40mg/m²/d on days 1-5. In both cases 4 further cycles were allowed in the case of incomplete but continuing response. A prophylactic regime was not mentioned. Patients relapsing after initial response to fludarabine or CAP could be switched the alternative regime; no information is given on switching where the participant was chemorefractory.

Specified outcomes were disease response, progression-free survival, overall survival and toxicity. Overall response rate was the primary outcome. A power calculation was done; the target number of patients for the trial as a whole (200) was met.

- Leporrier et al 1999⁶

As part of a larger trial which also considered CHOP (see below), iv fludarabine was compared to CAP in untreated CLL patients, Binet stages B and C. Approximately 350[‡] were allocated to fludarabine, which was given in standard dosage (25mg/m²/d for 5 days repeated every 28 days) for 6 cycles. Approximately 240[‡] were allocated to CAP for 6 cycles. Recruitment to the CAP arm of the study was stopped in February 1996 after the third planned interim analysis showed an excess of deaths. The CAP regime consisted of cyclophosphamide iv 750mg/m² on day 1; doxorubicin iv 50mg/m² on day 1 (50% decrease if in remission); oral prednisolone 40mg/m²/d on days 1-5. A further 6 cycles at 3 monthly intervals could

[†] This option was preferred, as there are fewer ambiguities in the available data when considering the results of the trial *in toto*.

[‡] The most recent report, a conference abstract, does not give precise denominators, results being mainly expressed as percentages. Total number randomised in all three arms is given as 938.

also be given [§]. A prophylactic regime was not mentioned. In the case of treatment failure during the first 3 cycles, fludarabine or CAP could be switched to the alternative regime after the third cycle

Specified outcomes were disease response, progression-free survival, overall survival and toxicity. Overall survival was stated to be the primary outcome. No information is given on whether a power calculation was done.

2.6.2 Included study quality

- French Cooperative Group on CLL et al 1996 ⁵

The study was generally well conducted. Allocation was likely to have been concealed and there was minimal loss to follow-up for the outcomes reported. It should be clearly noted that the results for progression-free survival only relate to those who responded ie approximately 50% of those randomised. The study was open to detection bias through lack of blinding. There were no features off-setting this apart from clear definition of all outcomes.

- Leporrier et al 1999 ⁶

Assessment of study quality was hampered by the limited reporting of the most recent results. However allocation was likely to have been concealed. Concerning loss to follow-up, the figure is claimed to be 16 of 938 randomised (2%) to all three arms of the study. However, most results are expressed as percentages without denominators making it difficult to verify the number accounted for in each outcome. The study was open to detection bias through lack of blinding. There were no features off-setting this apart from clear definition of most outcomes.

A further important issue needing to be taken into account in the interpretation of the results of the effectiveness of fludarabine relative to CAP is the possibility of duplication between the two studies. It is unclear the degree to which previously untreated CLL patients in the Leporrier et al ⁶ study, were also represented in the treated sub-group of the French Cooperative Group on CLL et al ⁵ study. Both studies commenced in 1990 and both involved the French Cooperative Group on CLL. The duplication is unlikely to be complete because other European countries contributed patients to the French Cooperative Group on CLL et al study, and the study by Leporrier et al has continued for much longer. Although the possibility of double counting the results from some patients remains, it has had to be ignored for the purposes of this report. However, should information emerge that the number of subjects duplicated is larger than expected, some reassessment of the results may be necessary in the future.

[§] Unclear whether this option was only for patients in fludarabine arm who responded; initial report mentions random allocation to further cycles of fludarabine or not.

2.6.3 Included study results

These are summarised in Table 3.

Table 3 Included study results of RCTs comparing iv fludarabine with CAP

Study	Outcome	Fl'bine	CAP	Difference (FI – CAP)	Comment
FrCGp 1996 ⁵	Response rates (complete + partial responses)	60/106 57%	42/102 41%	15% (95% CI 2% to 29%)	Favours FI
Lep'ier 1999 ⁶	Response rates (clinical/haematological remission)	?144/350 41% ^I	?36/240 15% ^I	26% (95% CI 19% to 33%)	Favours FI
Lep'ier 1999 ⁶	Response rates (not failure)	?256/350 73% ^I	?142/240 59% ^I	14% (95% CI 6% to 22%)	Favours FI
FrCGp 1996 ⁵	Progression-free survival - median (responders only)	817 days	270 days	547 days (p [log rank] =0.0001)	Favours FI
Lep'ier 1999 ⁶	Progression-free survival - median (?responders only)	Approx 900 days ^{II}	Approx 810 days ^{II}	Approx 90 days ^{II} (p [log rank] not given)	Favours FI; results could have occurred by chance alone
FrCGp 1996 ⁵	Overall survival - median (all participants)	1348 days	999 days	349 days (p [log rank] =0.27)	Favours FI; results could have occurred by chance alone
Lep'ier 1999 ⁶	Overall survival - median (?all participants)	Approx 2220 days ^{II}	Approx 2100 days ^{II}	Approx 120 days ^{II} (p [log rank] not given)	Favours FI; results could have occurred by chance alone

Notes:

I - Percentages only supplied; numerator inferred and assumes approximate number allocated is correct

II - Results expressed in paper in months; results converted to days by multiplying by 30 to facilitate ease of comparison with the results from other RCTs

III - Statistical significance of difference not formally tested

IV - WHO grade III or IV adverse events per cycle

V - Patients with grade III or IV toxicities

VI - Percentage and number of events supplied; denominator inferred

Table 3 continued

Included study results of RCTs comparing iv fludarabine with CAP

Study	Outcome		FI'bine	CAP	Difference (FI – CAP)	Comment
FrCGp 1996 ⁵	Toxicity - deaths		9/106 8%	3/102 3%	6% ^{III}	Favours CAP; results could have occurred by chance alone
Lep'ier 1999 ⁶	Toxicity - deaths		No data from most recent report of results			
FrCGp 1996 ⁵	Toxicity - severe adverse events ^{IV}	Thrombocytopenia	68/486 14%	58/446 13%	1% (95% CI -3% to 5%)	Favours FI for alopecia
		Anaemia	35/500 7%	35/438 8%	-1% (95% CI -4% to 2%)	
		Infections	21/525 4%	12/400 3%	1% (95% CI -1% to 3%)	
		Nausea & vomiting	2/500 <1%	7/425 2%	-1% (95% CI -3% to 0%)	
		Alopecia	1/500 <1%	84/453 19%	-19% (95% CI -22% to -15%)	
Lep'ier 1999 ⁶	Toxicity - severe adverse events ^V	All – mostly neutropaenia	157/?296 53% ^{VI}	122/?230 53% ^{VI}	0% ^{II}	No difference
FrCGp 1996 ⁵	Impact on quality of life		Not measured			
Lep'ier 1999 ⁶	Impact on quality of life		Not measured			
Notes:						
I - Percentages only supplied; numerator inferred and assumes approximate number allocated is correct						
II - Results expressed in paper in months; results converted to days by multiplying by 30 to facilitate ease of comparison with the results from other RCTs						
III - Statistical significance of difference not formally tested						
IV - WHO grade III or IV adverse events per cycle						
V - Patients with grade III or IV toxicities						
VI - Percentage and number of events supplied; denominator inferred						

The pattern of results confirms the advantages of fludarabine relative to CAP. The advantages of fludarabine appear to be present in terms of clinical benefit, particularly response rate and progression-free survival, and a more favourable adverse events profile, with the avoidance of alopecia. The only exception is the excess of deaths during treatment observed in the French Cooperative Group on CLL et al study. This is not statistically significant. No results on death during treatment were available from the most recent report of the Leporrier et al study, but an earlier report (1997) reported 3 toxicity related deaths in the fludarabine arm and 5 in the CAP arm.

2.7 Results – fludarabine vs CHOP

2.7.1 Included study characteristics

One RCT contributed information on this comparison ⁶. The study by Leporrier et al has effectively only been reported in conference abstracts ⁶. One reference does relate to a full journal article from 1993, but this reports very preliminary results.

As part of a larger trial which also considered CAP (see above), iv fludarabine was compared to CHOP in untreated CLL patients, Binet stages B and C. Approximately 350 ^{**} were allocated to fludarabine, which was given in standard dosage (25mg/m²/d for 5 days repeated every 28 days) for 6 cycles. Approximately 350 ^{**} were allocated to CHOP for 6 cycles. The CHOP regime consisted of vincristine iv 1mg/m² on day 1; doxorubicin iv 25mg/m² on day 1 (50% decrease if in remission); oral cyclophosphamide 300mg/m² and oral prednisolone 40mg/m² on days 1 to 5. A further 6 further cycles at 3 monthly intervals could also be given ^{††}. A prophylactic regime was not mentioned. In the case of treatment failure during the first 3 cycles, it is assumed that fludarabine or CHOP could be switched to the alternative regime after the third cycle, as this was stated to be the case for fludarabine and CAP (see above).

Specified outcomes were disease response, progression-free survival, overall survival and toxicity. Overall survival was stated to be the primary outcome. No information is given concerning whether a power calculation was done.

^{**} The most recent report, a conference abstract, does not give precise denominators, results being mainly expressed as percentages. Total number randomised in all three arms is given as 938.

^{††} Unclear whether this option was only for patients in fludarabine arm who responded; initial report mentions random allocation to further cycles of fludarabine or not.

2.7.2 Included study quality

Assessment of study quality was hampered by the limited reporting of the most recent results. However allocation was likely to have been concealed. Concerning loss to follow-up, the figure is claimed to be 16 of 938 randomised (2%) to all three arms of the study. However, most results are expressed as percentages without denominators making it difficult to verify the number accounted for in each outcome. The study was open to detection bias through lack of blinding. There were no features off-setting this apart from clear definition of most outcomes.

Unlike the assessment of fludarabine vs CAP, there are no issues concerning duplication of results.

2.7.3 Included results

These are summarised in Table 4

Table 4 Included study results of RCT comparing iv fludarabine with CHOP

Study	Outcome	Fl'bine	CHOP	Difference (FI – CHOP)	Comment	
Lep'ier 1999 ⁶	Response rates (clinical/haematological remission)	?144/350 41% ^I	?105/350 30% ^I	9% (95% CI 4% to 18%)	Favours FI	
	Response rates (not failure)	?256/350 73% ^I	?256/350 73% ^I	0% (95% CI -7% to 7%)	No difference	
	Progression-free survival - median (?responders only)	Approx 900 days ^{II}	Approx 840 days ^{II}	Approx 60 days ^{II} (p [log rank] not given)	Favours FI; results could have occurred by chance alone	
	Overall survival - median (?all participants)	Approx 2220 days ^{II}	Approx 2040 days ^{II}	Approx 180 days ^{II} (p [log rank] not given)	Favours FI; results could have occurred by chance alone	
	Toxicity - deaths		No data from most recent report of results			
	Toxicity - severe adverse events ^{III}	All – mostly neutropaenia	157/?296 53% ^{IV}	189/?315 60% ^{IV}	-7% (95% CI -15% to 1%)	Favours FI; results could have occurred by chance alone
	Impact on quality of life		Not measured			

Notes:

I - Percentages only supplied; numerator inferred and assumes approximate number allocated is correct

II - Results expressed in paper in months; results converted to days by multiplying by 30 to facilitate ease of comparison with the results from other RCTs

III - Patients with grade III or IV toxicities

IV - Percentage and number of events supplied; denominator inferred

The results provisionally suggest some advantage of fludarabine over CHOP. However, particularly taking into account the incomplete reporting of this RCT, the uncertainty about loss to follow-up and the fact that most of the advantages observed are not statistically significant, these findings are far from conclusive. Further, in contrast to the assessment of fludarabine relative to CAP, which the study by Leporrier et al also contributes to, there is no other RCT corroborating the findings for fludarabine in comparison with CHOP.

2.8 Adding fludarabine to chlorambucil

One RCT, already represented above, has assessed the effectiveness of adding fludarabine to chlorambucil². The dose of fludarabine used was slightly lower than normal (20mg/m²/d on 5 consecutive days every 28 days) as was the dose of chlorambucil (20mg/m² once every 28 days).

The comparison of fludarabine + chlorambucil with chlorambucil has not been formally included in this assessment because it does not contribute information on whether fludarabine alone is more or less effective than other currently used treatments in CLL. However although the results are not reported in full, we mention this comparison because there are indications that combination of fludarabine + chlorambucil is associated with excessive rates of life-threatening toxic effects. Recruitment to the fludarabine + chlorambucil arm of the study by Rai et al was stopped early as a result. In addition, an analysis of the same trial reported separately¹⁰ has raised the possibility that otherwise very unusual transformations of CLL to myelodysplastic syndrome and acute myeloid leukaemia may occur with the combined fludarabine + chlorambucil treatment. There were 6 cases (5 in F+C arm; 1 in F arm) in 521 of the participants reviewed after a median period of follow-up of 17.5 months, the total randomised being 544.

2.9 Fludarabine vs cladribine

Cladribine (2-chloro-deoxyadenosine) is another nucleoside analogue which has been speculated to have activity in CLL. Two RCTs were identified that compare this “new” agent with fludarabine^{11 12}. The trials are not formally included and no results from them are presented (or indeed are able to be presented). We mention them for interest and completeness. The first study¹¹ only includes a very small number of patients with CLL (the majority being non Hodgkin’s lymphoma – see our original report). The second¹² appears unlikely to be published because insufficient numbers of patients were recruited “due to problems of drug supply” (Samantha Christey, EORTC – personal communication).

2.10 On-going trials

Future assessments of the clinical and cost-effectiveness of fludarabine should not only be able to draw on the full reports of the RCTs of several of the studies mentioned above (including additional information on

impact on quality of life), but also on an important on-going RCT, the Leukaemia Research Fund sponsored MRC CLL4 study. This is comparing fludarabine or fludarabine + cyclophosphamide with chlorambucil in previously untreated CLL patients (Binet stages Ap, B and C) ¹³.

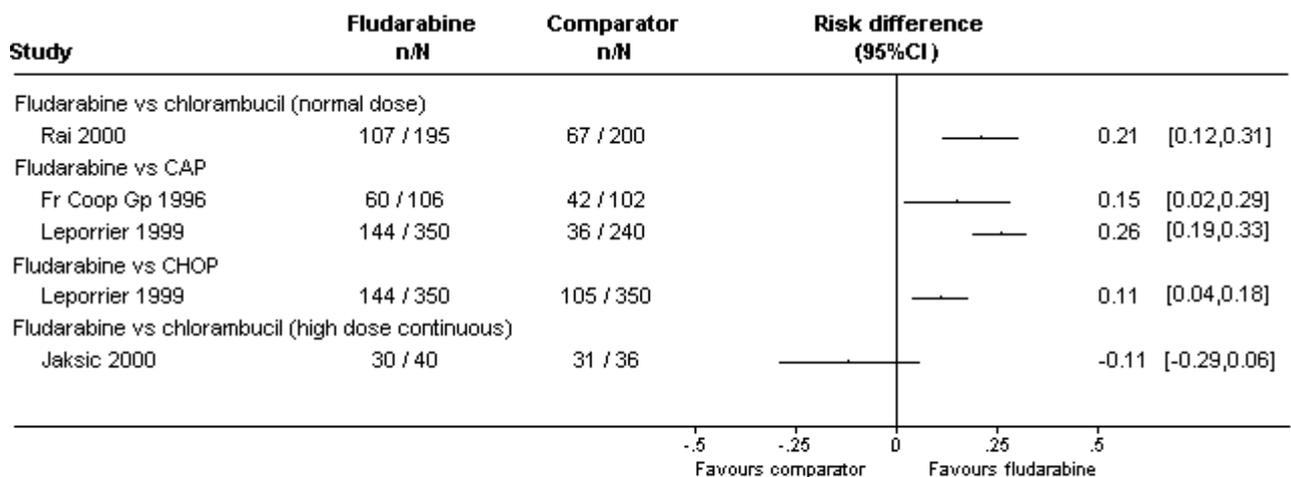
2.11 Conclusions

The five RCTs included suggest that in treating CLL:

- Fludarabine is more effective than chlorambucil at normal dosage (40mg/m² once every 28 days), particularly with respect to response rates and progression-free survival, but probably at the expense of increased side-effects, particularly infection.
- Fludarabine is more effective than CAP, particularly with respect to response rates and progression-free survival. The side-effect profile also favours fludarabine, particularly with respect to alopecia, an event the avoidance of which many patients are likely to weight highly.
- Fludarabine is possibly more effective and probably at least as effective as CHOP. Again provisionally the side-effect profile favours fludarabine. Firmer conclusions may be made when the results of the RCT on which this conclusion is based are fully reported.

An overview of the data on response rates is presented in Figure 1. A similar diagram could not be constructed for progression-free survival because of lack of information on the statistical dispersion of the survival data in several studies.

Figure 1 Overview of data on overall response rates in included RCTs comparing fludarabine with other treatments for CLL



Note: Overall response rate is generally complete + partial responses. In Leporrier et al this data was not available. For this study the data presented is for clinical + haematological remission.

The results from the included RCTs amplify the information available in our first report, giving a much clearer impression that fludarabine is at least as effective as three commonly used treatments in CLL – oral chlorambucil (40mg/m² every 28 days), CAP and CHOP. Although most of this evidence is derived from RCTs on previously untreated CLL patients, it seems reasonable to generalise the direction of effects observed to whether fludarabine is effective as second line therapy. However, it seems less reasonable to generalise the size of effects observed. Thus the addition to the analysis of RCTs in previously untreated CLL patients may not help with the quantification of net benefits when fludarabine is used as second line treatment. Consequently the ability to assess the cost-effectiveness of fludarabine used second line may also not have been improved.

The additional RCTs provide little new information on the assessment of impact on quality of life, so the accuracy of assessment of net benefit has also not been improved. Such information has clearly been collected in some of the additional trials considered, but as yet has not been fully reported. Its importance and the need to report it should be emphasised.

Whether fludarabine is more or less effective than chlorambucil used at intermediate or high doses is uncertain. The results of the RCT offer the prospect that use of oral chlorambucil at high dose may offer as good an opportunity to improve the treatment of CLL as fludarabine. This regimen deserves further investigation recognising that the results of the RCT on which the conclusions concerning high dose continuous chlorambucil are based so far are under-powered.

Finally we emphasise that this additional analysis should not be considered as an assessment of the clinical and cost effectiveness of fludarabine used as first line therapy in CLL. Many important uncertainties remain concerning this question, and the prospect that firmer conclusions will be possible when the CLL4 trial is completed strongly suggest that formal assessment should await the conclusion and reporting of this study. The opportunity to strongly support recruitment into this trial provided by the issuing of NICE guidance on use of fludarabine as second line treatment should be seized.

3 CLL3NR study

3.1 Methods

The study protocol and results were obtained directly from the Clinical Trial Service Unit (CTSU), University of Oxford. This data was used as the basis for the description of the study (including assessment of openness to bias), results and conclusions presented. Dr Sue Richards (CTSU, Oxford) amended and commented on a final draft of this chapter.

3.2 Results

3.2.1 Description of study

This was a follow-on study from the CLL3 RCT comparing chlorambucil with chlorambucil + epirubicin used as first line treatment of CLL (Binet stages Ap, B & C).

Those entered into the CLL3 study who had either showed no response after 6 courses of either initially allocated treatment, or who had progressed after less than 6 courses, and who in the opinion of the responsible physician required alternative treatment were eligible for the CLL3NR study. Each participant (there was no control arm) was then given fludarabine 25mg/m² iv daily for 5 days either by 30 minute infusion or as a bolus over a few minutes. The cycle was repeated every 28 days until a maximum response was achieved, with a minimum number of 3 cycles in the case of no response, and a maximum of 12 in the case of continuing response. Dose reductions were specified for treatment induced falls in neutrophil and platelet count. Supportive treatments (antibiotics, antifungal therapy, antiviral therapy and γ -globulin infusion) in specific situations were recommended.

The primary outcome was response at 6 months. Other measures included toxicity, WHO performance status, number of febrile episodes requiring antibiotics, number of days in hospital, number of transfusions required and vital status. Outcomes were based on return of forms completed by treating physicians at 6 months and 12 months after commencing fludarabine. There was no independent verification of the information fed back ie no requirement to submit blood films or bone marrow aspirates for independent verification of complete or partial response.

139 of all the patients randomised into CLL3 (426) were recorded as having no response on either a 6 month or 12 month form. Of these 14 died within 9 months, 4 deviated from the CLL3 first line protocol

treatment, 25 were not entered into the CLL3NR study for some other reason. The remaining 96 were the CLL3NR study participants.

3.2.2 Openness to bias

CLL3NR is an uncontrolled case-series. The fact that its starting point is an RCT, should not obscure this fact. As emphasised in the original report to NICE, the results of studies with such a design need to be interpreted with caution. They are open to considerable bias, particularly detection bias. In this study there was no independent assessment of outcomes to offset obvious lack of blinding, although the response criteria were well defined. The general problem of selection bias in case-series, is clearly a problem in CLL3NR, as all those eligible were not entered into the study. Attrition bias was not a problem as information was available on most patients at 6 months; the minimum number accounted for was 85 out of 96 ie a loss of 11% in terms of some measurements. Only one patient was lost to follow-up for survival.

Unfortunately, as with all case-series, in CLL3NR the lack of a randomly allocated control arm makes comparison of any outcomes in this study with other case-series employing similar or alternative therapies open to confounding.

A further specific problem highlighted by the range of times from randomisation into CLL3 and entry into CLL3NR (78 days to 1862 days; median 241 days), is the possibility that some of the 96 participants may have been ineligible as they were not true non-responders. According to the eligibility criteria the upper limit of this range should be approximately 6 months or 180 days. Further analysis of those strictly meeting the eligibility criteria are not yet available.

3.2.3 Main results^{††}

- Complete response rates

There were 13 complete responses at 6 months – 13/96; 14% (95% CI 7% to 20%). In this the 16 of the 96 participants dying before 6 months, one non-evaluable and one with unknown response are counted as non-responders.

- Overall response rates (complete + partial)

There were 63 complete and partial responses at 6 months – 63/96; 66% (95% CI 56% to 75%). Again, 18 of the 96 participants without 6 month response recorded are counted as non-responders.

^{††} Dr Sue Richards emphasises that the CLL3NR study has only had preliminary analysis done and that the results may change somewhat after further data cleaning.

- Toxicity

Neutropenia ($<1 \times 10^9/L$) and thrombocytopenia ($<50 \times 10^9/L$) were relatively common problems affecting 43 and 26 participants respectively at some stage during the six month fludarabine treatment period. Over the same period grade III or IV level side-effects for nausea/vomiting, alopecia, mouth problems, diarrhoea and cardiac function were uncommon affecting 4, 2, 2, 3 and 1 participants respectively. At 12 months there was no reported neurotoxicity and 4 cases of pulmonary toxicity.

- Febrile episodes requiring antibiotics

Information was available on 88 participants at 6 months.

44 participants had 0 episodes; 25 participants had 1 episode; and 19 participants had 2 or more episodes.

- Transfusions

Information was again available on 88 participants at 6 months.

49 participants had 0 transfusions; 7 participants had 1 transfusion; and 32 participants had 2 or more transfusions.

- Time in hospital over 6 months

Information was available on 87 participants at 6 months.

50 participants had 0 days in hospital; 10 participants had 1 to 6 days in hospital; 21 participants had 7 to 30 days in hospital; and 6 participants had more than 30 days in hospital.

- Mortality

16 deaths occurred within 6 months of commencing fludarabine. In follow-up thus far (median of 4 years) there have been 79 deaths.

- Other outcomes

There are currently no data on other commonly used outcome measures used in this area such as median progression-free survival and median overall survival (for responders and non-responders combined). In common with other completed studies in this area there is no direct measure of impact on quality of life.

3.3 Conclusions

In keeping with the observations about openness to bias, caution is required in interpreting all the results of this study. The likely effect of selection and detection bias is for the given results to overestimate the true levels for beneficial outcomes and underestimate levels for adverse events.

Despite this, the overall response rate obtained is encouraging. The point estimate of 66% is consistent with the range of response rates obtained in the systematic review of case-series examining impact of fludarabine in previously treated patients included in our original report – 28% to 73%. It has been claimed that the fact that this level of response has been obtained in a specific sub-set of previously treated patients with worse prognosis – those who have failed to respond to first line therapy (as opposed to mixed non-

responders and relapsed following initial success) – is particularly encouraging. However, drawing this conclusion may be inappropriate because:

- a) The results for response rate in CLL3NR include an unknown number of participants who are not true non-responders to first line therapy
- b) The conclusion implicitly relies on comparison with other case-series. As already stated such comparisons may be confounded by factors other than one of immediate interest (participants being non-responders to second line therapy); further all case-series are open to bias and the degree to which such biases might be operating could vary between each and so alone might be responsible for differences in response rates observed

Concerning toxicity, the nature and pattern of adverse events experienced is consistent with that observed in the studies included in the original report. The main side-effects are on blood counts, which of themselves may not have an adverse impact on the patient. That they do in some patients receives some support from the data presented on febrile episodes requiring antibiotics, transfusions and hospital days in the first six month period. Such data were not available for other studies included in the original report. However, these events should not be automatically attributed to fludarabine treatment in the CLL3NR study, as some events may be the result of progression of disease in those not responding.

Interpreting the current data from the CLL3NR is difficult. Some uncertainties may be resolved with further analysis; others will remain. Interpretation, particularly drawing conclusions about whether a new treatment represents an improvement over other treatments used in the same situation, will always be problematic in the absence of a randomly allocated control group.

4 Effectiveness evidence on oral fludarabine

4.1 Method

The main purpose was to identify any published research on the effectiveness of oral fludarabine and to evaluate the results of any comparative research identified.

The search was the same as that used in the original report, particularly that detailed in Appendix 6. The original search terms relating to the drug of interest did not specify whether the preparation was oral or iv, and thus the search strategies would have captured both. The outputs of the searches of MEDLINE (Ovid) 1996-Sept 2000, EMBASE (Ovid) 1980-Sept 2000, Science Citation Index (Web of Science) 1981-Oct 2000 and the Cochrane Library 2000 (Issue 3) from the original report were thus double-checked as part of this report to ensure that no studies relating to oral fludarabine had been overlooked. In addition the searches of MEDLINE, EMBASE and the Cochrane Library were updated to the end of March 2001. These additional searches were undertaken by Sarah Hancock, with advice from Anne Fry-Smith. The Fludara Product Monograph, the Schering submission to NICE, the American Society of Clinical Oncology conference (1997-2000) abstracts on-line [<http://www.asco.org/prof/me/html/00abstracts/menu.htm>] and the books of abstracts for the 1999 and 2000 American Society of Haematology conferences were also scanned for further potentially relevant citations and abstracts.

Potentially relevant material was assessed for relevance by the report author alone. Relevant material was appraised and summarised by the same.

4.2 Results

4.2.1 Quantity of material identified

Published research addressing any impact of oral fludarabine was remarkably sparse. Six potentially relevant published articles and abstracts ^{14 15 16 17 18 19} were identified. Three ^{14 15 16} referred to the pharmacokinetics of oral fludarabine; these are not considered further in this report, but were passed to the NICE secretariat for further assessment by someone with pharmacological expertise. One ¹⁷ was a case report of a rare, but potentially serious complication occurring in a patient receiving oral fludarabine. Another was a preliminary report of the first 15 patients in a case series of 56 examining the impact of a combined oral fludarabine and oral cyclophosphamide regimen in untreated CLL. The final published report ¹⁹ was a case-series of 78 patients with previously treated CLL ie second line therapy, given oral

fludarabine. In addition to these six published articles and abstracts, a further six citations were identified in the Schering submission (references 81 to 86). Unfortunately these all refer to internal Schering study reports which were not available for scrutiny as part of this report.

Only one of the studies was considered sufficiently relevant for detailed consideration ¹⁹. However, it needs to be noted that even this was not a true comparative study of the type that it was hoped would be available, and further it had not been published in full, only being available as a conference abstract. Despite this, it is considered as it is the main source of direct evidence of effectiveness on oral fludarabine used in the Schering submission to NICE.

4.2.2 Included study characteristics

The study, reported in abstract only, by Boogaerts and colleagues ¹⁹ is a case-series. Its population was stated as 78 patients (56M/22F) with symptomatic CLL (NCI-WG criteria) who had failed to respond or showed signs of disease progression during or after treatment with standard alkylating agent regimes (without anthracycline or mitoxantrone) ie second line use. Each patient had a mean of 2 prior treatment regimes. The distribution of Binet stages was A 23 (29%); B 24 (31%); C 31 (40%). No detail is given on how the patients in the study were drawn from the wider eligible population.

The intervention was oral fludarabine phosphate 40mg/m²/day for 5 days, repeated every 28 days for 6 to 8 cycles. A mean of 5 cycles was administered, with 60% of participants receiving 6 or more cycles. No information is provided on prophylactic treatment advised or dose reductions.

The outcomes of interest have to be inferred from the results presented. No primary outcome is stated. Little detail is given about the criteria used to assess outcome, other than that both the IWCLL and NCI criteria were used to define rates of response, three to five weeks after the last treatment cycle. WHO criteria seem to have been used to assess severity of adverse events and to measure performance status. There is no mention of methods that might have been used to offset the unblinded nature of outcome assessment.

4.2.3 Included study quality

As a case-series this study is highly susceptible to bias, particularly selection and detection. No features are reported which might mitigate the effects of these biases ie no reporting that patients were consecutively recruited from patients attending participating institutions who were eligible or no independent assessment of slides or bone marrow aspirates to confirm complete remission status. Loss to follow-up is difficult to

assess as no denominators are given for the results, generally expressed as percentages. Back calculating from the 95% CIs provided suggests that the denominator for the response rate calculations was either 73 (IWCLL criteria) or 71 (NCI criteria). Thus loss to follow-up appears to have been minimal for these outcomes. However as confidence intervals are not provided for other results, the same minimal loss to follow-up cannot be confirmed for these.

4.2.4 Included study results

- Complete response rates (IWCLL criteria^{§§})

21%.

- Overall response rates (complete + partial) (IWCLL criteria^{§§})

46% (95% CI 35% to 58%).

- WHO performance status ^{***}

At the end of treatment performance status had improved in 15%; remained unchanged in 55%; worsened in 30%.

- Toxicity

29 patients had 43 instances of serious adverse events. 5 definitely had a relation to the study drug; 13 probably; 10 possibly; 6 unlikely; 9 none.

WHO grade III/IV granulocytopenia, thrombocytopenia and anaemia occurred in 53%, 26% & 24% respectively.

25 patients required dose reductions, with 20 of these being due to myelosuppression.

There were 6 WHO grade III infections affecting 8% of patients. There were 35 infections of any severity affecting 45% of patients.

There were 4 cases of auto-immune haemolytic anaemia.

Peripheral neurotoxicity occurred in 6.4%.

WHO grade III nausea and diarrhoea in 1 and 3 participants respectively. 39% were affected by nausea, diarrhoea and vomiting of any grade

- Mortality

4 deaths were documented, 2 due to disease progression and 2 due to infectious complications.

No data was presented on survival or progression-free survival.

^{§§} Response rates using NCI criteria were similar.

^{***} Five grades. 0=able to carry out all normal activity without restriction; 1=restricted in physically strenuous activity but able to walk and do light work; 2=able to walk and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours; 3=capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4=completely disabled; cannot carry on any self-care; totally confined to bed or chair

4.3 Conclusions

In view of the biases identified, this study needs to be interpreted with caution.

The response rates are consistent with the range of overall response rates, 28% to 73% identified in the original report to NICE, for iv fludarabine used second line. However, on its own this falls short of making a definite assertion that oral fludarabine has an equivalent effect on response rates to the iv formulation. It is possible, that together with pharmacokinetic studies showing equivalent blood levels of fludarabine following oral and iv administration, such an assertion might be made more authoritatively. Even so whether oral fludarabine is considered effective, is heavily contingent on whether the iv preparation is thought to be effective.

An important point is that the pattern of side-effects seem similar to those experienced with iv preparations. Thus although administration of oral fludarabine may require less supervision than the iv preparation, the need for appropriate prophylaxis, careful follow-up and treatment of side-effects will remain. As with the cautionary note given on whether the data from the included study indicates an equivalent effect on response rates, it is impossible to say whether the frequency and severity of adverse events of oral fludarabine are exactly equivalent to the iv preparation.

Finally the results of the included study on oral fludarabine, provide the most direct measure encountered so far on the impact of second line fludarabine treatment in CLL on quality of life. As much caution must be exercised in interpreting the impact on WHO performance status as on the response rates given by the study by Boogaerts et al. However the number whose status improved following treatment, even given that it is over the period where function may be most compromised by the fludarabine treatment, seems disappointingly small. It confirms that the emphasis we placed in our original report on the need to assess impact on quality of life directly was reasonable, particularly in relation to future research in this area.

5 Overall conclusions

- The five RCTs of fludarabine in CLL outside second line treatment provide supportive evidence for the clinical effectiveness of fludarabine used second line. They demonstrate at least equivalent or improved impact on response rates and progression-free survival, in comparison with other commonly used drugs to treat CLL such as chlorambucil (40 mg/m²/d every 28 days), CAP and CHOP. In the case of comparison with chlorambucil, the advantages of fludarabine are probably off-set by increases in adverse events, particularly infections. This is not true in the case of comparison with CAP and CHOP. Limits on internal validity and information available, through incomplete reporting of the some of the RCTs, and limits on generalisability of size of the effects observed mean that quantification of net benefit and assessment cost-effectiveness may not have been improved to the same degree as the general assessment of clinical effectiveness.
- One RCT assessing the effectiveness of fludarabine outside second line treatment suggests that high dose continuous oral chlorambucil may offer as much opportunity to improve the treatment of CLL as fludarabine. Further research should be supported to fully evaluate this.
- Provisionally, combination therapy with fludarabine + chlorambucil should not used, and certainly not outside a rigorous evaluation of the suggested dangers of this regimen.
- Assessment of the clinical and cost-effectiveness of fludarabine used as first line therapy in CLL should await full reporting of the additional RCTs identified in this report, and the conclusion and reporting of the on-going CLL4 RCT. NICE guidance on second line therapy in CLL with fludarabine should be used as an opportunity to support recruitment to CLL4.
- The CLL3NR study adds little to the original assessment of the effectiveness of fludarabine, particularly given that only a preliminary analysis has been performed.
- Evidence on the effectiveness of oral fludarabine was sparse. The single included study indicates that compared to iv fludarabine similar responses rates can be achieved with the oral preparation, and that the side-effect pattern is similar. The assertion that this is sufficient evidence of equivalence depends on favourable assessment of the pharmacokinetic data, which is not part of this report. Irrespective of the findings of this, the judgement that oral fludarabine is effective is contingent on whether the iv preparation is judged to be so.
- The results of impact on WHO performance status in the included study on the effectiveness of oral fludarabine confirm that it is important to verify that impact on response rates is translated into useful impact on patient quality of life.

6 Appendix – Executive summary of original report

- Description of proposed service

Fludarabine is a recently developed chemotherapeutic agent. What is under consideration is whether the already well established use in its current licensed indication should be supported and further encouraged. The current licence is for use in patients with B-cell CLL patients with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen ie as a second line of treatment.

- Epidemiology and background

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

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

- Number and quality of studies, and direction of evidence

The systematic review of effectiveness identified two RCTs but only one of these contributed data to the analysis. Although well conducted this RCT was small comparing disease progression, survival and adverse events in 48 previously treated patients given fludarabine with 48 given CAP. Overall response rates were 48% (fludarabine) vs 27% (CAP) - difference 21% (95%CI: 2

to 40). Improvements in response rate were seen in both complete and partial response categories. The time to progression in responders was increased from a median of 179 days (CAP) to 324 days (fludarabine) but this was not statistically significant ($p=0.22$). No difference was seen in overall survival. In the whole trial, which included a further 100 previously untreated patients (total 196; 100 fludarabine; 96 CAP), adverse events were common in both arms, but nausea and vomiting, and alopecia and hair loss were markedly less for fludarabine. Deaths during the treatment period were greater for fludarabine than for CAP (9 vs 3), but this difference was not statistically significant.

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

- Summary of benefits

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

- Costs

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

- Cost-effectiveness and cost-utility

Apparently favourable estimates of the incremental cost-effectiveness of fludarabine relative to CHOP were identified. However they need to be interpreted very cautiously. The cost-utility of

fludarabine cannot be accurately calculated and so cannot assist a judgement on whether for a given investment of resources, encouraging use of fludarabine is likely to achieve more net benefit than investing in other areas of health care.

- Other important issues regarding implications

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

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- Need for further research

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

7 References

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