

CLL4

Chronic Lymphocytic Leukaemia Trial 4

A LRF sponsored trial from the MRC Adult Leukaemia Working Party. MREC (1) 98/101

A RANDOMISED COMPARISON OF CHLORAMBUCIL, FLUDARABINE AND FLUDARABINE PLUS CYCLOPHOSPHAMIDE.

This new study will compare conventional therapy with chlorambucil versus the new agent fludarabine, used alone or in a novel combination with cyclophosphamide. End points of the trial will be: **survival, response to therapy, duration of response, toxicity and quality of life.**

This protocol describes the MRC Adult Working Party protocol for CLL4 and the procedures for entering patients.

For patients that require further treatment after relapse or second line therapy for non-responders, a second randomisation will compare treatment guided by the protocol versus guided by the in-vitro drug sensitivity DiSC assay.

CLL4 will also provide an opportunity to investigate the prognostic value of five genetic markers by FISH analysis.

This protocol should not be used as an aide-memoire or guide for the treatment of other patients.

Every care has been taken in its drafting, but corrections or amendments may be necessary.

Clinicians are asked to read the whole protocol before commencing treatment.



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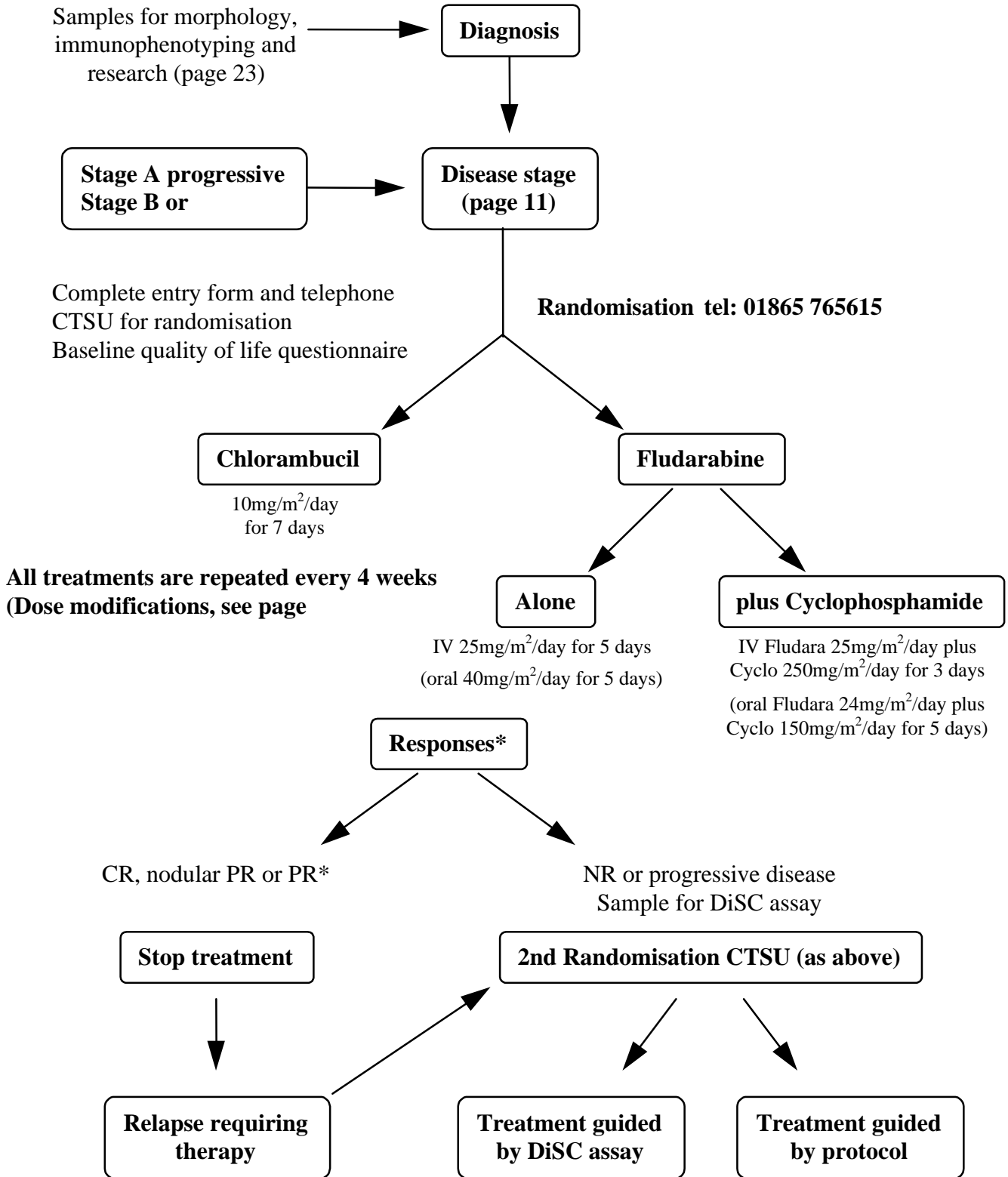
1. ETHICAL CONSIDERATIONS

CLL4 has been approved by the Multi-Centre Research Ethics Committee (MREC (1) 98/101) and will adhere to the MRC guidelines for good clinical practice in clinical trials (March 1998).

Before entering patients into CLL4, clinicians must ensure that the protocol has also received clearance from their local ethics committee. A prototype patient information sheet is enclosed (Appendix C, page 32)

Copies of the MRC guidelines for clinical trials can be obtained from the Cancer Therapy Committee Secretariat, MRC Head Office, 20 Park Crescent, London W1N 4AL.

2. PROTOCOL SUMMARY



* Best response should be assessed after 3-6 courses of or 3-12 courses chlorambucil (section 12, page 16)

3. INTRODUCTION

CLL is the most common leukaemia in adults over the age of 50. Over 1700 cases of CLL are diagnosed each year in the UK, and over 800 patients die from the disease in England and Wales alone. Although early stage CLL (stage A) has a good prognosis, not different from that of an age-matched normal population, late stage disease (stages B and C, or stage A but progressive) has a survival in the order of 40% at 5 years.

An overview of randomised trials comparing early versus deferred treatment for stage A has recently been completed (1). This included individual patient data for all relevant trials which began before 1990. Data on over 2000 randomised patients showed that there was no survival advantage obtained by immediate treatment of early stage disease, and that there might be a disadvantage. The MRC trials CLL1 and CLL2, with over 300 patients randomised to this question, have contributed substantially to the overview.

The recent MRC CLL3 trial compared chlorambucil, considered the standard treatment for CLL, with chlorambucil plus epirubicin, in late stage CLL. This was designed to test the hypothesis that adding an anthracycline might be beneficial in terms of overall survival, based on the results of a small French trial. CLL3 recruited 418 patients in a 7 year period (1990-1997), which is over 50% of the total previously randomised to this question worldwide. There was no evidence in this trial that an anthracycline confers a survival benefit, confirming meta-analysis results (1) in which data on about 1300 randomised patients was included. The latter showed that survival was not improved by combination chemotherapy (COP or CHOP) compared with chlorambucil, with a 5 year survival of 48% with either form of treatment (difference=0.8% SD 3).

Studies with a new group of chemotherapeutic agents, the nucleoside analogues, have suggested that they are useful in CLL. The most promising and most commonly used is fludarabine (Fludara), which has been shown to produce high response rates (2). It is known that among patients with CLL receiving the same treatment, those with a good response have better survival.

However, the question of whether the higher response rates seen with fludarabine result in longer survival has not yet been answered.

The unique mode of action of fludarabine, which affects DNA and RNA synthesis, including DNA repair, has opened up the possibility of using this agent in combination to potentiate the effect of other drugs. The MD Anderson Cancer Center have tested various drugs in combination with fludarabine and found cyclophosphamide (Cyclo), another agent with activity in CLL, to be the most promising, with a high level of responses in both untreated and previously treated patients (2, 3). In addition to clinical results, laboratory data have shown these drugs to be synergistic in vitro. The DNA repair that occurs after exposure to Cyclo is blocked by Fludara by its inhibition of DNA polymerase which is required for DNA repair. If fludarabine prolongs survival, the use of Cyclo in combination with it may have more than an additive effect.

There are few ongoing or completed randomised trials, comparing Fludara versus chlorambucil (4), Fludara versus CAP (Cyclo, doxorubicin plus prednisolone) (5, 6) and Fludara versus CHOP (Cyclo, doxorubicin, vincristine plus prednisolone) (6) with about 500 patients randomised in total. These trials show better response rates for Fludara, but do not demonstrate, as yet, survival benefit. Fludara is currently used as first line therapy in an MRC pilot study (7) for younger patients with CLL with encouraging results (response rate 69%) and has been used as second line therapy for non-responders in CLL3NR with response rates as good as first line therapy (response rate 79%, of which 17% were CRs). More data from randomised studies are needed to establish reliably, even in a meta-analysis, whether there is a survival benefit with Fludara. There are currently no randomised trials looking at the effect of adding cyclophosphamide to fludarabine.

Fludarabine and the combination of Fludara plus Cyclo may be more myelosuppressive than chlorambucil. Therefore an important part of the trial protocol will be to address the issue of prophylaxis and treatment of infection with recommendations for immunisation and

gammaglobulin replacement. The risks to patients are only slightly greater than those associated with standard therapy. In general, responders to treatment in CLL have fewer infections than non-responders, therefore a higher response rate with Fludara or Fludara plus Cyclo may counterbalance any greater myelosuppression.

Fludara is significantly more expensive than the standard treatment with chlorambucil which has been used for the last 30 years in the UK. This treatment is now licensed in its IV and oral formulation, but its effect on survival, duration of response and quality of life are unknown. Assessments of these are a prerequisite of any cost/benefit analysis of using it as initial treatment for all patients.

Many groups have investigated short term drug response 'in-vitro' methods for improving disease management in individual patients. Results seem to correlate well with patients response in a variety of malignancies, including CLL (8, 9, 10). In this trial, we will test the value of the DiSC assay (10) in patients that require further therapy after relapse or show disease progression or failure to respond with the first line regimen.

In the last three years, a number of cytogenetic abnormalities have been defined, which encompass approximately 60-80% of CLL patients. Although the commonest deletions and translocations at 13q14 are associated with a good prognosis, three other abnormalities, which can be detected reliably by fluorescence in situ hybridisation (FISH) are associated with an adverse prognosis. These are: trisomy 12, associated with an increased proportion of prolymphocytes, a high proliferative rate and more rapid disease progression seen, in 20% of patients (11, 12); 11q23 deletions, demonstrated in some series in up to 20% of patients, associated with younger age group, bulky lymphadenopathy and short survival (12, 13, 14); and p53 mutations/deletions involving the p53 locus at 17p13, associated with increase in prolymphocytes, poor response to therapy and transformation of the disease to large cell lymphoma, seen in 10% of patients (12, 15). These three abnormalities can be investigated simultaneously in interphase cells by FISH with

combinations of colour probes for 11q23, p53 and chromosome 12 as well as D13S25 to test for 13q14 deletion. Such a study has not been carried out prospectively in any large group of CLL patients or in the context of a randomised trial which includes new treatment variables. CLL4 and the proposed investigations may define more clearly the clinical significance of these genetic abnormalities, throw light on the clinical heterogeneity of CLL and open the way for new therapies in patients with poor prognosis. In addition, the accuracy of the diagnosis of CLL will be ascertained by means of central review of morphology and the use of a combination of monoclonal antibodies which has refined the distinction between CLL and other B-cell diseases (16).

4. OBJECTIVES

- 4.1. To ascertain whether Fludara prolongs the survival of previously untreated patients with CLL compared with chlorambucil, and whether the combination of Cyclo with Fludara has additional survival benefit;
- 4.2. To compare the response rate, the duration of remission of the three treatment modalities and the associated toxicity;
- 4.3. To investigate issues of quality of life (QOL) by means of EORTC QLC C30 questionnaires;
- 4.4. To determine whether the use of drug response information provided by the DiSC assay can improve response rate and survival in relapsed or non-responding patients;
- 4.5. To examine the prognostic value of five genetic markers: trisomy 12 and deletions at 6q21, 11q23, 13q14 and p53.

5. ELIGIBILITY

- 5.1. All patients with B-cell CLL, **previously untreated**, diagnosed by a persistent lymphocytosis (greater than $10 \times 10^9/l$) and bone marrow infiltration of at least 40%, **who require treatment**, with stage A progressive, stage B or stage C disease using the International (Binet) Staging System (see table on page 11).
- 5.2. Criteria for the diagnosis of CLL includes:

5.2.1 Peripheral blood morphology, excluding other forms of leukaemia and low grade lymphoma in leukaemic phase;

5.2.2 Cell markers which are included in the 'CLL score' (16) eg, CD5+, CD23+, SmIg (weak), CD79b-, FMC7-.

Peripheral blood morphology and markers will be reviewed centrally at The Royal Marsden NHS Trust (Professor D Catovsky and Dr E Matutes).

6. EXCLUSIONS

- 6.1. Patients with other life-threatening diseases; eg cancer;
- 6.2. Patients unwilling or unable to give informed consent;
- 6.3. Renal failure (creatinine clearance < 30 ml/min);
- 6.4. Hepatic enzymes and bilirubin greater than twice the upper limit of normal, unless due to CLL;
- 6.5. Pregnant women or women at risk of pregnancy;
- 6.6. Patients who for other reasons are not expected to complete the study;
- 6.7. Patients with a diagnosis other than CLL after central review of markers and morphology.

Note: Patients whose first language is not English will not be excluded from taking part.

7. DISEASE STAGE (BINET)

Stage	Organ enlargement*	Hb** (g/dl)	Platelets (x10 ⁹ /l)
A	0, 1 or 2 areas	≥10	≥100
B	3, 4 or 5 areas	≥10	≥100
C	not considered	<10 and/or	<100

* Each of the following counts as one: lymph nodes >1cm in the neck, axillae, groin, spleen and liver.

** Secondary causes of anaemia (iron deficiency, folate or B₁₂ deficiency) must be identified and treated before staging.

7.1. Stage A progressive is characterised by at least one of the following:

- i. A persistent rise in the lymphocyte count with doubling time <12 months;
- ii. A downward trend in the Hb and/or platelets;
- iii. $\geq 50\%$ increase in the size of the liver and/or spleen and/or lymph nodes.
Appearance of lymphadenopathy, hepatomegaly or splenomegaly if not previously present;
- iv. Constitutional symptoms attributable to the disease, eg pyrexia, night sweats, weight loss, once other causes have been excluded.

These criteria will also be used to define relapse (end of remission) in patients who have reached PR or CR.

8. LIST OF RECOMMENDED INVESTIGATIONS

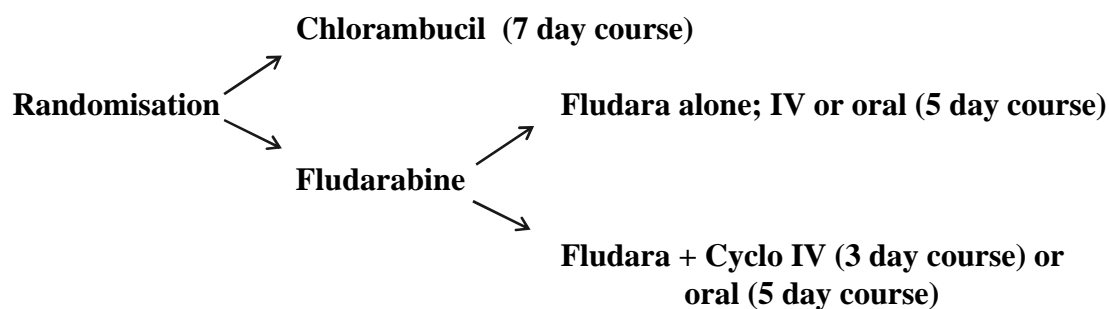
- 8.1.** Full blood count and differential (2 slides for central review; page 23);
- 8.2.** Bone marrow aspirate and trephine biopsy;
- 8.3.** Biochemical profile. Information on $\beta 2$ microglobulin and LDH will be required on the entry form (Appendix D, page 34);
- 8.4.** Chest x-ray and abdominal ultrasound or CT-scan (optional);
- 8.5.** Serum immunoglobulin and 'M' band;
- 8.6.** Direct antiglobulin (Coombs test); this information will be requested on the entry form (Appendix D, page 34);
- 8.7.** Samples for peripheral blood markers and FISH studies (see page 23);
- 8.8.** Samples in EDTA for DiSC assay (see page 23);
- 8.9.** Additional research samples both in heparin and clotted (see page 23);
- 8.10.** Completion of EORTC QLC C30 questionnaire (see page 38).

9. TREATMENT SCHEDULES

Eligible patients will be randomised between **chlorambucil** versus **fludarabine** based treatment.

Half of the patients will be randomised to **Fludara**, and these will be randomised between

Fludara plus Cyclo and **Fludara** alone. **All treatments will be given every 4 weeks.**



9.1. Patients randomised to chlorambucil

Chlorambucil $10\text{mg}/\text{m}^2$ will be given by mouth daily for 7 days every 28 days until maximum response is achieved, or up to one year. The daily dose may be divided into three (am, noon, pm) to reduce sickness.

9.2. Patients randomised to fludarabine will receive either:

- i. **Fludarabine** $25\text{mg}/\text{m}^2$ given iv for 5 days as a bolus injection, every 28 days, for a minimum of 3 courses and a maximum of 6, in order to achieve optimum response.
Fludarabine is supplied as a white lyophilized powder containing 50mg of fludarabine phosphate. Each vial is reconstituted with 2ml of sterile water for injection to give a 25mg/ml solution. It may be administered as a bolus injection. To administer as a bolus, the required amount of drug is drawn into a syringe and made up to 10ml with sterile normal saline 0.9%.
- ii. **Fludarabine** $25\text{mg}/\text{m}^2$ plus **cyclophosphamide** $250\text{mg}/\text{m}^2$, both given iv as a bolus injection, for 3 days, for a minimum of 3 courses and a maximum of 6, in order to achieve optimum response.

Note: Cyclophosphamide should be injected immediately before fludarabine for optimum effect. Anti-sickness therapy (but not dexamethasone) may be required

when using the combination of Fludara plus Cyclo. *Cyclophosphamide is supplied as anhydrous cyclophosphamide powder. Each vial is reconstituted with 5ml water for injection per 100mg of cyclophosphamide to give a 20mg/ml solution, which is used to administer as a bolus injection.*

iii. Alternative oral schedules:

Both Fludarabine and Cyclophosphamide are now available in tablet form. Patients may have a choice, if randomised to i) or ii) above, to take the drugs by mouth. The absorption of Fludarabine is 60% (17) and of Cyclophosphamide >75% (18).

a) **Oral Fludarabine** 40mg/m² each day for 5 days. Fludarabine is supplied in 10mg tablets which cannot be broken and the number of tablets to be taken is rounded up or down. *eg: patients of 1.5 or 1.6m² will take 60mg/day (6 tablets) and patients of 1.7 or 1.8m² will take 70mg/day (7 tablets).* It is recommended to take all the tablets at the same time each day before or with breakfast.

b) **Oral Fludarabine** 24mg/m² each day for 5 days. *eg: patients of 1.5 to 1.8m² will take 40mg a day.* **Oral Cyclophosphamide** 150mg/m² each day for 5 days.

Cyclophosphamide comes in 50mg tablets and again doses can be rounded up or down if required. **Note that it is recommended to take first the Cyclophosphamide tablets at breakfast time and the Fludarabine tablets at lunch time.**

If there is intolerance to the oral regimen, eg: nausea or vomiting or diarrhoea, which can be seen in 40-50% of cases, it may be preferable to switch to the IV regimen given over 3 days. Antiemetic drugs can be prescribed according to local practice.

9.3. Pre-treatment for stage C patients (Hb <10g/dl and/or platelets <100x10⁹/l not due to autoimmune phenomena). It is recommended that after randomisation, but before starting the allocated schedule, stage C patients should be given prednisolone - 30mg/m² daily for 3 weeks, plus 1 week tailing off, followed 1 or 2 weeks later by the randomised therapy.

10. AUTOIMMUNE HAEMOLYTIC ANAEMIA (AHA) AND IMMUNE THROMBOCYTOPENIA (ITP)

It is recommended to treat this problem first with prednisolone and/or other agents before using the allocated treatment. Although AHA and ITP may be triggered by Fludara, most instances have been in patients previously treated with alkylating agents. The incidence of AHA is no different in the three randomised arms of the current French trial (6). Nevertheless, the autoimmune complications of Fludara may be severe and it is important to be aware of this. Patients presenting with a positive direct Coombs test (without overt haemolysis) may be randomised, but care should be taken to monitor the development of AHA. We recommend that a direct Coombs test and reticulocyte count is done before each course of Fludara or Fludara plus Cyclo. Should autoimmune complications occur, please report to CTSU on a follow up form. Advice on management may be obtained from Professor TJ Hamblin.

11. DOSE MODIFICATIONS

Neutropenia and thrombocytopenia may be due to the disease. However, if the treating physician considers that the fall in counts is due to treatment the following guidelines should be followed for the next treatment course.

1. Neutrophils below $1 \times 10^9/l$ or platelets below $75 \times 10^9/l$, delay next treatment for 1 week;
2. If after 2 weeks delay the values have not changed, treatment could proceed at 50% of the dose;
3. If neutrophils are below $0.5 \times 10^9/l$ or platelets below $50 \times 10^9/l$ by the time a new course is due delay treatment until the counts rise to at least these levels, with dose modification as above if necessary.

Dose modifications for impaired renal function

Fludara should not be given with creatinine clearance less than 30ml/min (eligibility criteria). At the physician's discretion, patients with creatinine clearance between 30-60ml/min should have 50% of the dose of Fludara. Levels of creatinine should be monitored carefully in further courses and, eventually, doses may be gradually increased.

Antibiotic prophylaxis (see page 20 under Supportive Measures).

12. DURATION OF TREATMENT

The aim of the treatment is to achieve the best possible response either complete (CR) or partial (PR) or nodular PR. For a good response on either Fludara arm most patients will require 6 courses of treatment. Exceptionally, patients experiencing continuous response after 6 courses of Fludara (or Fludara plus Cyclo) may be given a further 2 courses (total 8). Patients randomised to chlorambucil will receive a maximum of 1 year of therapy in the first instance. Exceptionally, treatment may continue for a few more months if the clinician considers that a beneficial response is continuing. Patients showing no response or progressive disease after at least 3 cycles of chlorambucil, Fludara or Fludara+Cyclo should have their treatment discontinued and be treated with alternative protocols (see below).

13. ASSESSMENT OF RESPONSE

It is recommended that response should be assessed by means of a **bone marrow trephine biopsy** which will also enable comparisons with the original (pre-treatment) specimen. The distinction between CR and nodular PR can only be made with a trephine biopsy. Criteria for response; complete remission (CR), Nodular PR, partial remission (PR) or no response (NR) are given in Appendix A (page 30).

14. RELAPSE

Relapse (defined in this trial as disease progression, after an initial response, which requires treatment) **is one of the end points of CLL4**. The criteria for relapse are identical to those used to define stage A progressive (see page 11). For patients who relapse after a good response (CR, nodular PR or PR) or who do not respond to the initial randomised therapy (NR) or progress on treatment, reinitiation of original treatment or alternative treatment is required.

14.1. Relapse after 1 year of remission.

The initial therapy given may be repeated provided it was well tolerated and without major toxicity. If treatment needs to be changed, patients should be put into the second randomisation (see below).

14.2. Non-response, progressive disease on treatment or relapse within one year of remission.

For these patients who require a change of treatment, we propose a second randomisation to decide whether this 'second line' treatment will be guided by the results of the DiSC assay or by physician's choice following the protocol guidelines given below.

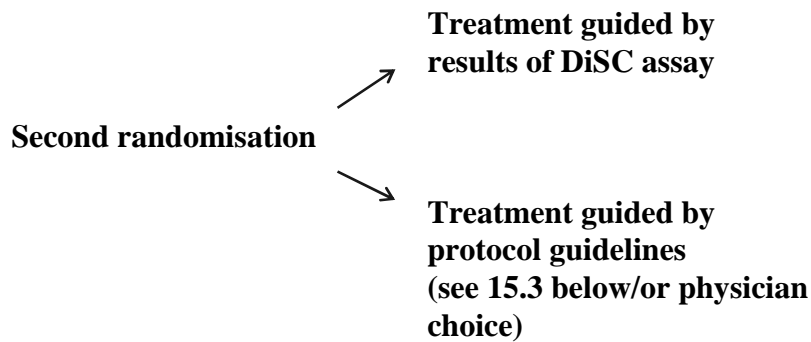
15. SECOND RANDOMISATION

For this second randomisation a new sample will be required for testing at Bath Cancer Research Unit (see page 23). The results of this test will only be made available to physicians treating patients randomised to treatment guided by DiSC assay. **Please note** that results from initial tests done at diagnosis are for research purposes and retrospective analysis only, they are **not suitable** to guide the second treatment and will not be available to treating physicians.

15.1. Outline of second randomisation

Once the treating physician considers that a patient treated on one of the first line therapies requires alternative treatment a new sample for DiSC assay should be submitted. A decision should then be made about the treatment to be used if allocated 'protocol guided therapy',

and a second randomisation obtained by telephoning CTSU. The comparison will be as follows:



15.2. Treatment guided by DiSC assay

CTSU will inform the Bath Cancer Research Unit when a patient is allocated to DiSC assay guided treatment. For these patients the results of the assay will be made available 7-10 days after the sample was submitted. The treating physician should then use the DiSC assay result to decide on the drug or drug combination most suitable for the patient. This treatment could include either of the first line treatments used in CLL4 that the patient did not receive, or the recommended combination suggested below as ‘protocol guidelines’, or any new agent or combination. Advice regarding the most suitable regimen may be obtained from Dr AG Bosanquet, the Trial Coordinator or any members of the CLL Working Group.

Whatever treatment you prescribe, it should be recorded on the appropriate follow-up form [D], including response (CR, nodular PR, PR, etc). Later treatment of patients randomised to this arm only, may be guided by DiSC assay and further samples could be tested if required.

15.3. Treatment by protocol guidelines

Patients randomised not to have information from the DiSC assay are treated by physicians choice. Guidelines are given below:

Approximately 25-30% of patients treated with chlorambucil and 15-20% treated with Fludara may be non-responders. Any of these patients may be treated with standard CHOP combinations every 4 weeks:

Cyclo 750mg/m² x day 1 (I.V.)
Doxorubicin 50mg/m² x day 1 (I.V.)
Vincristine 2mg x day 1 (I.V.)
Oral prednisolone 100mg x days 1-5.

Fludarabine treatment may also be used as second line treatment for those allocated chlorambucil initially. On the other hand, a CALGB trial showed that only a minority of non-responders to Fludara responded to chlorambucil, so chlorambucil is not recommended as second line treatment.

Treatment given and response to second line treatment should be recorded on Form [D]

(page 37)

16. ADVERSE EFFECTS

16.1. Chlorambucil. Experience in CLL3 showed that neutropenia and thrombocytopenia may be seen in 20% of patients. This effect was greater in non-responders (30%) than in responders (12%). Nausea may be experienced by 30% of patients and mucositis in 7%.

16.2. Fludarabine. This drug is more myelosuppressive than chlorambucil and can also cause severe CD4 lymphopenia and it may be associated with infections, in particular pneumonia and may precipitate autoimmune complications (see page 15). These effects are more marked in non-responders and in previously treated patients (c. 15%) than in previously untreated (5%). In CLL3NR (patients refractory to first line therapy), Fludara caused neutropenia in 50%, thrombocytopenia in 30%, nausea in 20% and mucositis in 10%. Oral Fludara may cause diarrhoea and/or nausea in 40-50% of patients.

16.3. Fludarabine plus cyclophosphamide. This combination has been used in close to 100 patients at the MD Anderson Cancer Center (Texas) using 30mg/m² of Fludara and 300mg/m² of Cyclo for 3 days. The doses proposed in CLL4 are 20% lower for both drugs. Toxicity with the higher doses (mostly in pretreated patients) included nausea/vomiting (40%); fatigue (25%); infections, including pneumonia (30%). Pilot studies in the UK indicate that the doses proposed for CLL4 are well tolerated and are not more

myelosuppressive than using Fludara alone. The oral regimen may cause a bit more nausea and diarrhoea than the IV regimen.

16.4. CHOP. This combination is widely used in lymphoma practice. Side effects are neutropenia, thrombocytopenia, mucositis, alopecia, nausea and fevers. Prednisolone may cause hyperglycemia, gastritis and upper gastrointestinal bleeding. Vincristine may cause constipation and peripheral neuropathy.

16.5. Serious adverse effects. All life-threatening, lethal and unexpected adverse effects including pulmonary toxicity must be reported to the Clinical Trial Service Unit or to the trial coordinator **within 24 hours**. A request for full details will then be sent to the clinician concerned. The trial coordinator will, in turn, report to MREC and all trial participants. Trial participants should inform the Medicines Control Agency any serious adverse reactions which they consider to be related to treatment, **via the yellow card system**. In addition, a serious unexpected adverse reaction to Fludara should be reported to Schering Health Care Limited. These include any reactions that are inconsistent with the summary of product characteristics in nature or severity. Full details should be sent to: Product Safety Department, Schering Health Care Limited, The Brow, Burgess Hill, West Sussex, RH15 9NE. Tel: 01444 232 323.

17. SUPPORTIVE MEASURES

Infection is a recurrent problem of patients with CLL, even without treatment. Chemotherapy may transiently increase this susceptibility by causing neutropenia and lymphopenia. We suggest the following measures.

17.1. Prophylactic cotrimoxazole (Septrin)

For patients receiving Fludara or Fludara plus Cyclo we recommend low dose Septrin, 480mg twice a day 3 days a week, eg Monday, Wednesday, Friday or 480mg daily 7 days a week. These doses have been shown to be adequate in AIDS patients to prevent *Pneumocystis Carinii* pneumonia (19). We recommend to start with the first course and

continue for **at least** 6 months after treatment is discontinued. Septrin is optional for patients randomised to chlorambucil.

17.2. Other antibiotics

In patients with a history of recurrent infection or those rendered neutropenic by treatment, prompt use of broad spectrum antibiotics following any episode of fever is essential. It is advisable to supply patients with a course of oral antibiotics, eg amoxicillin or augmentin to start at home at the first evidence of infection or unexpected fever.

17.3. Antifungals

These may occasionally be required for oral candidiasis/mucositis according to local practice.

17.4. Antivirals

Acyclovir is recommended, topically and in tablet form for herpes infections. For patients with a recent history of herpes zoster (eg within the last 6 months) who are rendered lymphopenic, prophylaxis with acyclovir 400mg twice a day may be given for at least 6 months from completion of therapy. Patients with herpes zoster should be admitted and be given early I.V. acyclovir in full doses.

17.5. Gamma-globulin infusion

For patients with very low serum immunoglobulins and a history of repeated respiratory infections, consideration should be given to the use of gamma-globulin infusions, eg 12-18g every 4 weeks, particularly during the periods of treatment.

17.6. Vaccines

We recommend that patients with CLL should receive annual influenza vaccinations. In addition anti-pneumococcal and haemophilus influenza (HiB) vaccinations are also advised. Although the antibody formation by CLL patients may be sub-optimal, pneumonia is the most common cause of death in this disease.

17.7. Antiemetics

It is likely that these will be necessary on the 3 days of the Fludara plus Cyclo treatment.

They should be used according to local practice. We recommend iv antiemetics for the first day of the injections and oral agents for the remaining days. **Corticosteroids (eg dexamethasone) should not be used as part of the antiemetic regimen as this will confuse the assessment of treatment response and will add immunosuppression.**

17.8. Growth factors

G-CSF or GM-CSF may be used according to local guidelines in patients with persistent neutropenia, eg $<0.5 \times 10^9/l$.

17.9. Blood products

Blood and platelet transfusions will be given at the discretion of the treating physician.

Patients treated with Fludara or Fludara plus Cyclo must receive irradiated blood products for all their future management to prevent the rare, but well documented occurrence, of transfusion associated graft versus host disease.

17.10. Allopurinol

It is advisable to give Allopurinol (300mg) once a day for 7 days for the first 2 to 3 courses of therapy whilst the WBC is elevated.

17.11. Splenectomy

This may be indicated in non-responding patients who remain with an enlarged spleen after an adequate trial of primary therapy. Continuation of therapy should be discussed with the trial coordinator. It is recommended that splenectomised patients should be treated with lifelong oral penicillin or amoxicillin 250mg twice a day or, if allergic to penicillin, an alternative eg erythromycin 250mg twice a day or clarythromycin 250mg once a day, in order to prevent overwhelming pneumococcal infection. In addition they should have pneumococcal and haemophilus influenzae immunisations. Patients should be issued with a splenectomy card and be given a supply of antibiotics for self-administration at the onset of

any respiratory infections. These should be augmentin 375mg 3 times a day for the majority, or cefuroxime 250mg twice a day if allergic to penicillin.

18. PRACTICAL ARRANGEMENTS

18.1. Samples for diagnosis, cell markers and FISH

20ml of blood in heparin and 2 blood films should be sent to Academic Department of Haematology and Cytogenetics, The Royal Marsden NHS Trust, Fulham Road, London SW3 6JJ for:

1. Cell marker studies, p53 protein and CD38 expression by immunophenotyping;
2. FISH analysis for trisomy 12, 6q21 deletion, 11q23 deletion, 13q14 deletion and p53 deletion;
3. Central morphological review of diagnosis;
4. Aliquots for cryopreservation (CLL bank).

These tests will be done free of charge for patients entered in CLL4.

Markers done locally are acceptable, but it is advisable to use the panel for the 'CLL score' (16). Samples for FISH and morphology review are still required from all patients. Bone marrows will not be reviewed centrally, but cases with diagnostic difficulties could be reviewed if requested.

18.2. Additional research samples (20ml of blood in heparin and 5ml clotted) for studies on 13q deletion and immunoglobulin V gene usage should be sent to Dr D Oscier, Department of Haematology, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW.

18.3. Samples for DiSC assay

10ml of blood in EDTA at first randomisation to be sent by first class mail to Dr AG Bosanquet, Bath Cancer Research Unit, Wolfson Centre, Royal United Hospital, Combe Park, Bath, BA1 3NG. This is a research sample and results will not be made available to trial participants at any stage.

10ml of blood in EDTA **at second randomisation**. Results will be available, free of charge, for patients randomised to DiSC assay guided treatment.

18.4. Cryopreservation of CLL cells

Samples of all cases will be cryopreserved at the CLL cell bank at the Royal Marsden NHS Trust (supported by the Kay Kendall Leukaemia Fund) whenever possible, both as viable cells and/or pellets for future study.

18.5. QOL

Completion of EORTC QLC C30 questionnaire (Appendix E) for baseline QOL data; send questionnaire completed to Dr AG Smith (CLL4 QOL) in Southampton (no stamp required). Subsequent questionnaires will be sent directly to the patient from CTSU with a return prepaid addressed envelope.

19. PROCEDURES FOR RANDOMISATIONS

19.1. First randomisation

An entry form (Form A) should be completed (example in Appendix D, page 34) before telephoning for randomisation to the Clinical Trials Service Unit in Oxford (Tel 01865 765615). The information on the form will be requested over the telephone and the treatment allocation given. Written confirmation will be sent from CTSU for checking against the form which should be kept in the patient's hospital notes. Randomisation will be done by computer balancing treatments with groups by age (<60, 60-69, 70+), stage of disease (A, B, C) and sex.

19.2. Second randomisation

Patients who require second line treatment should have a sample sent for DiSC assay (page 23) and then be randomised by a telephone call to CTSU (as above). Details that will be requested are trial number (or name and date of birth) and disease status (non-responder, progressive disease or relapse) and planned treatment if allocated 'protocol guided therapy' (CHOP, Fludara or other).

All patients will be flagged at the central NHS registry, so that only the very few who emigrate will be lost to follow-up in terms of survival. In the previous MRC CLL3 trial, less

than 3% of patients have been lost to routine follow-up and efforts will be made to ensure that the rate in CLL4 is at least as low as this.

20. FOLLOW UP AND QUALITY OF LIFE QUESTIONNAIRE

Follow-up will be done annually for 5 years for survival, disease status, toxicity and quality of life (Form [C], page 35). Follow-up for survival will continue indefinitely. A form will be used to record the response to first treatment, once treatment has been completed (Form [B], page 35).

Investigations to assess response and monitor therapy include: full blood count, differential count, reticulocyte count and direct antiglobin (Coombs) test, at the start and completion of therapy.

Imaging investigations (chest x-rays, ultrasound, CT scan) should be done when indicated to assess response at the clinician's discretion.

A **bone marrow trephine biopsy** is required before starting therapy and upon completion of treatment, eg 1-2 months after last course of therapy to assess the response. This may not be required in patients with clinical and laboratory signs of lack of response (non-responders) or those with disease progression.

The EORTC QLC C30 core questionnaire will be used to collect quality of life information directly from the patients (Appendix E, page 38). These will be requested:

- at the time of starting chemotherapy (baseline);
- at 3 months assessing chemotherapy related effects;
- at 6 months assessing concluding aspects of chemotherapy;
- at 12 months
- annually thereafter.

The questionnaire takes only a few minutes to complete and should be sent to Southampton (Appendix E, page 38) together with a completed QOL investigator form (Appendix F, page 40).

21. FAMILIAL CLL

A questionnaire for the Familial CLL Study will be available for patients willing to participate in this study. Further details are available from Benjamin Hilditch, Academic Department of

Haematology and Cytogenetics, The Royal Marsden NHS Trust, Fulham Road, London SW3 6JJ.

This study has been approved by The Royal Marsden NHS Trust Ethics Committee (No: 1212) and MREC (1) 99/82 and a number of centres which participated in MRC CLL3. The study is open to all patients with CLL even if they are not entered in CLL4 (eg patients who do not require treatment or who were previously treated). Once familial cases are identified, a special blood sample and a mouthwash sample for genetic linkage analysis will be requested with the patient's and doctor's agreement.

22. STATISTICAL CONSIDERATIONS

At the expected rate of about 100 patients per year, 500 patients will be randomised in 5 years. Comparison of 250 patients allocated to chlorambucil with 250 allocated to fludarabine based treatment will give more than 90% power to detect an absolute difference of 15%, from 40% to 55%, in survival at 5 years using a 2-sided p-value. There will be about 65% power to detect a difference of 10%. So there will be a good chance of detecting an important difference between the effect on survival of standard chlorambucil and fludarabine. In the comparison of fludarabine alone versus fludarabine plus cyclophosphamide, with 250 patients randomised, there will be 65% power to detect a 15% difference.

No current trial is large enough on its own to reliably demonstrate or rule out an absolute difference of 10% in 5-year survival, nor, indeed, are all the trials together. With 500 patients, CLL4 will double the number of patients randomised worldwide between fludarabine and chlorambucil. Combining the results of all such randomised trials will effectively increase the power to detect a 10% difference from 65% to 90% and give a much more reliable estimate of the size of any benefit than can be obtained from any one trial alone.

The main analyses will be intention to treat log rank survival. Chi-square tests will be used to compare differences between treatments in response, toxicity and quality of life. Separate analyses will be made within Binet stage of disease (A progressive, B or C), and within age groups (under

60 years, 60-69, 70 years and over). In addition, the effect of the various treatment schedules in patients with 11q23, trisomy 12, 13q14 deletion or p53 abnormalities will be examined.

With 25-30% of patients treated with chlorambucil and 15-20% of patients treated with fludarabine expected to be non-responders, plus those who relapse within one year of remission, about 125 may be available for the second randomisation. This gives about 75% power to detect a 25% difference in survival at 3 years from randomisation. By establishing before randomisation, for all such patients, the planned treatment if allocated 'protocol guided therapy', and obtaining a sample for DiSC assay, it will be possible to compare the outcomes of the randomised arms within the two subgroups (1) test-resistant to planned treatment (2) test-sensitive to planned treatment. If 'DiSC assay guided treatment' is beneficial, we would expect to see a substantial effect in group 1 and as few as 50 patients in this group would give at least 80% power to detect a change of 40% in survival, for example from 10% to 50% or 20% to 60%.

Analyses will be done annually after the first 200 patients have been entered, and reported to the Trial Data Monitoring Committee.

23. REFERENCES

1. CLL Trialists' Collaborative Group. Chemotherapeutic Options in Chronic Lymphocytic Leukemia: a Meta-analysis of the Randomized Trials. *Journal of the National Cancer Institute* 1999; 91: 861-868.
2. Keating MJ, O'Brien S, McLaughlin P, et al. Clinical experience with fludarabine in hemato-oncology. *Hematology and Cell Therapy* 1996; 38: S83-91.
3. O'Brien, Kantarjian H, Beran M, Freireich E, Kornblau S, Collier C, Lerner S, Gilbreath J, Keating M. Fludarabine and cyclophosphamide therapy in chronic lymphocytic leukemia. *Blood* 1996; 88: 480a.
4. Rai KR, Elias L, Shepherd J, et al. A randomised comparison of fludarabine and chlorambucil for patients with previously untreated chronic lymphocytic leukaemia. A CALGB, SWOG, CTG/NCI-C and EGOG inter-group study. *Hematology and Cell Therapy* 1997; 39: S58 (IWCLL abstract).
5. The French Cooperative Group on CLL. Johnson S, Smith AG, Loffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. *The Lancet* 1996; 347: 1432-1438.
6. French Cooperative Group on CLL. Randomized clinical trial comparing two anthracyclin-containing regimens (CHOP and CAP) and Fludarabine (FDR) in advanced Chronic Lymphocytic Leukemia (CLL). *Blood* 1999; 94 supplement 1 :603a (ASH abstract 2682).
7. Forsyth PD, Milligan DW, Davies FE et al. High-dose chemoradiotherapy with autologous stem cell rescue for patients with CLL is an effective and safe means of inducing molecular responses: an MRC Pilot study. *Blood* 2000; 96: 843a (abstract no: 3642).
8. Bosanquet AG, Bell PB. Enhanced *ex vivo* drug sensitivity testing of chronic lymphocytic leukaemia using refined DiSC assay methodology. *Leukaemia Research* 1996; 20: 143-153.
9. Bosanquet AG, Bell PB. Novel *ex vivo* analysis of nonclassical, pleiotropic drug resistance and collateral sensitivity induced by therapy provides a rationale for treatment strategies in chronic lymphocytic leukaemia. *Blood* 1996; 87: 1962-1971.
10. Bosanquet AG, Johnson SA, Richards SM. Prognosis for fludarabine therapy of chronic lymphocytic leukaemia based on *ex vivo* drug response by DiSC assay. *British Journal of Haematology* 1999; 106: 71-77.
11. Garcia Marco JA, Price CM, Ellis J, et al. Correlation of trisomy 12 with proliferating cells by combined immunocytochemistry and fluorescence in situ hybridization in chronic lymphocytic leukemia. *Leukemia*. 1996; 10: 1705-1711.
12. Döhner H, Stilgenbauer S, Fischer K, Bentz M, Lichter P. Cytogenetic and molecular cytogenetic analysis of B cell chronic lymphocytic leukemia: specific chromosome aberrations identify prognostic subgroups of patients and point to loci of candidate genes. *Leukemia*. 1997; 11: S19-24.
13. Döhner H, Stilgenbauer S, James MR, et al. 11q deletions identify a new subset of B-cell chronic lymphocytic leukemia characterized by extensive nodal involvement and inferior prognosis. *Blood*. 1997; 89: 2516-2522.
14. Neilson JR, Auer R, White D, et al. Deletions at 11q identify a subset of patients with typical CLL who show consistent disease progression and reduced survival. *Leukemia*. 1997; 11: 1929-1932.

15. Lens D, Dyer MJS, García-Marco JA, et al. p53 abnormalities in CLL are associated with excess of prolymphocytes and poor prognosis. *British Journal of Haematology* 99; 848-857: 1997.
16. Moreau EJ, Matutes E, A'Hern RP, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal antibody SN8 (CD79b). *American Journal of Clinical Pathology* 1997; 108: 378-378.
17. Boogaerts MA, Van Hoof A, Catovsky D et al. Acitivity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia (CLL). Submitted
18. Struck RF, Alberts DS, Horne K et al. Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous *versus* oral administration in a randomized, crossover trial. *Cancer Research* 1987; 47:2723-2726
19. Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. *Archives of Internal Medicine* 1996; 156: 177-188.

APPENDIX A - DEFINITIONS OF RESPONSE

A.1. Complete response (CR)

All of the following must be true:

Absence of lymphadenopathy by physical examination and appropriate imaging; no hepato- or splenomegaly; absence of constitutional symptoms; blood counts:

Neutrophils $\geq 2.0 \times 10^9/l$
Platelets $\geq 100 \times 10^9/l$
Haemoglobin $\geq 13g/dl$ for men
 $\geq 11g/dl$ for women
Lymphocytes $< 3.5 \times 10^9/l$

Bone marrow aspirate normal cellularity $< 30\%$ lymphocytes and **no evidence of lymphocytic infiltration in trephine biopsy.**

A.2. Nodular partial response (nodular PR)

As CR including the BM aspirate, **but evidence of discrete or moderately large nodules of residual CLL** in a trephine biopsy. Minimal interstitial lymphocyte infiltration may be present.

A.3. Partial response (PR)

This is a clinical assessment. All of the following must be true:

At least 50% reduction in organomegaly, namely lymphadenopathy, hepatomegaly and splenomegaly. Blood lymphocytes $< 15 \times 10^9/l$; neutrophils $\geq 2.0 \times 10^9/l$ or 50% improvement from baseline; platelets $\geq 100 \times 10^9/l$ or 50% improvement from baseline; haemoglobin $\geq 12g/dl$ for men or $\geq 11g/dl$ for women or 50% improvement over baseline, not supported by transfusion.

A.4. No response (NR)

May be defined as any response which does not include the above.

APPENDIX B - WHO TOXICITY GRADING AND PERFORMANCE STATUS

WHO toxicity grading

Grade	1	2	3	4
Nausea / Vomiting	Nausea	Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Alopecia	Minimal hair loss	Moderate, patchy alopecia	Severe alopecia	Total alopecia
Oral	Soreness / erythema	Erythema, ulcers, can eat solids	Ulcers, requires liquid diet	Feeding not possible
Diarrhoea	Transient < 2 days	Tolerable but > 2 days	Intolerable, requiring therapy	Haemorrhagic dehydration
Cardiac Function	Asymptomatic, but abnormal cardiac sign	Transient symptomatic dysfunction, no therapy required	Symptomatic dysfunction, responsive to therapy	Symptomatic dysfunction, not responsive to therapy

WHO Performance Status

Grade 0 - Able to carry out all normal activity without restriction.

Grade 1 - Restricted in physically strenuous activity but able to walk and do light work.

Grade 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.

Grade 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

Grade 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX C - CLL4 PATIENT INFORMATION SHEET

Introduction

You are invited to take part in a nationwide study designed to establish the best treatment for Chronic Lymphocytic Leukaemia (CLL), which affects the blood, lymph glands and bone marrow.

The trial is a comparison between :-

- the standard treatment with a drug called **chlorambucil** taken by mouth (tablets)
- a relatively new agent, **fludarabine**, which is given intravenously (into a vein) or by mouth (tablets).
- a combination of **fludarabine** and **cyclophosphamide**, both given intravenously or by mouth (tablets).

The treatment you receive will be selected by a process called **randomisation**; that is, it will not be chosen by you or your doctor, but by a computer and it is like the toss of a coin. This is to prevent bias in the results of the trial.

There is already information available suggesting that both fludarabine and its combination with cyclophosphamide may lead to remission, that is clearance of the leukaemic cells, at a higher rate than chlorambucil. However it is not yet known whether there are advantages in long term survival, quality of life and duration of the remission.

What will I have to do?

If you agree to take part in this study, you will be asked to have blood tests, a bone marrow biopsy and x-rays. These will be repeated at certain times during the study which is planned to last 5 years. You will be randomised to one of the three treatments listed above. All three treatments are given every four weeks until maximum response is achieved, then stopped. **Chlorambucil** is taken orally for 7 days each month for up to a year. **Fludarabine** is given as an intravenous injection for 5 days each month for six months, but it is also available in tablet form - you may need to take 6 or 7 tablets a day for 5 days. **Fludarabine plus cyclophosphamide** is given as an intravenous injection for 3 days each month for six months or by mouth spread over 5 days, in total you may need to take between 12 to 14 tablets each day. These treatments may continue for slightly longer if your doctor feels they continue to be beneficial. All the treatment courses will be given as an outpatient. The choice of whether you have oral form (tablets) or intravenously (injections) will depend on you, by agreement with your doctor. The efficiency is the same, but you may have symptoms such as nausea or diarrhoea with the tablets. If the symptoms are severe, the drugs may not be absorbed well and your doctor may advise you to switch to the injections. You will be asked to attend once every 4 weeks for blood tests before each course. You will be assessed each month to see whether or not you are receiving any benefit from the treatment and to make sure that there are no problems.

At the start of the study you will be asked for an extra blood sample to test for any possible faulty genes and to complete a simple questionnaire asking about your quality of life. This information will not be traceable back to an individual patient and will not affect any treatment you may have now or in the future and is intended for a study of the genetic basis of CLL. You will also be asked to complete a Quality of Life questionnaire again at 3, 9 and 12 months and once a year afterwards. This is to give us information about how the treatment affects your everyday activities. The questionnaire takes only a few minutes to complete.

You will be followed up in clinic regularly for five years after the end of the trial treatment. Some of your blood samples may be stored frozen for future research use.

What are the possible risks/benefits?

The risks and benefits apply to all arms of the trial. The major side-effect of these treatments is to lower the number of normal cells made by the bone marrow. Your red blood cells may be decreased, and it may be necessary for you to have a blood transfusion. You may also be more likely to develop infections. If an infection develops you may need to be treated with antibiotics. You may be given prophylactic (preventative) antibiotics. In addition the treatments may cause a sore mouth, nausea, vomiting and

diarrhoea, tiredness and skin rashes. We can give you tablets to control most of these problems should they arise. An anti-sickness injection will be given on the first day of the intravenous combination treatment and tablets on the following 2 days. Very rarely, haemorrhagic cystitis (pain and blood on passing urine), and pneumonia have been reported. The side effects may be greater with fludarabine alone or in combination with cyclophosphamide, but this disadvantage may be counterbalanced by greater effectiveness. At present, we do not know whether the potential benefits outweigh the greater risk of infections.

Women of child-bearing potential, and all men, must use effective contraception for the duration of treatment and for six months afterwards.

Second randomisation

If the treatment you are given stops working at any stage, there is a second part to this study designed to investigate the effect of a laboratory test of drug sensitivity to decide the choice of your next treatment. The test is designed to identify which drugs will be effective and which may not be effective against your leukaemia. However, it can delay treatment for 7-10 days while the test is performed and has not been proven to be effective in prolonging survival. Hence this part of the trial will compare by randomisation:

- your physician's choice of treatment, guided by the study protocol,
- treatment guided by the laboratory results, which will be made available to your physician.

Do I have to take part?

Your participation in this study is voluntary. Refusal to participate will not affect your treatment or the relationship with your doctor. If you agree to take part and then change your mind, you may withdraw at any time without giving a reason. Treatment will be stopped if there are any unacceptable side effects or if it is clearly ineffective and alternative treatments will be offered to you. Your legal rights are not affected by giving your consent to take part in this study. Your general practitioner will be informed of your treatment with your permission. It may be necessary for your records to be inspected by regulatory bodies. Personal information about you will be kept strictly confidential and will not be seen by anyone not involved in the study.

What do I do now?

You will be given time to think about the research and discuss it with your family or friends. You can tell the doctor of your decision next time you see him/her.

For further information please contact:

The Royal Marsden NHS Trust on

020 7352 8171 - London
020 8642 6011 - Sutton

Professor D Catovsky, 020 7808 2880 (London)
Dr E Matutes, 020 7808 2876 (London)
Haematology Registrar Bleep: 007 (London)
Bleep 446 (Sutton).

Given as example; each hospital
will provide the corresponding
local information

APPENDIX D - ENTRY AND FOLLOW-UP FORMS

CLL4 - ENTRY FORM [A]

Please return completed form to:

FREEPOST RLJ-UUUU-UUAC, CTSU, Richard Doll Building, Old Road, Headington, Oxford OX3 7LF
or Fax: +44-(0)1865-743986

Please complete this section before phoning for randomisation

Consultant Hospital

Patient's full name Sex

Date of birth...../...../..... Date of diagnosis...../...../.....

Hb (g/dl) Platelets (x10⁹/l) BM lymphocytes%

Any enlargement of: Spleen Yes No
Liver Yes No
Lymph nodes in: Neck Yes No
Axillae Yes No
Groin Yes No

Please telephone CTSU for randomisation (+44-(0)1865-765615) and note the information given:

Stage A B C CLL trial number

Treatment allocated: Chlorambucil Fludara Fludara plus Cyclo

Date phoned/...../.....

WBC (x10⁹/l) Lymphocytes% β 2 microglobulinmg/l

DAG test: +ve -ve not done

LDH: Patient Normal range

For stage A, indicate features of progression:

Lymphocyte doubling <12 months Yes No
Increase in nodes/spleen, etc Yes No
B symptoms Yes No
Drop in Hb/plat/PMN Yes No

Please provide patient with QOL questionnaire.

CLL4 - FIRST TREATMENT FORM [B]

Please return after completion of first treatment (about 6mths (FDR) or one year (ChI)) to:
FREEPOST RLUJ-UUUU-UUAC, CTSU, Richard Doll Building, Old Road, Headington, Oxford OX3 7LF
or
FAX: +44-(0)1865-743986

Consultant Hospital

Patient's full name CLL trial number

Treatment given Chlorambucil Fludara Fludara plus Cyclo Oral or IV Fludara

Date started/...../..... No. of courses

Was full dose given? Yes No Date completed/...../.....

Response Date of best response/...../..... **All data recorded in this section should be at this date**

Best response CR NPR PR NR PD Not assessable

Hb (g/dl) Platelets ($\times 10^9/l$)

WBC ($\times 10^9/l$) Lymphocytes% Neutrophils%

BM lymphocytes% BM biopsy? Yes No

DAG test +ve -ve not done

Any enlargement of: Spleen Yes No Liver Yes No

Lymph nodes in: Neck Yes No Axillae Yes No

Groin Yes No

TOXICITY DURING THIS TREATMENT PERIOD

Neutropenia ($<1 \times 10^9/l$) Yes No Non-haematological (with WHO toxicity grade, see back of form)

Thrombocytopenia ($<50 \times 10^9/l$) Yes No Grade

Haemolytic anaemia Yes No Nausea/vomiting

Alopecia

Number of days in hospital Mucositis

Diarrhoea

Number of febrile episodes requiring antibiotics Other Yes No

If Yes specify:

Type Grade

PATIENT STATUS

Performance status (WHO; see back of form) Vital status Alive Dead

If died: Date of death/...../..... Cause of death

Autopsy done? Yes No

CLL4 - FOLLOW-UP FORM [C]

Please complete this form yearly for the first 5 years from entry and return to:
FREEPOST RLUJ-UUUU-UUAC, CTSU, Richard Doll Building, Old Road, Headington, Oxford OX3 7LF
or
Fax: +44-(0)1865-743986

Date/...../.....

Consultant Hospital

Patient's full name CLL trial number

Disease status

- Never responded Stable disease
 Relapse (progression requiring therapy)

If progression: Date when documented/...../.....

- Evidence of progression: Downward trend Hb/plt
 Lymphocyte doubling time <12 months
 Progressive organomegaly

Have you initiated further therapy? Yes No

- If yes, treatment: Chlorambucil Fludara
 Fludara plus Cyclo CHOP
 Other. Specify
-

Vital status

Alive Dead

If died: Date of death/...../..... Cause of death

Autopsy done? Yes No

CLL4 - 2ND LINE TREATMENT FORM [D]

Please complete this form for all patients treated with 2nd line therapy (different from initial treatment) at the end of this phase of treatment, and return to:
FREEPOST RLJ-UUUU-UUAC, CTSU, Richard Doll Building, Old Road, Headington, Oxford OX3 7LF
or Fax: +44-(0)1865-743986

Date/...../.....

Consultant Hospital

Patient's full name CLL trial number

Second randomisation

Was second randomisation done? Yes No

- If No, reason Patient refusal
 Clinical, please specify
- Other, please specify

If Yes, was recommended treatment given? Yes No

- If No, reason: Patient refusal
 Clinical, please specify
- Other, please specify

Treatment given

- CHOP Fludara Fludara plus Cyclo
 Other. Please specify

Date initiated/...../..... No. of courses given

Response CR NPR PR NR PD Not assessable

Vital status

Alive Dead

If died: Date of death/...../..... Cause of death

Autopsy done? Yes No

APPENDIX E - CLL4 QUALITY OF LIFE QUESTIONNAIRE

EORTC QLC C30 (version 2.0)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers.

The information that you provide will remain strictly confidential.

Please fill in your initials:-

Your birthdate (Day, Month, Year)

Today's date (Day, Month, Year)

— — —

— — —

— — —

	No	Yes
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a long walk?	1	2
3. Do you have any trouble taking a short walk outside of the house?	1	2
4. Do you have to stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

