

-MRC CLL 5 EudraCT No: 2006-001967-40

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MRC CLL 5 Trial

THE VALUE OF AUTOGRAFTING YOUNGER PATIENTS WITH HIGH RISK CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

A RANDOMISED PHASE III INTERGROUP TRIAL

Co-ordinated by the EBMT CLL Subcommittee (Chairman : M. Michallet)

on behalf of the EBMT Chronic Leukemia Working Party (CLWP)

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TRIAL ORGANISATION

This trial is being organised under the auspices of the European Bone Marrow Transplant Group (EBMT) and involves the principal research groups investigating chronic lymphocytic leukaemia in Europe. The trial questions asked can only be answered in a large international collaborative study. The MRC has agreed to support the UK commitment to the trial. Randomisation will be carried out by the Clinical Trial Service Unit at Oxford but registration and follow up forms will be handled by the EBMT Data Centre at Leiden.

Randomisation:
(Monday-Friday
9 a.m.-5 p.m.)

Clinical Trial Service Unit (CTSU)
Tel 01865 240972
Fax 01865 404849
email Randomisation@ctsu.ox.ac.uk

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1 BACKGROUND AND RATIONALE

1.1 Introduction

Chronic lymphocytic leukaemia (CLL), the most frequent adult leukaemia in western countries is a clonal haematopoietic disorder with proliferation and accumulation of small lymphocytes of B lineage ⁽¹⁻³⁾. Since the median age at diagnosis is 65 years, in many patients CLL will not affect life expectancy although the disease is incurable with conventional treatment. However, in patients with an advanced stage (B or C according to the Binet classification ⁽¹⁾) with adverse prognostic factors, such as high leukocyte count, diffuse bone marrow infiltration, short lymphocyte doubling time (LDT), unfavourable cytogenetics, or elevated beta-2 microglobulin, survival time is considerably reduced ⁽⁴⁻¹⁴⁾. Although CLL is usually a disease of the elderly, it is increasingly diagnosed in younger people. A recent report indicates that about 20 % of patients are less than 55 years old ⁽¹⁵⁾. CLL in young adults has no major distinctive features, the prognostic factors are the same as those in older patients and median survival is less than three years for young patients with advanced CLL ⁽¹⁵⁾.

1.2 Therapeutic Approaches

1.2.1 Chemotherapy

The choice of therapy for CLL in stages B and C remains difficult with median survival time of 5 years and 22 months respectively ⁽¹⁶⁾. The disease can be treated with alkylating agents with or without prednisolone ⁽¹⁶⁾. The addition of anthracyclines may improve the outlook but the median survival remains less than 4 and 6 years for stages C and B respectively ^(16,17). Comparative studies between the use of chlorambucil with or without corticosteroids ⁽¹⁸⁻²⁰⁾ and alkylating agent-based regimens ⁽²¹⁻²⁵⁾ have not demonstrated superiority of any one regimen for stages B and C. The majority of the responses observed with these different regimens are partial remissions ⁽¹⁸⁻²⁶⁾.

1.2.2 Purine Analogues

More recently, fludarabine ⁽²⁷⁻³⁴⁾, 2-chlorodeoxyadenosine (2CDA) ^(35,36) and deoxycorformycin ⁽³⁷⁾, have been explored in previously treated CLL patients. Increasingly purine analogues are being used as initial therapy for CLL patients ^(29,37,38). Randomised comparisons between fludarabine and other therapeutic regimens ⁽³⁹⁻⁴²⁾ have demonstrated that fludarabine achieves more complete responses. A recent report ⁽⁴³⁾ of the response to fludarabine

regimens as initial therapy of 174 CLL patients has shown a median survival of 63 months and for responders, a median time to progression of 31 months. Patients who were refractory to fludarabine had a median survival of only 48 weeks. These results justify the consideration of innovative dose-intensive therapies ⁽⁴⁴⁾.

1.2.3 Allogeneic and Autologous Haematopoietic Stem Cell Transplantation (SCT)

The available information demonstrates that the survival of patients with CLL and adverse prognostic features is poor. Since this is not acceptable in young individuals, treatment modalities are required which have the potential to provide long-term remissions or to completely eradicate the disease. To date, the only potentially curative approach for CLL is high-dose therapy followed by either autologous or allogeneic stem cell transplantation.

1.2.3.1 Allogeneic stem cell transplantation

Although allotransplantation adds immunotherapeutic effects to the cytotoxic effects and may, thus, be curative, its use in patients with CLL has been difficult and contentious. This is partly due to the fact that many patients with CLL are older and/or have indolent disease which does not justify aggressive treatment. Even in experienced centres, the treatment-related mortality (TRM) of allogeneic SCT in patients with CLL has been reported to be as high as 36% ^(45,46,47). This figure further increases if registry data are taken into account. A recent update of the EBMT database comprising 188 allografted patients with CLL showed a TRM of 49% at 36 months post transplant, which is much greater than after standard indications such as acute leukaemia or chronic myeloid leukaemia ^[2-4]. The causes of these discouraging results are not completely clear, but patient age, selection of poor risk patients with advanced disease and extensive pre-treatment, and the CLL-associated incompetence of the immune system may all contribute to the high TRM observed. The recent development of conditioning regimens with reduced intensity may help to improve the tolerability of allo-SCT in patients with CLL ^[5; 6]. The information available to date is too limited to justify the investigation of allografting for CLL in a large phase-III multicentre study. Where a physician considers that an allogeneic transplant would be in the patient's best interests then this may be offered.

1.2.3.2 Autologous stem cell transplantation

In contrast to allogeneic transplantation, autografting for patients with CLL has increased significantly over the past years, with 225 cases in the EBMT database and a growing number of published single centre series ^[3; 9-14]. Due to the ability to mobilise peripheral blood stem cells and other improvements of supportive therapy, the mortality of the

procedure is low and was clearly below 10% in 1999. High-dose radio-chemotherapy followed by autologous SCT can induce or maintain long-term complete remission. Nevertheless, in most series a steady decline of the event-free survival curve is observed due to relapses occurring up to 5 years post transplant, and it is still not clear if autografting can be curative. The probability of relapse varies greatly between different series and this may depend on differences in patient selection and perhaps also on technical details such as the stem cell source and purging. Due to the low toxicity of the procedure, the outcome of autografted patients is characterised by overall survival figures of more than 75% at 3 years post transplant and, thus, is generally superior to that after allotransplantation, at least in the early post-transplant years.

The largest single-centre series of patients treated with autologous SCT for CLL has been reported by the Dana-Farber Cancer Center⁽⁶¹⁾. One hundred and fifty two patients with advanced CLL underwent myeloablative therapy including total body irradiation (TBI) and cyclophosphamide followed by reinfusion of autologous bone marrow (BM) purged with anti-B-cell monoclonal antibodies and complement. There were 8 treatment-related deaths (5%). With a median follow-up of about 30 months, only 14 patients have relapsed, but an additional 63 patients (of 136 with a marker available) show persistent disease at the molecular level.

At the University of Kiel⁵³, 45 patients with poor-risk CLL have been re-infused with immunomagnetically purged autologous stem cell grafts following preparation with TBI/cyclophosphamide. Engraftment was delayed in patients receiving BM (n=3) but there was prompt recovery of ANC $>0.5 \times 10^9/L$ after a median of 9 [8-13] days and platelets $>20 \times 10^9/L$ after a median of 10 [7-214] days) in patients restored with peripheral blood progenitor cells (PBPC) (n=42). There were two procedure-related deaths, and one of 5 patients with recurrent disease died due to progressive disease. With a median follow-up of 12 (3-67) months the projected 3-year event-free survival is 85%.

The EBMT has recently updated data on the outcome of 225 autologous transplants from the EBMT registry⁽⁶⁵⁾. The median age was 50 years. The median interval between diagnosis and transplant was 30 months and before transplantation, 51% of patients were in complete remission. Eighty-one per cent of patients received PBPC, as source of stem cells. Cell selection was performed in 33% of cases. Ninety-three percent of evaluable patients had stable engraftment. At 3 years from transplant survival was $78 \% \pm 4\%$, whilst risk of relapse and TRM were $45 \% \pm 8\%$ and $14\% \pm 3\%$ respectively.

The Medical Research Council has been conducting a Pilot study ⁽⁵⁹⁾ of autografting in CLL since 1996. One hundred and ten patients have been entered and information is available on 59 patients who have undergone autologous transplantation. Of these 78% became PCR negative for IgH CDR III re-arrangements post autograft. All patients who were in morphological CR at the time of autograft were PCR negative post-transplant and only 5/29 of these patients have had a molecular relapse. Overall the survival is excellent in the transplanted patients with a projected OS of over 80% at three years. The transplant related mortality was about 3%.

Although a number of single-centre or multi-centre SCT studies have been performed or are currently underway, the impact of autologous SCT on the prognosis of CLL is still unclear. The MRC under the umbrella of the EBMT is proposing a randomised phase III trial of autologous SCT to study the influence of first- or second-line autologous SCT on the course of poor-risk CLL.

Myeloablative regimens

Although encouraging results have been observed after high-dose chemotherapy alone followed by autologous SCT ⁽¹⁴⁾, in the vast majority of published data on stem cell transplants for CLL, the myeloablative regimen contained TBI because CLL cells are very sensitive to irradiation. On the other hand, it is unlikely from the results of conventional therapy that cytotoxic drugs alone can eradicate CLL ^(5; 6). A retrospective analysis from the EBMT⁽⁵⁴⁾ also suggested that TBI based regimens were superior to chemotherapy although selection bias could not be discounted as a cause for the difference. Thus, TBI/cyclophosphamide still appears to be the gold standard for autografting of patients with CLL, although regimens employing high-dose chemotherapy alone may have similar efficacy.

Stem cell source

Due to their favourable engraftment kinetics, mobilised PBPC have now replaced bone marrow as the principal source of stem cells ⁽⁴⁾. A variety of G-CSF-based mobilisation regimens are currently in use. Very preliminary data indicate that the mobilisation efficacy of more intensive protocols, such as the Dexa-BEAM regimen, appears to be somewhat better than that of classical cyclophosphamide plus G-CSF combinations ^(9; 13-15). This superior stem cell yield however, is at the expense of increased toxicity and cost.

Other variables that may influence mobilisation efficacy are stage, time from diagnosis, extent of pre-treatment and previous exposure to fludarabine.

Purging

The performance of systems for ex-vivo B cell depletion from stem cell grafts has been further refined during the recent years. With modern CD34+ selection devices, such as Isolex 300i or Clinimacs, it is possible to eliminate 3 to 4 log of CLL cells from fresh leukapheresis products ^[17]. The purging efficacy can be further increased by incorporating a step of negative B cell depletion into the procedure ^[18]. This manoeuvre also allows the elimination of presumptive CD34+ CLL cells. In spite of sophisticated purging technologies, there is still uncertainty about the clinical benefit^[9]. In this trial no recommendations are made about purging techniques, but where used this must be recorded.

1.3 Standard Treatment

For high risk CLL patients who have achieved a good response after one or two lines of treatment, “no further treatment” is presently the standard. Further treatment with autologous SCT has given promising results in non-randomised studies, but its role remains to be evaluated.

1.4 Quality of life

One of the recommendations of the Consensus Conference on Intensive Chemotherapy plus Stem-Cell transplantation in Malignancies: Lyon France, June 1993 is that studies of quality of life, and intermediate and late toxicity should be an integral part of all phase III trials evaluating treatment efficacy. However, there are only 20 studies focusing on QoL issues during the treatment period. They are typically small (only one study with 100 patients and 17 with less than 25). All studies included only bone marrow transplantation, without any data on peripheral blood SCT despite the fact that the number of patients treated with the latter is rapidly increasing. While it is important to document late effects, it is necessary to document time to recovery and the impact of the whole procedure on patients' quality of life. The intensive care period is characterised by both psychosocial stress and adjustment. The long period of treatment may result in some types of social and familial disruption. The difficulties that patients face during the first weeks of treatment may be increased if there are medical complications and possible re-hospitalisations.

These issues are important to clarify and the CLL5 QoL study meets requirements to evaluate the impact broadly on patient functioning

2 OBJECTIVES OF THE TRIAL

This is a prospective randomised phase III trial designed to determine the outcome of autologous SCT compared to no further treatment at present in patients with high risk CLL who have reached a complete remission (CR), a very good partial remission (VGPR) or a nodular partial remission (NPR) (see appendix I for definitions) after first or second line therapy.

2.1 The primary endpoints

1. Event Free Survival from randomisation (see appendix I for definition)
2. Overall survival from randomisation

2.2 The secondary endpoints

1. Time to disease requiring therapy (see appendix II for definition) from time of remission
2. Quality of life
3. Feasibility of first line versus late stem cell transplant
4. Feasibility of peripheral blood mobilisation

For autografted patients only

Morbidity and mortality of the transplant procedure

Time to neutrophil and platelet recovery

The proportion of patients achieving a molecular complete remission and the duration of remission (UK only)

Duration of hospitalisation

Amount and type of grade 4 toxicity

3 PATIENT ELIGIBILITY

3.1 Inclusion criteria

Patients must satisfy all of the following:

- B CLL CD5+/CD23+,
- There is no upper age limit but patients must be judged physically able to withstand high-dose chemotherapy and the suitability of this treatment may be discussed with the Transplant Centre
- Binet stage (at initiation of first line treatment) B, C, or progressive A (see appendix II for definitions of stage)
- Complete Remission (CR) or Very Good Partial Remission (VGPR) or Nodular Partial Remission (NPR) (see appendix I for definitions of response) assessed by bone marrow biopsy after first or second line treatment
- Written informed consent.

3.2 Exclusion Criteria.

- Age less than 18
- WHO Performance status > 2 (see appendix III for definition)
- Any T-cell leukaemia, NHL, Richter syndrome, mantle cell lymphoma, PLL
- HIV seropositivity.
- Inadequate renal or liver function, i.e. creatinine and bilirubin >1.5 times the upper limit of normal
- Severe heart failure, requiring diuretics or ejection fraction of less than 50%
- Severe concomitant neurological or psychiatric disease
- Pregnancy /lactation
- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; these conditions should be discussed with the patient before registration in the trial.
- Patients will be excluded if an allograft is planned

4 RANDOMISATION

Randomisation should be done after meeting all the eligibility criteria (including the verification of the exclusion criteria described in section 3. 2) and before any harvest is done. Patients will be randomised between Treatment arm W (Watch and wait. i.e. No further treatment until required) and Treatment arm T (Autologous Stem Cell Transplantation). Patients randomised to arm W should have blood stem cells harvested and stored so they can be used, if indicated, in the future.

Randomisation procedure

Patients will be randomised by contacting the Clinical Trial Service Unit (CTSU) in Oxford between 9 a.m. and 5 p.m., Monday to Friday (tel: 01865 240972, fax 01865 404849, email Randomisation@ctsu.ox.ac.uk)

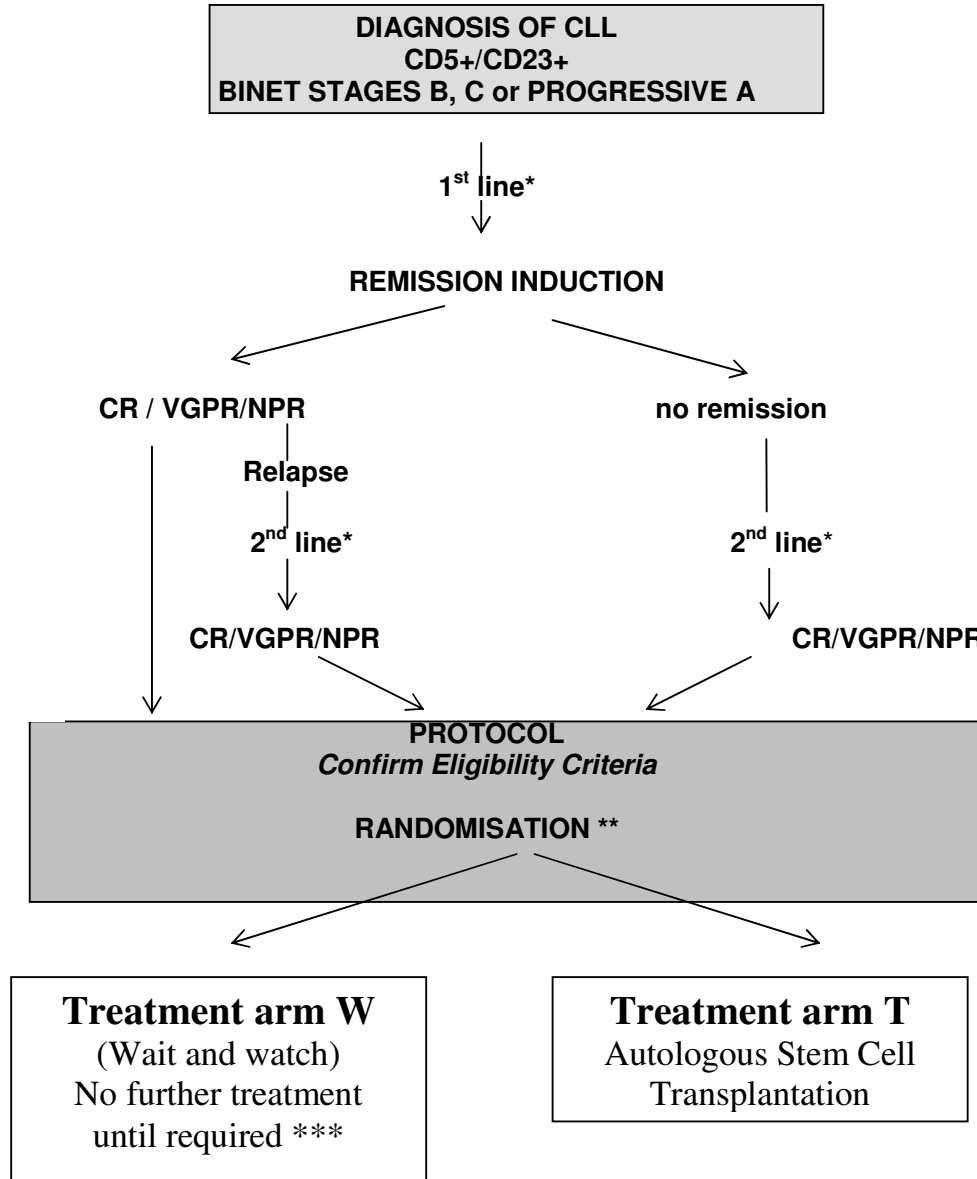
Please complete and have available your randomisation form at the time of telephoning / faxing / emailing. The information required is:

- Which group? (EBMT/MRC/French/German)
- Centre identification (EBMT centre no. or Hospital name, city, country)
- Name of responsible physician
- Fax number (if randomising by fax)
- Has patient given written informed consent? (must be yes)
- Have you checked that the patient is eligible (see section 3.2)? (must be yes)
- Patient's initials
- Patient's hospital identification number
- Date of birth
- Binet stage of disease at initiation of first line treatment (A progressive, B or C, see appendix II for definitions)
- Current status of disease (complete remission, very good partial remission, or nodular partial remission, see appendix I for definitions)
- Was this achieved after first or second line therapy? (1 or 2)

A patient trial number and treatment allocation will then be given.

The CTSU will liaise with the EBMT Statistical Centre at Leiden who are carrying out all other data collection and administration.

5 STUDY DESIGN



* The treatment recommended before randomisation is agreed by each participant group (see section 6) although any therapy leading to CR, VGPR or NPR is acceptable

** Before any harvest is done

*** Harvest (PBPC and/or BM) is recommended

6 INDUCTION and RE-INDUCTION TREATMENT

6.1 . Randomisation in this trial occurs *after* the achievement of a CR, NPR or VGPR. This is not a trial of induction therapy; however it is recommended that induction treatment is with one of the following schedules.

6.1.1 **Fludarabine** 25*mg/m² iv x 5 days, repeat every 28 days for a maximum of 8 cycles.
*or 40mg/m² orally.

6.1.2 **Fludarabine** 25mg/m² plus **cyclophosphamide** 250mg/m², both given iv as a bolus injection, for 3 days, repeated every 28 days for a minimum of 3 courses and a maximum of 6, in order to achieve optimum response. This combination can be given orally over 5 days: Fludarabine 24mg/m² and Cyclophosphamide 150mg/m².

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.

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 1.5 to 1.8 m² will take 70mg/day (7 tablets). It is recommended to take all the tablets at the same time before breakfast.*

Cyclophosphamide is supplied in 50mg tablets and the dose should be rounded up or down to give the closest dose. When given with oral fludarabine the cyclophosphamide should be given at breakfast and the fludarabine at lunch time.

6.1.2.1 Irradiated blood products

All patients receiving fludarabine should receive irradiated blood products to prevent transfusional graft versus host disease.

6.1.3 CHOP

cyclophosphamide	750mg/m ² iv day 1
doxorubicin	50mg/m ² iv day 1
vincristine	1.4 mg/m ² iv (2mg maximum) day 1
prednisolone	100mg po 5 days

Repeat every 28 days for a maximum of four cycles

6.1.4 Dexa-BEAM

dexamethasone 3 x 8 mg (days 1 to 10) po

BCNU 60 mg/m² (day 2) iv

etoposide 75 mg/m² (days 4 to 7) iv

cytarabine 100 mg/m² q12 h (days 4 to 7) iv

melphalan 20 mg/m² (day 3) iv

lenograstim 150µg/m²/day sc day 11 until neutrophil recovery.

Repeat after 28 days for a maximum of two cycles.

6.2 Assessment of response

This is dependent on

- Assessment of lymphadenopathy and hepatosplenomegaly
- FBC
- Bone marrow aspirate and trephine biopsy

See Appendix I for full definition.

7 PBPC AND/OR BM HARVEST, CONDITIONING REGIMEN, TOXICITY AND SUPPORTIVE CARE

All patients who have reached CR, VGPR or NPR will be randomised between arm W (no further treatment) versus arm T (autologous stem cell transplantation)

7.1 Peripheral Blood Progenitor Cells (PBPC) and/or Bone Marrow (BM) harvest

7.1.1 Peripheral Blood Progenitor Cells harvest

7.1.1.1 Stem Cell Mobilisation

Following treatment with fludarabine (or Fludara plus Cyclo), it is recommended that PBSC mobilisation is delayed at least 2 months from the last cycle of fludarabine.

The recommended schedule is :

- Cyclophosphamide 2g/m² iv day 1 with Mesna (100% of the dose of Cyclophosphamide iv)
- Lenograstim 150µg/m²/day sc days 5 –12
- Apheresis days 11, 12, ± 13 (or when WBC > 2 x 10⁹/l) - see below

An alternative schedule for mobilisation **only for patients randomised to the autograft arm (arm T)** is

Dexa-BEAM:

- Dexamethasone 3 x 8 mg (days 1 to 10) po
- BCNU 60 mg/m² (day 2) iv
- Etoposide 75 mg/m² (days 4 to 7) iv
- Cytarabine 100 mg/m² q12 h (days 4 to 7) iv
- Melphalan 20 mg/m² (day 3) iv
- Lenograstim 150µg/m²/day sc day 11 until the last day of apheresis

N.B. Dexa-BEAM must not be used for patients randomised to arm W (no autograft)

7.1.1.2 Stem cell collection

PBPC collections will be performed on 2 to 4 consecutive days following the haemopoietic recovery phase as soon as the leukocyte counts have reached 2 x 10⁹/l or as soon as the peripheral CD34+ counts exceed 2 x 10⁷/l .

The PBPC harvest should contain:

- Nucleated cells > 1 x 10⁸/kg body weight
- CD34+ cells > 2 x 10⁶/kg body weight (or > 4 x 10⁶/kg if purging is attempted)
- and/or CFU-GM > 5 x 10⁴ /kg body weight

If these numbers are not met after 4 days the patient will be considered as a failure of mobilisation and the mobilisation will be discontinued. There is an option for a second attempt at mobilisation when the blood count has recovered and the bone marrow is normocellular and this will not require further chemotherapy priming with Cyclophosphamide (or DexaBEAM).

7.1.2 Bone Marrow harvest

Autologous **bone marrow harvest** will only be performed in the case of failure to harvest enough peripheral blood stem cells. A minimum of 2×10^8 mononuclear cells/kg body weight is required. The BM should be assessed before marrow collection with morphologic examination. The BM must not have evidence of morphological disease, except nodular infiltration (NPR). All other evidence of residual disease (persisting abnormal cytogenetics or any other identified clonal abnormalities (i.e CD5/CD23) will be monitored before and after autologous transplant, but will not be criteria of exclusion from autologous transplant.

BM should always be taken as a back-up if there is any doubt about the quality of PBPC obtained. In addition, bone marrow may be used to complement PBPC if there are doubts about the adequacy of stem cell mobilisation.

7.1.3 Purging.

Purging (negative and/or positive selection) of BM or PBPC is permitted but must be recorded and is not recommended in the UK following experience in the MRC Pilot.

7.2 Conditioning Regimens

Two standard types of pre-transplant regimens are recommended:

- Cyclophosphamide: 60 mg/kg body weight on 2 consecutive days (+ Mesna) + TBI, 10 Gy with lung shielding. The schedule for TBI should be one with which the transplant centre is familiar. Doses may vary from 8 to 14.4 Gy.

OR

- BEAM
BCNU 300 mg/m² iv day -6
Cytosine Arabinoside 200mg/m² iv 12 hourly days -5 to -2
Etoposide 100mg/m² iv 12 hourly days -5 to -2
Melphalan 140 mg/m² day -1

7.3 Post Transplant growth factors :-

The use of granulocyte-colony stimulating factor is allowed after transplantation according to local practice.

7.4 Toxicity and supportive care

7.4.1 Mobilisation and Transplantation Toxicity

All treatment schedules used in this protocol cause pancytopenia and can induce septic or haemorrhagic complications.

In the UK transplants should only be performed in centres experienced in autografting and at BCSH Level 3.

Note: Unexpected toxicity and toxic death should be reported to the study co-ordinator immediately, refer to appendix IV.

7.4.2 Supportive care

Attempts should be made prior and during chemotherapy/radiotherapy to control any medical problems, such as bleeding, infection and metabolic abnormalities. Tumour lysis syndrome should be prevented by allopurinol, hyperhydration and if necessary frusemide. Electrolyte abnormalities should be checked and monitored. All patients will receive platelet transfusions according to local protocol to reduce the risk of haemorrhage. Patients with fever should receive empiric broad spectrum antibiotics. Antibiotics should be given as prescribed by the sensitivity studies, whenever a pathogen has been isolated.

8 CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

8.1 Before randomisation

The following should be performed within 15 days before randomisation but after CR/VGPR/NPR has been established :

- Signed and dated informed consent
- Quality of life questionnaire given to patient
- Medical history and physical examination
- WHO performance status
- liver and spleen size
- lymph node enlargement
- full blood count (FBC) and anti globulin test
- Biochemistry (urea and electrolytes, LFT, uric acid)
- Chest X-ray
- ECG
- *Immunophenotyping in blood (CD5, CD 20, CD 19, CD 23, Kappa/Lambda)
- **IgH rearrangements and DNA extraction (EDTA)
- cytogenetics (FISH analysis)

ideally from a sample taken at diagnosis. If possible a sample should be analysed (or stored) for V_H gene hypermutation.

***Immunophenotyping** can be done locally but samples (EDTA) should also be sent (UK centres only) by first class post to :-

**Professor Gareth Morgan
Haematological Malignancy Diagnostic service
The Algernon Firth Building
Leeds General Infirmary
Leeds
LS1 3EX
Tel 0113 243 2799
Fax 0113 233 3404**

***Please ensure that
samples do not
arrive over the
weekend***

**** Must be sent to Professor Morgan – UK centres only**

8.2 Follow up required for trial

8.2.1 Every four months during first year from randomisation, and six monthly thereafter:

- FBC
- Clinical status
 - Lymphadenopathy
 - Liver enlargement
 - Splenomegaly
 - UK centres, autograft arm only: bone marrow aspiration (EDTA) for molecular monitoring to HMDS, Leeds (address see above)

9 QUALITY OF LIFE (QOL)

The aim of the QoL project is to compare quality of life between the two randomised arms: **arm W** (no further treatment) versus **arm T** (autograft).

There will be seven assessment points corresponding as far as possible to the time at which clinical follow-up forms are due:

- baseline (at randomisation),
- at 4 months, 8 months, 1 year, 2 years, 3 years and 4 years post-randomisation

See appendix V for further details of QoL

10 STATISTICAL CONSIDERATIONS

For patients with stage B, C or progressive A disease in the age group ≥ 15 and ≤ 65 years, the progression-free survival (PFS) at 5 years after randomisation without further treatment can be expected to be about 30% at best. Applying autologous stem cell transplantation will hopefully lead to a PFS 5 years after randomisation of 50%. To detect an absolute difference of 20% using a two-sided significance level of 0.05 and a power of 0.90 requires 134 patients in each arm. So altogether about 270 patients need to be randomised.

The randomisation will be stratified according to participation groups and minimised on Binet stage, disease status (CR/VGPR/NPR) and whether achieved after first or second line therapy. For the French group, minimisation will also be on type of centre. After randomisation of the first 100 patients the data will be examined by the Independent Data Monitoring Committee (IDMC) to check the feasibility and safety of the protocol. After randomisation of 200 patients a formal interim analysis will be applied with respect to overall survival from randomisation and PFS from randomisation and reported to the IDMC, who will recommend modification or stopping of the trial only if, in their view, there is proof beyond

reasonable doubt that for all, or for some types of patients, one treatment is clearly indicated or clearly contra-indicated.

The analysis of QoL data will be by treatment allocated at randomisation. For each of the individual items in the QoL questionnaire adequate descriptive statistics will be provided. An overall sum score will be computed and used in a repeated measurements analysis of variance which allows for missing data (BMDP 5V or SAS Proc Mixed). Such analysis will be required since missing data are likely to arise in any prospective QoL trial that requires long-term follow-up due to patient death or physical incapacity. Summary questions in the QoL questionnaire (overall health and overall QoL) will be analysed separately in the same way. The two treatments will be compared both with respect to differences in average sum score and the slopes of the regression lines of sum score on follow-up time.

11 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An IDMC has been appointed by the Chronic Leukaemia Working Party (CLWP) of the EBMT. Toxicity data will be discussed at each meeting of the EBMT CLWP, but efficacy results will not be presented at group meetings before the trial is closed to recruitment.

12 QUALITY ASSURANCE

12.1 EBMT Data Centre

Randomisation will be carried out by the CTSU in Oxford who will inform the EBMT Data Centre in Leiden. Registration, Clinical Record Forms and Quality of Life forms will be sent out from the Data Centre. Data forms will be entered in the database of the EBMT Data Centre. Computerised and manual consistency checks will be performed on newly entered forms and query forms will be issued in cases with inconsistencies.

Consistent forms will be validated by the Data Manager and entered on the master database. Inconsistent forms will be kept "on hold" until full resolution of inconsistencies.

12.2 On site Centre

On site quality control will only be performed in cases with a high incidence of inconsistencies.

13 ETHICAL CONSIDERATIONS

13.1 Patients' protection

The responsible investigator will ensure that this study is conducted in agreement with either the declaration of Helsinki or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice, issued by the European Union. Local Ethical Committee approval must be obtained before starting the trial.

13.2 Subject identification

The name of the patient will not be asked by the principal co-ordinator. A sequential identification number will be automatically attributed to each patient randomised in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients initials (maximum of 4 letters), date of birth and local hospital patient number (if available) will also be reported on forms.

13.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol, whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study, before they are randomised. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. The patient information sheet and consent form are enclosed (appendices VI and VII)

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APPENDIX I: DEFINITIONS OF RESPONSE, PROGRESSION AND DISEASE REQUIRING THERAPY

Response⁽⁶⁸⁾

Complete Remission (CR) Cheson et al⁽⁶⁸⁾.

Is defined by

- Absence of lymphadenopathy
- No hepatomegaly or splenomegaly
- Normal FBC
 - Neutrophils $> 1.5 \times 10^9/l$
 - Haemoglobin $> 11g/dl$
 - Platelets $> 100 \times 10^9/l$
 - Lymphocytes $< 5 \times 10^9/l$
- Bone marrow trephine and aspirate containing $< 30\%$ lymphocytes (normal immunophenotype) with normal cellularity and absence of lymphoid nodules in trephine biopsy.

Very Good Partial Remission (VGPR)

VGPR is defined by

- Absence of lymphadenopathy exceeding 2cm
- No hepatomegaly or splenomegaly
- normal FBC
 - Neutrophils $> 1.5 \times 10^9/l$
 - Haemoglobin $> 11g/dl$
 - Platelets $> 100 \times 10^9/l$
 - Lymphocytes $< 5 \times 10^9/l$
- Trephine or aspirate
 - $< 50\%$ lymphocytes

Nodular Partial Remission (NPR)

Nodular PR is defined same as CR but with

- bone marrow trephine containing nodules of CLL cells.

Progression

Progression following a CR, a VGPR or NPR is defined as reappearance of leukaemic cells in the blood ($>10 \times 10^9/l$) or the finding of more than 50% lymphocytes in the BM, a 50% increase in lymph gland dimensions, or the development of hepatosplenomegaly ⁽⁶⁸⁾

Relapse can be suspected in case of unexpected cytopenia, and is obvious in the case of overt reappearance of circulating leukaemic cells. In any case, relapse must be documented by blood and BM smears. A diagnosis of extra-medullary relapse should be based on tissue diagnosis in case of clinical symptoms.

Event Free Survival

Event free survival is defined as survival from commencement of treatment within the protocol to disease progression, or death.

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Disease requiring therapy

Presence of at least one of the following symptoms:

- B symptoms
- symptomatic or progressive lymphadenopathy
- symptomatic splenomegaly
- progressive reduction of haemoglobin* and/or platelets* which in the view of the clinician requires treatment.

*exclude haemolysis and ITP

APPENDIX II: DEFINITION OF BINET STAGE

Stage	Organ enlargement*	Hb** (g/dl)	Platelets (x10⁹/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.

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. ≥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.

APPENDIX III: 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 IV: EVALUATION OF TOXICITY

Adverse events and side effects

All adverse events will be recorded on the case report forms; the investigator will decide if those events are transplant-related (unrelated, unlikely, possible, probably or almost definitely) and this decision will be recorded on the forms for all adverse events. Adverse events definitely not transplant related will not be considered as side effects or toxicity, but recorded separately.

General evaluation of side effects

Haematological toxicity will be assessed on the basis of at least weekly blood counts. Non haematological acute side effects will be assessed and reported separately according to the common toxicity criteria defined by the CTC-NCIC.

Toxic death is defined as death due to toxicity. This must be reported on the follow-up form. The cause of death must be reported as toxicity. The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

APPENDIX V: QUALITY OF LIFE (QOL)

The study will utilise the EORTC QLQ-C30 (version 3),¹ a leukaemia-specific module¹¹ and study specific items for known co-morbidity not assessed by the prior measures. This study questionnaire pack has been developed specifically for this study and should not be used for other purposes.

The following effects will be investigated:

- Physical functioning
- Psychological functioning
- Intellectual functioning
- Occupational functioning
- Sociability
- Sexual health
- Global health status
- Treatment specific co-morbidity

The study will be valuable in two ways:

- (i) Details of the consequences of the different leukaemia therapies will be available to assist with future decisions about choice of treatment.
- (ii) Greater awareness of the psychosocial side effects of leukaemia therapy will facilitate their management.

Eligibility

All patients entered into the CLL5 trial, able to complete a study questionnaire are eligible.

Centre Participation

Each centre that is entering patients into CLL5 will be contacted and invited to participate in the QoL study. If a clinician decides that a particular patient should not be asked to participate in the QoL study, or if the patient does not wish to participate, the reason(s) should be given and a brief assessment of the patient's background medical details will be requested from the clinician.

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Appendix V

Standard Procedure in the Local Centres.

1) Supply of Baseline Questionnaires.

The Baseline questionnaires can either be downloaded from the website in the centre or downloaded by the central co-ordinator and posted to the centres. They can also be made available by Email or as paper copies by the data centre in Leiden on request.

Each centre should ensure that they hold at least two Baseline questionnaires in reserve, so that they are readily available to give to the patient at randomisation.

Please ensure that

- 1) the pages are stapled together to form a booklet***
- 2) details of the local contact is printed on the front page so that patients know who to ask if they have any problems with the questionnaire***
- 3) the relevant return address is printed on the last page***
- 4) the patient's TRIAL NUMBER and the DATE is entered on the front page.***
- 5) a prepaid addressed envelope is available to give to the patient with the questionnaire.***

When the supply falls to the last questionnaire either download another one or request a further supply from the Central Co-ordinator.

2) Issue of Questionnaires at Randomisation

1. Identify eligible patients
2. Ensure eligibility criteria are met
3. Print the appropriate randomisation form and either contact Oxford by telephone or fax the form to Oxford (or (soon) email it to Oxford)
4. On receipt of the randomly allocated treatment from Oxford, fill in the patient registration form and fax or send it to Leiden Data Centre.

5. Enter the patient's TRIAL NUMBER and the DATE on the front of a baseline Quality of Life questionnaire and give it to the patient with a reply paid envelope. The patient should be asked to complete the questionnaires and post to the central co-ordinator in the envelope provided.
6. If for any reason the clinician doesn't feel it is appropriate to enter a particular patient into the Quality of Life study, or if a patient refuses to take part, an Investigators Form should be completed for that patient and sent to the central co-ordinator. (Investigator's Form to be downloaded from the Web Site., or it can be supplied by the Central Co-ordinator on request)

Quality of Life Questionnaires – General Guidelines.

Availability of QoL Questionnaires.

QoL Questionnaires in English, Dutch, French and Italian are now available on the website. They are .pdf files in an archive created with WINZIP.

Questionnaires can be made available to the centres in one of four ways.

1. Via the WEB SITE.

If the centres are able to access the website they can produce their own copies directly.

2. Via the country's CENTRAL CO-ORDINATOR, who will download the ZIP file from the website and print off copies to send to the centres.

3. Via EMAIL.

Copies of the questionnaires can be sent by email directly to the centres from the data centre in Leiden for the centres to print themselves.

4. Via the data centre in LEIDEN.

If necessary, paper copies can be produced by the data centre in Leiden and sent on to the centre.

The following points concerning the production of the questionnaires should be noted carefully.

- 1. When producing printed copies the pages should be stapled together to form a booklet. This will be easier for the patient to handle and avoid pages getting lost.***
- 2. The contact person's name for the country should be added to the front page of the questionnaire.***
- 3. The return address for the country should be added to the last page.***

4. Prepaid addressed envelopes should be provided for the return of the questionnaires to the central co-ordinator.

5. Before a questionnaire is given to a patient, the TRIAL NUMBER allocated by the randomisation centre in Oxford MUST be written on the front page of the questionnaire booklet, together with the date the booklet is being given.

Supply and Issue of Questionnaires at Follow-up

1. About one month before a follow up is due, a QoL follow up form with reply envelope will be received from the central co-ordinator for each patient randomized. This will have the patient's trial number recorded on the front cover. A reply paid envelope for return of the questionnaire to the central co-ordinator should be provided.
 2. The questionnaire and envelope will either:-
 - a) be given to the patient at a clinic visit (i.e. 4 month, 8 month, 12,24,36 and 48 months)
- or**
- b) be posted to the patient if for any reason the patient does not attend at the right time.
3. The patient will be asked to complete the questionnaire and post it to the central coordinator.
4. In the event of the patient not returning the questionnaire, the central co-ordinator will alert the centre so that either the patient can be encouraged to comply, or information regarding the reasons for non compliance can be reported on an investigator's form. (Investigator's Form to be downloaded from the Web Site., or it can be supplied by the Central Co-ordinator on request)

Content of Quality of Life questionnaires

As this is a prospective study the questionnaires have been designed to include different aspects at different time points, as follows: -

a) Baseline.

EORTC QLQ-C-30 version 3 ⁽¹⁾

- Demographics
 Patient's evaluation of questionnaire
- b) 8 weeks, 6 months, 1 year**
 EORTC QLQ C-30 version 3 ⁽¹⁾
 Leukaemia module ⁽²⁾
 Patient's evaluation of questionnaire
- c) 24 months**
 EORTC QLQ C-30 version 3 ⁽¹⁾
 Leukaemia module ⁽²⁾
 Late effects ⁽³⁾
 Sexuality and Fertility ^(3,4)
 Demographics (marital status and employment status only)
 Patient's evaluation of questionnaire

NB. Socio demographic data is being collected at baseline in the main trial. However, the demographics above are included to elucidate any changes in marital or employment status that occur as a result of the disease or its treatment.

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APPENDIX VI: MRC CLL5 PATIENT INFORMATION SHEET

Version 2, 26 Sept 2001

A Medical Research Council prospective randomised study to compare autologous stem cell transplant versus no further treatment in patients with high risk chronic lymphocytic leukaemia who have achieved a good response to treatment

Introduction

You are being asked to take part in a multi-centre randomised trial that is being conducted in many hospitals throughout the UK. It is run through the Medical Research Council and has been subject to ethical approval by your local hospital. This UK trial is part of a larger study taking place across Europe which is co-ordinated by the European Bone Marrow Transplant Group.

Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Background

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in western countries. It is a disease that affects the blood, lymph glands and bone marrow. You have high risk CLL which means that your life expectancy is shorter than it is for people without CLL. You have had a good response to treatment, but chemotherapy only rarely makes all the biological signs of the disease disappear. The current standard is that no further treatment should be given now even though some of these signs may still be present. It is very likely that the disease will recur at some point and autologous stem cell transplantation (a transplant using cells from your own body rather than from a donor) is often given then, as it can lead to the disappearance of all biological signs of the disease. With an autologous transplant certain cells in your own blood (called stem cells) are collected. You are then given high doses of chemotherapy and radiotherapy to destroy the remaining traces of leukaemia in your body. This also damages your body's healthy cells, but the collected cells are transplanted back into your bone marrow to help it recover. Currently we do not know if it would benefit more patients if autologous stem cell transplantation was given at the earlier stage that you are now at, rather than waiting until the CLL has progressed.

This trial is a comparison between no further treatment at present and an autologous stem cell transplant. Whether or not you receive a transplant 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. You have a fifty-fifty chance of being put in the autologous transplant group. We need about 300 patients with high risk CLL to participate in the trial for us to be able to tell reliably if autologous transplantation at this stage makes a difference to survival. Patients in the “no further treatment at present” group can still receive an autologous transplant at a later stage.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be asked to sign a consent form and given a copy of both it and this information sheet to keep. If you decide to take part you are still free to change your mind or withdraw at any time and without giving a reason. This will not affect the standard of treatment or care you receive. Your legal rights are not affected by giving your consent to take part in this study.

What does the trial involve for me?

If you agree to take part in this study you will be asked to have a clinical examination, blood tests, a chest x-ray, a heart function test and tests to see how well your CLL is being controlled (blood tests and a bone marrow biopsy).

You will then be randomised to either autologous transplantation or simple surveillance of the disease. After randomisation you will have a course of chemotherapy and we will remove stem cells from your blood (called harvesting) ready for use in an autologous transplant. This will be carried out even if you are put in the no further treatment group, for use if your disease progresses. In all cases your doctor will need to see you regularly to monitor your disease. A clinical examination, and blood tests will be done at each visit, which should be every 4 months in the first year and then every six months for the two following years. If you have a transplant then a bone marrow sample will also be needed every 4 months in the first year and then at six month intervals. Some of the blood and bone marrow samples will be used for medical research. You will also be asked to fill in a quality of life form at entry into the trial and at 4, 8, 12, 24, 36 and 48 months after this. It only takes a few minutes to complete and gives us valuable information about how your every day activities are affected by your disease and treatment.

	Randomisation	4 mths	8 mths	1 year	18 mths	2 years	30 mths	3 years	4 years
Blood test	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bone marrow*	Y	Y*	Y*	Y*	Y*	Y*	Y*	Y*	Y*
Quality of life form	Y	Y	Y	Y		Y		Y	Y

* Bone marrow samples other than the first one are requested only from patients receiving transplant.

What are the possible side effects?

The chemotherapy that you have already received has some side effects. The most common effects are

- a reduction in white blood cells which can be accompanied by fever and may require an antibiotic treatment
- a reduction in red blood cells (anaemia) which can cause fatigue and may require blood transfusion
- a reduction in blood platelets which may cause bleeding and require transfusions of platelets

The other side effects that can occur are nausea, vomiting, sores and problems with sensitivity in the lower limbs. There is a high risk that you will temporarily lose your hair.

Autologous transplantation and the high dose chemo- and radiotherapy that precede it also have side effects similar to those listed above, most common is an increase in the risk of infection both during and after the procedure. Irritation to the lining of the mouth and gullet is common (mucositis) and lasts about 7 days. The transplant will only be carried out in centres experienced in this type of treatment. Normally the blood count will recover in 14 days and patients can expect to be in hospital about three weeks for the autograft procedure. There is also a risk that transplantation can lead to death. In CLL the risk could be as much as 10%.

After autologous transplantation there is a high risk of permanent sterility therefore men will be given the opportunity to have sperm frozen. At present there is no generally available method for freezing the eggs of women although it is sometimes possible to freeze embryos. Your doctor will discuss these issues with you. It is possible that if a woman is pregnant when given a transplant it will harm the unborn

child. Pregnant women must not therefore take part in this study, nor should women who are breast feeding as this may also be harmful to the child. Women who are at risk of pregnancy may be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive during the course of this study. Effective contraceptives include the pill, barrier methods (e.g. condoms), hormonal implants, contraceptive injections, intrauterine devices and sterilisation. Any woman who finds that she has become pregnant while taking part in the study should tell her research doctor immediately. Women of childbearing age who receive a transplant will usually find that their periods stop after the transplant and hormone replacement treatment will be given if indicated.

Will my taking part in this study be kept confidential?

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. All personal information which is collected about you during the course of the research will be kept strictly confidential and will not be seen by anyone not involved in the study. You will not be identified in any report or publication.

For further information please contact:

Dr Don Milligan on 0121 424 3699
or
Professor D Catovsky on 020 7808 2880

Given as an example: each hospital will provide the corresponding local information

Thank you for considering taking part in this study.

APPENDIX VII: PATIENT CONSENT FORM

Study Title: MRC CLL5 - A Medical Research Council prospective randomised study to compare autologous stem cell transplant versus no further treatment in patients with high risk chronic lymphocytic leukaemia who have achieved a good response to treatment

	Yes	No
I have read the patient information sheet for this trial and have received a copy to keep.	<input type="checkbox"/>	<input type="checkbox"/>
I have been given the opportunity to ask questions about the trial and have received satisfactory answers to all of my questions.	<input type="checkbox"/>	<input type="checkbox"/>
I am aware that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	<input type="checkbox"/>	<input type="checkbox"/>
I accept that some of the blood and bone marrow samples taken may be used for biomedical research.	<input type="checkbox"/>	<input type="checkbox"/>
I give permission for responsible individuals from the trial research team and regulatory authorities to review my medical records.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that information which identifies me will be kept confidential to those concerned with my care and the trial research team.	<input type="checkbox"/>	<input type="checkbox"/>
I give permission for the anonymised information provided for the trial to be used in future medical research.	<input type="checkbox"/>	<input type="checkbox"/>
I agree to take part in the above study	<input type="checkbox"/>	<input type="checkbox"/>

Patient:

Name: Signature Date:
(Name In Block Letters)

Investigating doctor:

Name: Signature Date:
(Name In Block Letters)

Witness:

Name: Signature Date:
(Name In Block Letters)

Appendix VIII

SERIOUS ADVERSE EVENT REPORTING

In this trial it is important that *unexpected* serious adverse events are reported immediately to the Chief investigators.

DEFINITION OF A SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined as any untoward medical occurrence at any dose that:

- Is fatal
- Is life threatening (defined as an immediate risk of death from the event as it occurred)
- Results in persistent or significant disability or incapacity
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (Exception: Hospitalisation for elective treatment of a pre-existing condition that did not worsen during the study is *not* considered an adverse event. NOTE: complications that occur during hospitalisation are adverse events and if a complication prolongs hospitalisation, then the event is serious)
- Is a congenital anomaly/birth defect in the offspring of a patient who has received study medication
- Though not included in the above definitions, may jeopardize the patient or may require intervention to prevent one of the outcomes listed above unless clearly related to current disease

The investigator should exercise medical and scientific judgement when deciding whether expedited reporting is appropriate in other situations not strictly meeting the criteria outlined above.

SERIOUS ADVERSE EVENTS AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSARS) SHOULD BE IMMEDIATELY REPORTED TO THE GROUP'S CHIEF INVESTIGATORS (MRC: Dr D. Milligan)

SAE forms can either be downloaded from the EBMT website or made available by e-mail from the CLL V Trial Manager (UK)

SAE/SUSARS to be faxed to :

Dr Donald Milligan on 0121 766 7530 or CLL V Trial Manager (UK) on 0121 424 3155