Objective:

To investigate, in a randomized controlled trial, the role of bone marrow transplants in adults aged 20-55 years with Philadelphia negative Acute Lymphoblastic Leukaemia (ALL), and in adults up to the age of 65 years with Philadelphia positive ALL. Among patients with Philadelphia negative ALL, the outcome of treatment with allogeneic transplantation will be compared with either myeloblastic chemo radiotherapy (VP16+TBI) with autologous transplantation or intensive consolidation and maintenance chemotherapy. Patients with Philadelphia positive Acute Lymphoblastic Leukaemia (detected either cytogenetically or by molecular biological) methods will be eligible to receive the oral tyrosine kinase inhibitor, Imatinib and an allogeneic bone marrow transplant from a matched unrelated donor (MUD) / Haploidientical donor.

WARNING

(1) This document is intended to describe a Medical Research Council collaborative study in acute lymphoblastic leukaemia in adults, and to provide information about procedures for entering patients. The Council does not intend the protocol to 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. Before entering patients into the trial, clinicians must ensure that the trial protocol has received clearance from their local ethical committee.

(2) NEVER give intrathecal and intravenous chemotherapy to the same patient, on the same day.

Clinicians are asked to read the whole protocol before commencing treatment.
ACUTE LYMPHOBLASTIC LEUKAEMIA IN ADULTS
Revised MRC UKALL XII/ECOG E2993

Please register all patients by telephone (01865-765615) as soon as possible after diagnosis, when informed consent has been obtained.

START TREATMENT

Establish Philadelphia status of patient and report this to CTSU as soon as possible – contact details below. Please note that Imatinib administration now begins with Phase II of induction. Ph status must be established quickly and reported to CTSU in order to receive drug supply on time.

Philadelphia positive:
Follow Philadelphia positive arm of trial, including use of Imatinib

Philadelphia negative:
Continue on main protocol treatment.
If no related donor available, telephone for randomisation between autograft and chemotherapy before the end of intensification.

Forms: When you telephone CTSU with the patient’s Ph status, a record book will be sent to you. Alternatively these are available from the CTSU web site (www.ctsu.ox.ac.uk) under leukaemia trials, UKALLXII, or can be obtained from CTSU on request.

Contact details: Phone: 01865 765615
Fax: 01865 743986
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ABBREVIATIONS

Auto BMT  Autologous Bone Marrow Transplant
Allo BMT  Allogeneic Bone Marrow Transplant
ALL     Acute Lymphoblastic Leukaemia
AT III  Anti-thrombin III
BFM     Berlin-Frankfurt-Munchen group
BMT     Bone Marrow Transplant
CFU-GM  Colony forming unit – granulocyte/macrophage
CI      Chief Investigator
cGY    centiGray
CML     Chronic Myeloid Leukaemia
CMV    Cytomegalovirus
CNS    Central Nervous System
CR     Complete Remission
CSA    Cyclosporin
CTSU   Clinical Trial Service Unit
DDX    Doctors and Dentists Exemption Certificate
DMC    Data Monitoring Committee
EBMT   European Bone Marrow Transplant group
ECOG   Eastern Cooperative Oncology Group
EFS    Event Free Survival
EORTC European Organisation for Research and Treatment of Cancer
FAB    French American British
FISH   Fluorescent In Situ Hybridisation
GFR    Glomerular Filtration Rate
GVHD   Graft versus Host Disease
HDMTX  High Dose Methotrexate
HGF    Haemopoetic Growth Factor
HHV6   Human Herpes Virus 6
HLA    Human Leucocyte Antigen
MRC    Medical Research Council
MRD    Minimal Residual Disease
MTX    Methotrexate
MUD    Matched Unrelated Donor
NSAID  Non Steroidal Anti Inflammatory Drug
OS     Overall Survival
PBSC   Peripheral Blood Stem Cells
PBSCCT  Peripheral Blood Stem Cell Transplant
PCP    Pneumocystic Carnii Pneumonia
PCR    Polymerase Chain Reaction
Ph +ve Philadelphia positive
Ph –ve  Philadelphia negative
PI     Principal Investigator
PSCR   Peripheral Stem Cell Rescue
PTT    Partial Thromboplastin Time
SAE    Serious Adverse Event
TBI    Total Body Irradiation
VP16   Etoposide
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References
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1. ETHICAL CONSIDERATIONS

The Trial Protocol must be approved by the local ethical committee before patients are entered. A statement of MRC policy on ethical considerations in the clinical study of cancer therapy, including the question of informed consent, is available from the Cancer Therapy Committee Secretariat, MRC Head Office, 20 Park Crescent, London WI IN 4AL, and may be used to give guidance to participating investigators and to accompany applications to the local ethical committee. Information on ethical considerations in clinical research is also available from the MRC website at www.mrc.ac.uk.

The right of a patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if it is felt to be in the patient's best interest, and the reason for doing so should be recorded. Similarly, the patient must remain free to withdraw at any time from protocol treatment without giving reasons and without prejudicing any further treatment. In either case, the patient will need to remain within the study for the purposes of follow-up and data analysis.

2. OBJECTIVES

2.1 Philadelphia negative

2.1.1 To conduct a randomised controlled trial comparing the effect of marrow ablative therapy using VP16 and total body irradiation (VP/TBI), followed by autologous bone marrow rescue (Auto BMT or Peripheral Stem Cell Rescue) with conventional consolidation and maintenance chemotherapy in adult patients with Philadelphia negative ALL aged between 20 and 55 years inclusive who have no HLA compatible donor.

2.1.2 To examine, in a non-randomised study, differences in outcome in adult ALL in those patients who have an HLA compatible donor, who will be allocated allogeneic BMT (Allo BMT), versus those without an HLA compatible donor, who will be randomised to autologous transplant or conventional chemotherapy.

2.2 Philadelphia positive

2.2.1 To compare the outcome of allogeneic transplant (including matched unrelated donor (MUD) and Haploidentical transplant) and autologous transplant in patients with Philadelphia chromosome positive disease, as defined by either cytogenetics or molecular biology in patients aged between 15 and 65 years.

2.2.2 To establish the effect on EFS and OS of Imatinib, given in addition to chemotherapy, during phase 2 induction, consolidation and as maintenance after allogeneic or autologous transplantation. Please note for Philadelphia positive patients the upper age limit is 65 years.

3. BACKGROUND

Adult patients with acute lymphoblastic leukaemia (ALL) currently have a 75% chance, or better, of entering complete remission (CR) with modern chemotherapy. \(^{(1-3)}\) Most patients, however, eventually relapse \(^{(4-8)}\). The best approach to prevent relapse through consolidation therapy is controversial. Results with chemotherapy given as an intensive consolidation followed by maintenance therapy have been highly variable with reported 5-year disease-free survival rates in the range of 10% to 42% \(^{(1-3, 9,10)}\). Patients exhibiting a high risk for relapse - defined as age more than 35 years, leucocyte count at diagnosis greater than 30 x 10\(^6\)/l, presence of Philadelphia chromosome and achievement of remission after more than 4 weeks
of intensive chemotherapy - have an overall probability of continuous CR at 5 years of only 18-28%. This result compares poorly with the few patients without any of these adverse features, who have a 60% 5-year event-free survival (EFS)\(^{(2-3)}\).

Use of allo BMT in first CR of ALL results in a 40-63% EFS for 2-10 years\(^{(11-13)}\). The actuarial relapse rate for this group ranged from 10%-40% with more than 90% of the recurrences occurring within the first two years. Allo BMT, however, is only available for the one third of patients who have a histocompatible sibling. The benefit of allo BMT also declines with increasing age due to the heightened risk of death from infection and the increasing frequency and severity of graft versus host disease (GVHD)\(^{(14-16)}\). In one recent study, older age (>18 years) was the predominant clinical factor associated with acute GVHD\(^{(17)}\). Of adults with ALL, more than 50% are over 40 years old and this age group is less frequently referred for allogeneic BMT because of the substantial hazards.

Auto BMT or autologous peripheral stem cell transplant (APSCT) is an alternative approach to allogeneic transplantation. Auto BMT does not require a histocompatible donor, lacks the risk of GVHD, and can be used more safely in patients over 40 years old. Although auto BMT permits the same intensive therapy as allogeneic transplant, it lacks the potential benefit of graft versus leukaemia, which in humans is associated with GVHD\(^{(15-16)}\). In addition, the patient's remission marrow may well contain occult leukaemic cells that may be reinfused after preparative therapy is completed.

Auto BMT in the European Bone Marrow Transplant (EBMT) experience of more than 200 patients has shown a 41 % EFS rate at 56 months for standard risk patients transplanted in first CR, with no statistically significant difference between purging and non-purging\(^{(21)}\) of the marrow. The 4-year probability of relapse was only 26% ± 12% (95% confidence interval) in this group\(^{(22)}\). More recently Carey et al. reported their auto BMT results for lymphoma and ALL without purging\(^{(23)}\), where the actuarial EFS in the 13 patients with ALL in first CR receiving auto BMT was 48% with a follow-up of 3 years. Gilmore et al. reported a 32% EFS at 7 years among 27 high risk ALL patients suggesting that in vitro purging appeared not to improve patient outcome\(^{(24)}\). Thus, auto BMT in ALL without purging can be highly effective and the value of purging has never been clearly defined.

To date randomised trials aimed at establishing the value of BMT versus chemotherapy in first CR ALL are few and too small to be able to detect a moderate difference, but final results from these trials are not yet available. The retrospective comparison of chemotherapy and allo BMT in two cohorts of German patients, showing no benefit of one treatment over the other has significant flaws and failed to identify all sources of bias in comparing the groups in this fashion\(^{(25)}\).

4. **TRIAL DESIGN FOR PHILADELPHIA NEGATIVE PATIENTS ONLY**

*(See section 16 for Philadelphia positive patients)*

All eligible patients will receive a uniform induction therapy based on the successful German protocol\(^{(1-10)}\). The modification is in accord with the risk-adapted German multicentre trial which has complete remission rates of 80%. All patients will receive a course of high-dose methotrexate to decrease both the risk of CNS relapse and the potential bone marrow contamination with residual disease at the time of marrow harvesting\(^{(27,28)}\).

Patients will then proceed to bone marrow harvest or collection of peripheral blood stem cells (P.B.S.C.s) Small aliquots of bone marrow/stem cells should be sent for molecular and genetic monitoring. Patients who are under 50 years, have an HLA compatible donor, and who are considered suitable by the local transplant centre, will then be allocated to receive an allo BMT. Exceptionally, patients between the ages of 50 and 55 years inclusive, may also be allocated to receive an allo BMT. All other patients will be randomised either to myeloablatative chemoradiotherapy with autologous transplant OR four courses of intensive consolidation and maintenance chemotherapy.
5. JUSTIFICATION FOR TREATMENT OPTIONS

Modern chemotherapy of a variety of kinds gives adult patients an 80% chance or better to enter complete remission although most patients eventually relapse, despite intensive consolidation chemotherapy followed by maintenance therapy for a period of around two years after remission achievement (3). Since the Berlin-Frankfurt-Munchen group (BFM) results are the best hitherto reported for adult ALL a modification of this regimen has been chosen for this cooperative study.

5.1 High-dose methotrexate

In a programme which includes transplantation, both autologous and allogeneic, overall dose intensity must be maintained throughout the protocol and consolidation must follow quickly after induction, and transplant in turn quickly after consolidation. If CNS irradiation is to be delayed because of the possibility of receiving TBI as part of a transplant operation then at least one of the consolidation courses should be effective CNS as well as systemic therapy. The alternatives are high-dose methotrexate or high-dose cytosine arabinoside. Initial preliminary data from the EORTC group appear to suggest that following high-dose cytosine arabinoside haematological recovery was delayed in some patients. This gave the possibility that we would be unable to standardise the time from this high-dose therapy to transplant, either autologous or allogeneic. For that reason, high-dose methotrexate was selected as the late consolidation module pre transplant.

5.2 Consolidation and maintenance therapy

Prevention of relapse is the essential issue in the management of adult ALL and the precise role of consolidation with early intensification and long term maintenance therapy is still somewhat unclear. However, again, best overall results for adult ALL occur with protocols such as the BFM (1,10).

5.3 Myeloablative therapy with ABM or PBSC rescue

As detailed in “Background” (Section 3), the fraction of ‘cured’ patients following auto BMT performed in first remission compares favourably with results of the same group of patients treated with either allo BMT or with conventional chemotherapy. The best form of myeloablative treatment is not firmly established. For patients in first remission however, the preferred choice seems to indicate total body irradiation since better results have been achieved with this than with other myeloablative regimens. It is possible that Bulsulphan/Cyclophosphamide might achieve similar clinical results but there is insufficient evidence to confirm this. Myeloablative therapy with auto BMT or PBSCT in first remission would have the additional benefit of considerably shortening the total therapy to around six months (see Section 10.3). Thus even if there were similar overall and disease-free survival for the auto BMT group compared to those in the conventional chemotherapy group, most patients in the auto BMT group would have been treated for a considerably shorter period of time. Thus for many reasons, auto BMT only has to be as good as conventional chemotherapy and not necessarily better. On the other hand, the long term effects of TBI in survivors may be significant in comparison with any seen after consolidation and maintenance chemotherapy: for example, infertility is inevitable. VP16 has been chosen in this protocol as an adjunct to total body irradiation. The best results of transplant in adult ALL come from the Stanford group of Blume who initially described using TBI/VP16 as their transplant ablation protocol (27,28,30).

5.4 Total Body Irradiation (TBI)

Total body irradiation has an accepted role in the conditioning regimens of BMT for acute lymphoblastic leukaemia, as described in section 5.3 (above).
Further practical details relevant to the administration of TBI in this protocol are given in section 15.6.

5.5 **Allogeneic transplantation**

All suitable patients less than 56 years with a fully matched donor will be eligible to proceed to myeloablative therapy and allogeneic transplant in their first remission. As discussed above, the use of allo BMT in first CR of adult ALL results in a 40-60% disease-free survival for 2-10 years \(^{11-13}\). These patients had a lower actuarial relapse rate which ranged from 10-40% and more than 90% of the recurrences occurred within the first two years. The problems of allogeneic transplant are that only a small number of patients have a fully histocompatible sibling, perhaps one third to one quarter.

In addition to this problem, the benefits of allogeneic transplant may decline with increasing age because of transplant related risk from infection and graft versus host disease. Adult ALL patients of more than 40 years of age are less frequently referred for allo BMT because of the substantial hazards. In this trial by offering allo BMT to those patients with fully histocompatible siblings we will be able to investigate whether the risk of the transplant might outweigh the benefits of shortening the treatment. The influence of the effect of age on BMT will also be assessed.

5.6 **Management of Ph+ve patients (see also Section 16).**

Patients who are Ph+ have a very poor prognosis even with intensive chemotherapy\(^2\). There have, however, been some patients who have survived free from relapse long term after an allogeneic or MUD BMT. It is anticipated that even the use of auto BMT or intensive chemotherapy may be of limited benefit. The specific bcr-abl Tyrosine kinase inhibitor, Imatinib is now available for study in Ph+ patients and there is increasing evidence of its safe use and possible benefits when co-administered with ALL-chemotherapy (see Section 16). This amended protocol incorporates Imatinib into the treatment schedule of Ph+ve patients at an earlier time-point, i.e. during phase 2 induction.

6. **INCLUSION AND EXCLUSION CRITERIA**

6.1 **Eligibility for the trial**

1. **Patients aged between 20 and 55 years inclusive with previously untreated acute lymphoblastic leukaemia are eligible.** All such patients must be screened cytogenetically for Ph+ chromosome and by PCR for BCR-ABL oncogene for Philadelphia positive ALL (see Section 16). Please note for Philadelphia positive patients the upper age limit is 65 years

2. Patients must have morphological proof of ALL and diagnosis must be made from bone marrow morphology with greater than 25% lymphoblasts by the FAB criteria.

6.2 **Exclusions from the trial**

1. Patients with prior malignancy for which chemotherapy or radiotherapy has been given are ineligible.
2. Patients with AML, MDS or other antecedent haematological disorder, or lymphoid transformation of chronic myeloid leukaemia are ineligible.
3. All patients should be previously untreated although previous corticosteroid therapy is acceptable.
4. Patients with intercurrent life threatening disease will be excluded.
5. Pregnant or lactating women will be excluded.
6.3 Eligibility for randomisation

Patients less than 56 years of age without a compatible sibling will be RANDOMISED to receive either auto BMT or PBSCT without purging - using the same conditioning regimen as the allogeneic transplant or to receive further intensive consolidation/maintenance chemotherapy. Patients between 50 and 55 years of age who have a compatible sibling, may also be randomised between autologous transplantation or further chemotherapy, if they are considered to be unsuitable for an allogeneic transplant.

6.4 Exclusions from randomisation

1. Patients less than 50 years of age with a compatible sibling will be eligible for allogeneic bone marrow transplant using high dose VP16 and TBI as conditioning regimen. These patients will be assigned to receive this mode of therapy unless they decline it. Exceptionally patients aged 50-55 years could be considered at the discretion of their physician and local transplant centre. (see Section 6.3).

2. Patients who have had craniospinal irradiation as treatment for CNS disease are not eligible for randomisation or allograft because of the neurotoxicity associated with TBI and should follow the chemotherapy arm (see Section 11.5). Such patients should be discussed with a Coordinator.

7. PROCEDURE FOR ENTRY INTO THE TRIAL AND DIAGNOSTIC SAMPLES REQUIRED

7.1 Patient Registration

Patients fulfilling the criteria for admission to the trial (see Section 6) should be entered into the trial by ringing the Clinical Trial Service Unit (CTSU) in Oxford; telephone number 01865 765615. There is one randomisation point, i.e. the randomisation between Auto BMT (or PBSCT) and conventional chemotherapy and this applies to all patients, apart from those for whom an allogeneic BMT is planned following remission and consolidation.

Registration for UKALL12 will now be immediately after diagnosis. Changes to the registration procedure have been made to avoid any possible bias that could be introduced by a failure to register patients who begun induction therapy but suffered an early demise. This change does mean that a patient’s Philadelphia status will not be known at trial registration. This should be reported by telephone as soon as it is known so that the correct record booklet can be sent out and arrangements can be made for Imatinib, free of charge, to be supplied for patients with Ph+ve disease.

The information required at the time of registration is:

1. Name of physician in charge of patient
2. Patient's full name
3. Sex
4. Date of birth
5. Highest WBC pre-treatment
6. Known to have CNS involvement: Yes / No / Not known
7. Date treatment started
8. Is cytogenetic and molecular analysis being done locally?
9. When Philadelphia status is known, telephone to report it. You will be asked again for the immunophenotype, if it was not previously known.

A patient record book will be despatched at the time of registration.
7.2 **Diagnostic material**

CTSU will remind you to send the following samples, which should be taken before treatment begins. **THIS IS OBLIGATORY. All patients must have morphological, immunological, cytogenetic and molecular assessment.** Whenever cytogenetics or molecular biology cannot be done locally, samples will be processed centrally. Immunophenotyping should be carried out locally.

Blood and bone marrow samples should be sent so as to ensure delivery within 24 hours. Samples due to be dispatched on a Friday please ring both contacts (see below), so that arrangements can be made for their collection.

7.3 **Morphology**

It is no longer necessary for morphology to be examined centrally. Participants are therefore now asked only to store 6 unfixed, unstained slides from each patient. Although subsequent use is unusual, stored slides can be a vital source of material for future use.

Immunophenotyping by flow cytometry is important to differentiate between T-Cell, B-Cell and null cell ALL. This should be carried out locally.

7.4 **Cytogenetics**

Cytogenetics and molecular genetic analysis is important to establish early on the presence or absence of Philadelphia positivity (Ph+) and to delineate other important prognostic subgroups of adult ALL.

Cytogenetic analysis will be an important aspect of the final assessment of the trial; it is therefore crucial that optimum techniques are employed. If this can be achieved in the local centre, the result should be sent to the CTSU as soon as possible. Central cytogenetic analysis can be provided by Dr Christine Harrison at the LRF database, who has a coordinating and advisory role for the cytogenetic analysis in this trial. Where analyses are performed locally, extra material should be stored locally for subsequent trial purposes.

7.5 **Molecular genetic analyses: Minimal Residual Disease (MRD) assays - screening and monitoring for bcr-abl and other abnormalities**

The BCR-ABL translocation and many other relevant genetic abnormalities can be detected by PCR assay. This method is very sensitive and can detect low levels of leukaemic cells and can often be quantitative. This assay will be performed in the laboratory of Dr Letizia Foroni. Assays for various other chromosome translocations are also carried out, if appropriate specimens are received. All molecular data will be coordinated with cytogenetics for each patient. Specific consent for storage and banking of this material is required as part of the consent process for patient entry into the trial. Please use the patient consent sheets prepared for the trial.

**Sample collection should be collected at the time-points indicated on the diagram (page 52). PLEASE NOTE THAT RECEIPT OF SPECIMEN AT PRESENTATION IS VITAL FOR SUBSEQUENT MRD MONITORING**

*Blood:* 10 ml of blood in EDTA should be taken and sent to Dr Foroni

*Marrow:* A total of 2.5 ml of bone marrow in EDTA to Dr Foroni

**BCR-ABL PCR Assay**

10 ml blood
2.5 ml marrow

To: Dr Letizia Foroni
Department of Haematology
Royal Free Hospital School of Medicine
Pond Street
London NW3 2QG
8. PROCEDURE FOR RANDOMISATION

Randomisation of Philadelphia negative patients with no sibling donors, and patients 50 years or above who are unfit for allogeneic transplantation, will occur around weeks 10-11. These patients must be in remission; they will be randomised to an autologous transplant (peripheral blood stem cells or bone marrow) (PBSCT or auto BMT), or chemotherapy which includes CNS prophylaxis, four courses of consolidation and maintenance chemotherapy (auto BMT vs chemo). Patients eligible for randomisation but not randomised are excluded from the main trial comparison but the CTSU should be notified of patients' details and of the specific line of therapy chosen. The reasons for not randomising a patient should be few but must be documented clearly on data collection form. This might include significant heart or lung problems but if in doubt call one of the clinical co-ordinators.

Information required at the time of randomisation:

1. Patient's UKALL XII trial number or full name and date of birth.
2. Date of achievement of remission.
3. Number or name of centre at which BMT is to be performed if allocated.

Randomisation cannot be carried out unless these details are provided.

9. PLAN OF TREATMENT

9.1 Remission induction therapy

Allopurinol should be given as soon as possible after diagnosis as a daily dose of 300 mg per day by mouth and continued until at least day 29 of the first phase of chemotherapy. All patients will receive phase I and phase II of induction chemotherapy. Patients not in complete haematological remission at the end of phase I will continue into phase II induction therapy. Patients who have not achieved a complete remission at the end of phase II should be taken off study and receive further (non-study) treatment at the discretion of their clinician.

9.2 Induction drug administration schedule

Two phases (I & II) of induction chemotherapy are used. Doses are calculated on a corrected ideal weight basis for obese patients and on a real weight basis for other patients, whichever is less. Ideal body weight can be measured using different formulae, (one suggestion can be found in Appendix 3)

9.2.1 Induction chemotherapy Phase I

NEVER GIVE INTRATHecal AND INTRAVENOUS CHEmOTHERAPY ON THE SAME DAY.

Daunorubicin 60 mg/m² i.v. by slow i.v. infusion on days 1,8,15 and 22. May be given as a slow IV bolus if the patient has no central access.

Vincristine 1.4 mg/m² (maximum 2 mg) by i.v. push on days 1,8,15 and 22.

Prednisolone 60 mg/m² p.o. (either enteric-coated or not) daily on days 1-28 in 3 divided doses inclusive. Prednisolone can be stopped or dose tailed (physician's choice).

Allopurinol 300 mg daily p.o. days 1-29 inclusive.

Asparaginase (E.coli) medac 5,000 iu/m² on days 17, 19, 21, 23, 25, 27, 29 (7 doses in total) A test dose of 1000 iu intradermally should be administered before treatment commences.

Prevention of L-asparaginase induced thrombophilia: Particularly in the pilot study, but also in a number of patients in the trial, there have been instances of serious thrombotic problems, particularly within the central nervous system. At present, no trial patients have died because
of this complication. The following advice regarding management of asparaginase-induced thrombophilia is recommended:

Levels of anti-thrombin III (ATIII) and/or fibrinogen and/or partial thromboplastin time (PTT) should be monitored while the patient is receiving the 12 days of L-asparaginase. Levels should be monitored at least twice during this period. It is suggested that if the level of fibrinogen is below 0.8 g/litre and/or the level of ATIII is below 70% and/or the PTT is >70 seconds at any time after day 8 of L-asparaginase, then replacement therapy with fresh frozen plasma will be given.

**Methotrexate 12.5 mg intrathecally and CSF examination** on day 24 only (except in patients with CNS leukaemia at diagnosis - see Section 11).

### 9.2.2 Induction Treatment Plan

Bone marrow aspiration and biopsy should be performed on day 28 or on recovery of counts. Irrespective of remission status, the protocol treatment should continue and Phase I should be initiated on day 29 or when white cell count is greater than $3.0 \times 10^9$/L. All Ph+ve patients should have repeat cytogenetic and molecular biological analysis at this time and MRD to be sent to Letizia Foroni at Royal Free Hospital.

### 9.2.3 Induction Chemotherapy Phase II

**NEVER GIVE INTRATHecal AND INTRAVENOUS CHEMOTHERAPy ON THE SAME DAY.**

For patients with Ph positive disease, Imatinib will now be given with Phase II induction, please see section 16.

Phase II should begin on day 29 following initiation of induction Phase I. However it should be postponed until the white count is greater than $3.0 \times 10^9$/L in patients with delayed haematological recovery. Phase II consists of the following:

- **Cyclophosphamide** 650 mg/m² i.v. in 250 ml of normal saline over 30 minutes on days 1,15 and 29 of Phase II.
- **Cytosine arabinoside** 75 mg/m² i.v. in 100 ml of 5% Dextrose or Normal Saline over 30 minutes per day on days 1-4 inclusive, 8-11 inclusive, 15-18 inclusive and 22-25 inclusive of Phase II.
- **6-mercaptopurine (MP)** 60 mg/m² p.o. daily on days 1-28 inclusive of Phase II.

**INTRATHECAL METHOTREXATE IS NEVER GIVEN ON THE SAME DAY AS INTRAVENOUS CHEMOTHERAPY**

Methotrexate 12.5 mg intrathecally on days -1 (Day -1 refers to the day before commencement of phase II), 7,14 and 21 of Phase II with no folinic acid (Leucovorin) rescue.

**CSF examination to be done with each dose of IT methotrexate.**

### 9.2.4 Prevention of *P* carinii infection during Phases I & II

There has been a significant number of infections during the prolonged period of cytopenia experienced during the first and second blocks of treatment. In particular, there has been a significant incidence of pneumocystis and aspergillus.

**PCP prophylaxis:** In relation to pneumocysts prophylaxis, it is recommended that patients receive Co-trimoxazole 960 mg b.d. 3 times per week, but if the WBC does not tolerate this then inhaled Pentamidine at a dose of 300 mg every 4 weeks or 150 mg every 2 weeks is recommended. Specific equipment and facilities are required for this treatment. Hepa air filtration is desirable.
9.2.5 Prevention of Fungal Infection

Patients with prolonged neutropaenia and/or receiving high dose steroid therapy are at risk of invasive fungal infections.

Participants should consider seriously either 1) the use of prophylaxis against fungal infections and/or 2) very early institution of anti-fungal therapy in febrile episodes, for example, consider introducing empirical anti-fungal therapy within 72 hours of a fever which is clearly not resolving with first-line antibiotic therapy. Participants should adhere to whatever are their local policies regarding choice of anti-fungal prophylaxis and therapy.

However, please note that a serious interaction between the triazole antifungals (itraconazole, voriconazole) and vincristine should be taken into account. Metabolism of vincristine is inhibited by either of these two drugs and neurotoxicity can be potentiated. These drugs ought not to be given together.

9.3 HLA typing and donor search

This should be done as soon as possible where relevant following Phase I of induction chemotherapy in relation to matched sibling donors or matched unrelated donors. Typing and donor search may need to be done during or after Phase II in patients without CR at the end of Phase I.

9.4 Definition of remission

The bone marrow aspirate should be normocellular, contain less than 5% blast cells and show evidence of normal maturation of other marrow elements, or, <5% blasts with reduced cellularity if the peripheral blood count is normalising.

For patients with partial remissions, i.e. 5-25% (BM2) blast cells, after Phase II of therapy the treatment will be deemed to have failed. These patients are not eligible for randomisation though might still be treated with high dose methotrexate and L-asparaginase and continue on one of the protocol treatments.

9.5 Randomisation to Auto BMT or PBSCT versus chemotherapy

Patients without an HLA matched sibling will be randomised between transplant and chemotherapy during week 10 or 11, i.e. after completion of Phases I and II of the induction therapy and prior to the intensification module. Randomisation at this point will allow a further month (during intensification) to organise referral, if required, to a transplant centre.

9.6 Intensification module with high dose methotrexate

The intensification module begins two weeks after completion of Phase II of induction, i.e. at the beginning of week 11, and ends in week 14. However, it should be postponed until the white cell count is greater than 3.0 x 10^9/L and platelets greater than 100 x 10^9/L in those with delayed haematological recovery. The intensification module consists of three separate pairs of injections of high dose methotrexate and L-asparaginase. (For guidelines on the administration of high-dose methotrexate and folinic acid rescue, see Appendix 1.)

Methotrexate 3 g/m^2 i.v. on days 1, 8 and 22 of the intensification course (see Appendix 1).
Asparaginase (E.coli) medac 10,000 iu i.m. on days 2, 9 and 23 of the intensification course.
(NB this is a flat dose rather than calculated on surface area.
(See appendix 3, section 1, for details of test dose)
Leucovorin rescue 15 mg/m^2 i.v. in 50 ml of 5% Dextrose, or as an IV bolus 36 hours after the beginning of the methotrexate infusion and then for at least 72 hours depending on the methotrexate level (see Appendix 1). Oral therapy can be given for the 2nd and subsequent doses if the patient is not vomiting.
The following measures should be given to limit nephrotoxicity and mucositis with high dose methotrexate

1. Urinary alkalinisation to a pH of >7.0 is achieved by the administration of sodium bicarbonate (see Appendix 1).
2. The patient should be hydrated with at least 3 litres of i.v. fluid per day before, during, and after each course.
3. If the serum creatinine increases by more than 50% above baseline at 24 hours and/or the methotrexate level is greater than 5 x 10^{-6} M then the leucovorin rescue is increased (see Appendix I).
4. Recommendations for methotrexate dose modifications in cases of impaired renal function before 2nd and 3rd infusions
   - GFR >50 ml/min: No dose adjustment necessary.
   - GFR 10-50 ml/min: Use HALF dose.
   - GFR <10 ml/min: DO NOT GIVE.

9.6.1 Recommendations if methotrexate is delayed
A number of patients have had to have either one or all of these methotrexate doses delayed. If there is a delay, the following is recommended:

Delay for one week, and if the blood count has still not reached the required level of white cell count 3.0 x 10^{9}/L and platelets >100 x 10^{9}/L then perform a bone marrow aspirate to confirm continuing remission. If remission is confirmed, give rhG-CSF (Lenograstim) until the counts reach the required level, and then proceed. If this strategy still leads to a delay of more than 2 weeks in the course, it is recommended that a coordinator is consulted. We will usually recommend that 50% of the methotrexate dose is given provided there is at least some degree of bone marrow function at the time.

10. ARRANGING THE BONE MARROW or PERIPHERAL BLOOD STEM CELL HARVEST

10.1 Criteria for bone marrow or PBSC harvest
All patients who have achieved CR, and have received Phases I and II of induction chemotherapy and intensification with high dose methotrexate and L-asparaginase and who remain in 1st CR should be harvested. Bone marrow harvest will be carried out as soon as possible after recovery of neutrophils to 1.0 x 10^{9}/L and platelets to 100 x 10^{9}/L from the third high dose methotrexate/ asparaginase, i.e. the week 14 course. It is hoped that the period between the start of intensification and the first day of TBI for a transplant patient will not exceed 7 weeks. Randomisation to immediate transplant or not should already have been made about four weeks previously. This should allow a month or more for arrangements to be made for the bone marrow harvest and the transplant. In the event of any difficulties in the arrangements for bone marrow harvest, contact a Clinical Coordinator. It is very important to ensure that once a randomisation is made it is complied with.

10.2 Bone marrow harvest
Harvest of 1.0 x 10^{8}/kg nucleated cells from multiple bone marrow sites will be deemed sufficient for autograft and no patient should be reinfused with more than 3.0 x 10^{9}/ kg nucleated cells. The harvested bone marrow should be examined morphologically, cytogenetically and by molecular biological techniques. Pilot ampoules (6-10) should be stored locally for subsequent trial investigations. Patients should be consented separately for this with the sample donation to research informed consent form. Please send samples of harvested BM for MRD investigations. For those patients randomised to maintenance chemotherapy, the harvested bone marrow will be kept for possible use as a late autologous bone marrow transplant. These patients must have a remission which exceeds six months before this harvested marrow can be used.
10.3 Peripheral blood stem cell harvest

Mobilisation and collection of peripheral blood stem cells is now permitted in this study. Chugai have agreed to provide discounted Lenograstim (Granocyte; rHuG-CSF) for peripheral blood stem cell mobilisation for patients allocated to allogeneic transplantation or undergoing randomisation (see Appendix 9) The following criteria must apply for their collection and use to avoid compromising the study.

- In Ph –ve patients, no additional chemotherapy to the protocol therapy may be given.
- In Ph +ve patients, Chemotherapy and rHuG-CSF mobilisation is acceptable as outlined in Section 16.

Administration of haemopoietic growth factor after the third high-dose methotrexate is the most appropriate way to mobilise peripheral blood stem cells in patients who are Philadelphia–ve. Although not a conventional method, it has proved successful in this study and has the advantage of enabling peripheral blood stem cell collection at the same stage in therapy as the bone marrow harvest.

Begin 10µg/kg G-CSF subcutaneously, starting 24 hours after the final (day 23) L-asparaginase of the high dose MTX block. The optimal time for PBSC collection is approximately 1 week later.

Bone marrow harvest should still be performed unless the harvest centre is confident that peripheral blood stem cell numbers suffice for an autograft or back-up.

- Collection of peripheral blood stem cells and their use as rescue for the autologous BMT remains optional, not essential. The requirements for an adequate peripheral blood stem cell harvest are not well defined at present. The following represents an example which is meant as a guide only to a minimum requirement. Transplant centres carrying out autologous PBSCT within the UKALL XII study should be confident of their own criteria for an adequate harvest prior to a transplant.
  - Mononuclear cells >3 x 10^6/kg.
  - CFU-GM >20 x 10^4/kg (>50 x 10^4/kg may provide more reliable platelet recovery).
  - Ideally a CD 34 positive cell count of 200 x 10^4 /kg should be collected but 100 x 10^4 /kg is sufficient to proceed. The use of a combination of peripheral blood stem cells and bone marrow harvest is permitted.

All patients in this study have a bone marrow harvest; therefore, all patients may undergo peripheral blood stem cell collection at the discretion of the patient’s physicians.

There will be no purging in this trial of any autologous marrow or PBSCs at any stage.

FOR PERIPHERAL BLOOD HARVEST OF PH+VE PATIENTS SEE Section 16.

11. CNS TREATMENT

11.1 Prophylactic CNS therapy
NEVER GIVE INTRATHECAL TREATMENT ON THE SAME DAY AS INTRAVENOUS CHEMOTHERPAY.
All patients will receive prophylactic intrathecal methotrexate (12.5 mg) on day 24 of the first phase of induction and days –1 (Day -1 refers to the day before commencement of phase II) 7, 14 and 21 of the second phase of induction.

11.2 Patients in CR receiving chemotherapy
Those not receiving bone marrow transplantation will have cranial irradiation 2400 cGy in 12 fractions over 16-19 days between the intensification therapy and the start of consolidation.

Intrathecal cytosine arabinoside 50 mg should be given weekly x 4 concurrently with radiotherapy, then one day of intrathecal cytosine arabinoside 50 mg on each of four occasions three months apart during the maintenance therapy, i.e. for one year.

11.3 Patients in CR receiving BMT
Transplant patients should have a diagnostic LP in the few days before BMT at which 12.5 mg of intrathecal methotrexate should be given. Transplant patients will not receive prophylactic CNS irradiation during intensification therapy.

11.4 Patients in CR on maintenance therapy
Cytosine arabinoside 50 mg should be given intrathecally on 4 occasions 3 months apart for the first year of maintenance therapy. This should not be given on the same day as intra-venous vincristine, but two weeks after.

11.5 Treatment of CNS leukaemia (see Appendix 2)
Prophylactic therapy of the CNS is employed in this study but an initial lumbar puncture is not performed at diagnosis unless clinically indicated. The first lumbar puncture is scheduled at day 24. If overt CNS leukaemia is known to be present at diagnosis, methotrexate 12.5 mg intrathecally or 10 mg via an Omaya reservoir should be given weekly until blasts are not present in the spinal fluid. 2400 cGy cranial irradiation and 1200 cGy to the spinal cord could then be administered concurrently with phase II of the induction chemotherapy, but if cranial irradiation is given, patients will not be eligible for randomisation or for allogeneic BMT using total body irradiation. If it is intended to transplant these patients, DO NOT GIVE CRANIO-SPINAL IRRADIATION.

Note: re CNS treatment: If a patient does receive cranial radiotherapy and is then required to have a bone marrow transplant, at least six months must elapse before whole body radiotherapy is given as part of the transplant after cranial radiotherapy.

12. POST INTENSIFICATION THERAPY
Following successful completion of Phase I and Phase II (i.e. those in CR) and high dose methotrexate/asparaginase the following will occur:

Every patient will have bone marrow harvested and cryopreserved (see Section 10). Additionally PBSCs can be harvested and cryopreserved.

Patients aged 20-50 years with an HLA-identical sibling will receive high-dose VP16 and fractionated TBI as ablative therapy followed by allogeneic BMT. Patients aged 50-55 yrs could be considered at the discretion of their physician and local transplant centre

Patients less than 50 years of age who do not have an HLA-matched sibling and all patients 50 to 55 years inclusive (with an HLA matched sibling donor but deemed to be
unsuitable for an allogeneic BMT), are randomised to receive either an auto BMT or PBSCT following myeloablation with VP16 and TBI or to receive consolidation and maintenance chemotherapy.

13. STANDARD CONSOLIDATION FOR PATIENTS RANDOMISED TO CHEMOTHERAPY ONLY
Patients will receive four courses of consolidation, numbers 1, 2, 3 and 4. The first course of consolidation will begin after prophylactic CNS therapy when the white count has reached \( >3.0 \times 10^9/L \) (neutrophils \( >1.0 \times 10^9/L \)) and the platelets are higher than \( >100 \times 10^9/L \). There should be no less than 28 days between the first day of each cycle designated day 1, and day 1 of the previous cycle. Cycle 4 however should start not less than 60 days after day 1 of cycle 3.

**Cycle 1** will begin following the cranial irradiation when the white count is greater than \( 3.0 \times 10^9/L \) and platelets greater than \( >100 \times 10^9/L \). It will be:

- Vincristine 1.4 mg/m\(^2\) (maximum 2 mg) i.v. on days 1, 8, 15 & 22 only by i.v. push.
- Cytosine arabinoside 75 mg/m\(^2\) i.v. in 100 ml of normal saline or 5% dextrose over 30 minutes on each of days 1-5 inclusive.
- Etoposide (VP16) 100 mg/m\(^2\) i.v. in 500 ml of normal saline given over one hour on each of days 1-5 inclusive.
- Dexamethasone 10 mg/m\(^2\) p.o. on days 1-28 inclusive.

**Cycle 2** begins four weeks from the first day of cycle 1 when the white count is \( >3.0 \times 10^9/L \) and platelets \( >100 \times 10^9/L \), and consists of:

- Cytosine arabinoside 75 mg/m\(^2\) i.v. in 100 ml of 5% dextrose over 30 minutes on days 1-5 inclusive.
- Etoposide (VP16) 100 mg/m\(^2\) i.v. in 500 ml of normal saline over one hour on days 1-5 inclusive.

**Cycle 3** begins four weeks from day 1 of cycle 2 or when white count is \( >3.0 \times 10^9/L \) and platelets \( >100 \times 10^9/L \). It consists of:

- Daunorubicin 25 mg/m\(^3\) by slow i.v. infusion on days 1, 8, 15 and 22. May be given as a slow IV bolus if the patient has no central access.
- Cyclophosphamide 650 mg/m\(^2\) i.v. in 250 ml of normal saline over 30 minutes on day 29 only.
- Cytosine arabinoside 75 mg/m\(^2\) i.v. in 100 ml of 5% dextrose over 30 minutes on each of days 31-34 inclusive and 38-41.
- Tioguanine (TG) should be given 60 mg/m\(^2\) daily p.o. on days 29-42

**Cycle 4** begins 8 weeks following the start of cycle 3 or when the white count is \( >3.0 \times 10^9/L \) and platelets \( >100 \times 10^9/L \), and is identical with cycle 2, i.e.

- Cytosine arabinoside 75 mg/m\(^2\) i.v. in 100 ml of 5% dextrose over 30 minutes on days 1-5 inclusive.
- Etoposide (VP16) 100 mg/m\(^2\) i.v. in 500 ml of normal saline over one hour on days 1-5 inclusive.
14. MAINTENANCE CHEMOTHERAPY FOR THOSE RANDOMISED TO CHEMOTHERAPY

Patients completing the four cycles of consolidation continue on maintenance chemotherapy. This consists of:

- Mercaptopurine 75 mg/m² p.o. daily.
- Oral Methotrexate 20 mg/m² p.o. once a week
- Vincristine 1.4 mg/m² (maximum 2 mg) i.v. every 3 months
- Cytosine arabinoside 50 mg intrathecally (IT) every 3 months for 1 year (see CNS therapy):

  GIVE TWO WEEKS AFTER IV VINCRISTINE, NEVER ON THE SAME DAY.

- Prednisolone (EC or not) 60 mg/m² for 5 days p.o. every 3 months at the same time as the Vincristine.
- Septrin (co-trimoxazole) prophylaxis p.o. 2 tablets (960 mg) b.d. 3 days per week (Mon, Wed Fri).

The maintenance chemotherapy should continue for 18 months from the point of initiation of the consolidation therapy, i.e. for 18 months from week 20.

SEE APPENDIX FOR DOSE REDUCTIONS.

15. MARROW OR PERIPHERAL STEM CELL TRANSPLANTATION

15.1 HLA typing for allogeneic BMT
This should be carried out as soon as the lymphocyte count has reached 1 x 10⁹/L following phase I of induction chemotherapy. All patients under 50 years with an HLA A B and DR identical family donor are offered allogeneic BMT, if considered suitable by the transplant centre. Exceptionally patients aged 50-55 yrs could be considered at the discretion of their physician and local transplant centre. Patients with a donor should receive their BMT within 8 weeks from the start of intensification.

15.2 Randomisation between autologous BMT and chemotherapy for patients not suitable for allogeneic BMT or those <56 years without donors.
This is carried out at about weeks 10-11, before the first intensification.

15.3 Selection of BMT Centre
Transplants should be carried out in participating transplant centres (see Appendix 8). MUD transplants should only be undertaken in centres with previous experience. In cases of difficulty, contact Professor Goldstone, Dr Fielding or Dr Marks.

15.4 Autologous bone marrow harvest or peripheral blood stem cell harvest
Bone Marrow Harvest is carried out after the third high dose MTX after the peripheral blood count has recovered (neutrophils 1.0 x 10⁹/L and platelets 100 x 10⁹/L). Harvest marrow no sooner than 4 weeks and no later than 7 weeks after the start of intensification with MTX and L-asparaginase. N.B. Any PBSC collections should be carried out at the same time. (see Section 10.3)

In the week before harvesting, a bone marrow aspirate should be performed to confirm continuing remission. Marrow harvesting to be carried out according to the local practice. Minimum nucleated cell harvest should be 1 x 10⁹/kg recipient weight. Between 1 and 3 x 10⁹ cells/kg to be reinfused. The method of marrow cryopreservation will be that normally used in each centre. **No purging procedure will be carried out.**
15.5 Allogeneic and autologous transplant: preparative regimen

Day -7 to day -4. Fractionated TBI, two fractions per day (see 15.6)
Day -3 Etoposide 60mg/kg
Days -2 and -1 no chemotherapy or TBI. Start cyclosporin on day -1
D 0 Return of stem cells

Note that at least 48 hours must elapse between delivery of the Etoposide and the return of the bone marrow transplant (or peripheral stem cells).

15.6 Total Body Irradiation

There are differences in the delivery of radiotherapy between the United States and the UK. The TBI regimen for the UK should therefore be one of:
750 cGy in a single fraction in a dose rate of >10 cGy per minute
or
1050 cGy if the dose rate is <5 cGy per minute.
or
Fractionated radiotherapy: This is given to a total of 1440 cGy in 8 fractions according to local protocols

The difference between the USA and the UK is because in the UK the dose is taken to be the maximum lung dose, whereas in the USA, the dose is as delivered at the umbilicus. This amendment will lead to the total radiation dose in the USA and the UK being equivalent.

It is recognised that individual UK centres use different TBI techniques and obtain satisfactory results. In this study, an attempt to standardise the technique will be made in order to better evaluate therapeutic efficacy and toxicity from BMT. The prescribed dose is to the lung. Patients should receive TBI in the above scheme using a linear accelerator or a cobalt unit operating at the SSD/FSD which gives an adequate or largest available field size. The total dose administered will be 1440 cGy for fractionated TBI (8 fractions of 180 cGy), or 1050 cGy or 750 cGy for single fraction TBI, depending on dose rate as indicated above. Fractions should be separated by at least 5 hours. No lung shielding will be used. Radiotherapy boosts during TBI are permitted to the cranium and/or testicles of males. The usual dose would be 580 - 600 cGy per boost.

Sedation and anti-nausea can be achieved with combinations of:
Metoclopramide 20 mg iv
Lorazepam 1-3 mg iv
Dexamethasone 8 mg iv
Ondansetron 8 mg iv or Granisetron 1 mg iv

15.7 Total Body Irradiation measurements

The whole body dose is defined as the maximum dose to the lungs measured by thermoluminescent dosimetry or diodes over 20 minutes for single fraction treatments, and for one whole fraction for fractionated treatments. The calculation of dose will be made for the following sites: Lung, abdomen, pelvis. If compensators are used to give a homogeneous body dose, doses should be measured with compensators in place. Depth dose data, build-up depth and beam flatness must be determined by phantom measurements at the extended treatment distance.

15.8 Etoposide administration (to be given at least 48 hours prior to BM or PBSC re-infusion)

High-dose etoposide should be administered by a syringe driver, in a plastic syringe (plastic ones only become opaque if drug remains in syringe > 24 hours), without dilution into a central venous catheter over 4 hours.

Etoposide can cause cardiac arrhythmias and/or tachycardia. Patients should have a baseline ECG prior to starting the infusion and be coupled to a cardiac monitor throughout. Regular recordings of pulse and blood pressure should be made throughout the infusion, which can be
slowed if necessary. Maintenance of blood pressure using fluid support or colloids may be necessary.

Etoposide causes nausea, and it is appropriate to use prophylactic antiemesis, for example with ondansetron or high-dose metoclopramide. In conjunction with TBI and post-BMT methotrexate, it causes moderate to severe mucositis.

For extravasation, refer to local hospital policy.

**At least 48 hours must elapse between delivery of etoposide and infusion of stem cells or bone marrow.**

### 15.9 Supportive care post BMT

Give blood products irradiated to 2500 cGy. Give CMV negative blood products to CMV negative recipients. HGF (Haemopoetic growth factor) may be used according to clinical need and local practice.

### 15.10 GvHD prophylaxis

Combinations of Cyclosporin (CSA) and methotrexate are acceptable using local protocols. Please use "short methotrexate" (MTX 15 mg/m² day 1, 10 mg/m² days 3, 6 and 11 post BMT), and start CSA iv on day -1 before BM, converting to oral CSA when mucositis has resolved.

T-cell depletion is permitted.

### 15.11 Baseline and follow-up investigations

The following investigations should be performed before and after Auto and Allogeneic BMT:

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Time: months from BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
</tr>
<tr>
<td>Lung function</td>
<td>*</td>
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<tr>
<td>Thyroid function</td>
<td></td>
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<tr>
<td>Eye examination</td>
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<tr>
<td>Dental review</td>
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</tbody>
</table>

### 15.12 Post-BMT prophylaxis for p-carinii

All patients should receive Septrin (Cotrimoxazole) (960 mg) b.d. **three times a week** for 6 months post transplant. If this is contra-indicated, patients should receive pentamidine (see Appendix 3)
16. MANAGEMENT OF PHILADELPHIA POSITIVE DISEASE (Ph+ve).

16.1 Aims of the modification for Treatment of Ph+ve patients:

1. To examine, in a non-randomised study, post induction, the effect of Imatinib, beginning with Phase II of induction, on EFS and OS in patients with Ph positive ALL.
2. To quantify minimal residual disease (MRD) in these patients before the introduction of Imatinib and to follow (using PCR and FISH) the course of MRD after treatment with Imatinib.
3. To determine the significance of continued detection of MRD post allogeneic or autologous transplantation to disease outcome.
4. An allogeneic transplant will be carried out in patients with an appropriate donor (sibling, unrelated or related single haplotype donor).
5. An autologous transplant will be carried out in patients without an appropriate donor, or in patients who have a potential donor but are ineligible for all BMT. Imatinib will be administered as maintenance therapy post allogeneic or autologous transplantation until disease progression.

16.2 Additional Inclusion criteria
All patients must fulfil the following criteria:

- Previously untreated Ph+ve acute lymphoblastic leukaemia (with the exception of patients aged 15 to 20 who initially began phase 1 chemotherapy on UKALL2003).
  1. Such patients must be screened for the presence of the Ph+ chromosome by cytogenetics and by PCR.
  2. Patients must have morphological proof of ALL with a diagnosis made from bone marrow morphology showing >25% lymphoblasts by the FAB criteria.
- 3. Patients must give specific written informed consent to enter the Imatinib study.
- Note: Patients with Ph+ve acute lymphoblastic leukaemia can be still included from the age of 15 to 65 years. Patients aged 15 up to their 20th birthday will have originally entered UKALL2003. Once found to be Ph+ve, such patients can transfer back to UKALL XII, Ph+ve arm at phase 2 induction, in order to receive Imatinib and subsequently be assigned to BMT.

16.3 Exclusion criteria

- Prior malignancy for which chemotherapy or radiotherapy has been given.
- ALL following an antecedent haematological disorder.
- Prior therapy for ALL (previous corticosteroid therapy and emergency treatment for mediastinal compression is acceptable).
- Intercurrent life threatening disease.
- Pregnant or lactating women.

16.4 Background

Adult patients with Ph+ve acute lymphoblastic leukaemia have a poor outcome without allogeneic transplantation. Ph+ve patients, in UKALL XII to date, are older than Ph-ve patients with a median age of 35 years (range 15-60) versus 27 years (15-60 p<0.001). They have a higher leucocyte count at diagnosis, median 25.7 x 10^9/l (range 1.5-350 x 10^9/l) vs. 12.1 x 10^9/l (range 0.6-780), (p=0.001). They have a good remission rate of 75% but this is lower than patients who are Ph-ve at 87% (p=0.001).

Ph+ve patients have a 5-year overall survival of 24%, which is much less than that of Ph-ve patients at 44% (p=0.001). EFS is much poorer than that of Ph-ve patients (19% vs. 37%). The survival at 5 years of patients, excluding those not in remission at 12 weeks, with Ph+ve disease, who have no donor is 27% with a relapse risk of 72%. This suggests that some form of allogeneic transplant is the only therapy which may offer these patients a significant improvement in EFS.
The survival rate for Ph+ve patients, who actually received a transplant, is 43% at 5 years. For Ph+ve patients who receive chemotherapy only, excluding early failures, there is only a 5-year survival of 19%, with EFS of 17% at 5 years. The number of patients who have received an autograft in the current MRC UKALL XII/ECOG 2993 trial is too few to comment but other groups have claimed benefits to auto-transplant in this setting.

Therefore, patients with Ph+ve disease should have allogeneic transplant treatment where possible in first remission.

16.5 Application of Imatinib to the UKALL XII protocol

All eligible patients will receive standard phase I induction therapy as specified in Section 9.2.1. Ph+ve ALL patients will then receive four weeks treatment with Imatinib combined with Phase II. Following this, those patients with a sibling or MUD or related single haplotype match will go on to allogeneic transplantation, whilst those with no donor will have an autograft. After allograft or autograft patients will receive Imatinib as maintenance therapy.

Note: Ph+ve ALL patients will not receive further high dose methotrexate and other consolidation and maintenance in the protocol including interferon.

Patients who are not in remission after phase I and II of induction will be ‘off study’. The clinical coordinators are happy to discuss possible therapeutic options for those patients, if necessary.

16.6 Justification of treatment options

16.6.1 The induction therapy

Induction therapy on UKALL XII/ECOG 2993 has been highly successful at producing a high remission rate despite prolonged hospitalisation, predisposition to bacterial and fungal infections and venous thromboses. The CR rate for Ph+ve patients exceeds 70% but they relapse early. We have been unable to find a superior induction protocol.

16.6.2 Introduction of Imatinib for all patients starting at Phase II induction

The molecular consequence of the t:9:22 translocation resulting in the Philadelphia chromosome is the creation of a fusion protein BCR-ABL. Patients with chronic phase CML express a 210 kDa BCR-ABL protein whereas patients with Ph+ve acute lymphoblastic leukaemia express either the 210 kDa BCR-ABL protein or the 185 kDa BCR-ABL protein. These fusion proteins are constitutively activated tyrosine kinase with increased activity and the activity is required for the transforming abilities of the BCR-ABL oncoprotein. An inhibitor of the BCR-ABL protein tyrosine kinase could be a potentially useful therapeutic agent for CML and also for Ph+ve ALL. Knowledge of the structure of protein tyrosine kinase inhibitors has allowed for the synthesis of inhibitors with increased potency and specificity and one such class of compounds are the 2-phenylaminopyrimidine derivatives. One compound in this class, CGP 57148, is a potent inhibitor of the ABL protein kinase and is now known as Imatinib. All ABL kinases including p210 BCR-ABL, p185 BCR-ABL are inhibited by similar concentrations of CGP 57148. It is available as an oral formulation and phase I trials in CML patients were begun in June 1998. Results from those patients show that the drug is generally well tolerated. Adequate bioavailability and pharmacokinetics have been observed with once daily administration.

There is now increasing experience of the use of this drug in the treatment of Philadelphia positive adult ALL. The initial rationale for introducing Imatinib immediately after the phase I and II induction was that 90% of the patients who had entered morphological CR would still have some evidence by PCR of residual BCR-ABL. However, data are now emerging from a number of studies worldwide where Imatinib has been used even earlier in the course of the disease (refs ASH abstracts nos. 2736-2742 and Towatari et al, Blood, 2004. 104 p3507) Accumulating evidence suggests that the earlier addition of Imatinib might increase the number of patients entering haematological CR and even molecular remission. This might increase the number of patients in whom first remission allografting is an option and might render...
autografting a more attractive approach for patients for whom no allogeneic donor is available. Furthermore, there appears to be little additional toxicity associated with the earlier use of Imatinib. This amendment introduces the Imatinib at the beginning of phase II of induction. By so doing, we aim to increase the overall CR rate and the rate of achievement of molecular remission at relapse.

16.6.3 Lack of further high dose methotrexate and other consolidation and maintenance in the protocol.
Since allogeneic transplantation has been successful in some Ph+ve patients and as patients failing to remit or relapsing early with Ph+ve disease do badly, transplantation will be carried out as early in the protocol as possible; for this reason patients in CR will receive transplant earlier by omitting high dose methotrexate.

16.6.4 Justification for matched sibling allogeneic transplantation, matched unrelated donor transplantation and related single haplotype transplantation.
As described above, the current UKALL XII/ECOG 2993 trial shows relatively acceptable results for both matched sibling allogeneic transplants and matched unrelated donor transplants. Furthermore, recent data on the treatment related mortality of related single haplotype mismatch transplants shows that in the context of patients who do badly on conventional chemotherapy and who do relatively well with a sibling allograft or a MUD, a related single haplotype transplant is now acceptable treatment. On this protocol we will learn specifically of the long-term toxicities and possibilities of a cure from this form of treatment.

16.6.5 Justification for Autologous PBSC (or ABM) transplantation Ph+ve patients who do not have an allogeneic option and receive conventional chemotherapy have a dismal outlook. Interim analysis of 145 patients receiving autologous transplantation on the current UKALL XII/ECOG 2993 trial, show a long term survival of 31% and a procedure related mortality of only 7%. Autologous PBSC transplantation with TBI is justified for those patients who do not have an appropriate allogeneic match and we propose to continue to use Etoposide and TBI conditioning for both the autologous and allogeneic transplants. The use of PBSC is desirable although in exceptional circumstances the use of ABM is acceptable.

16.7 Post Autologous and Allogeneic transplant Imatinib as maintenance therapy
In order to establish the feasibility of safely administering Imatinib and study its impact on relapse rate post allogeneic and autologous stem cell transplantation, all patients will receive Imatinib as maintenance therapy indefinitely or to the time of relapse. Dose modification may be necessary as outlined in appendix 5. Once Imatinib is commenced we recommend therapy until the time of florid relapse since there are no data to address the length of therapy at the current time. Patients can end on-study Imatinib treatment after being treated with Imatinib for two years following diagnosis (although patients requiring the drug beyond this period will still have access to it). Follow up information can continue to be collected.

16.8 Plan of treatment
Due to the design of this protocol, it is important that assessment of cytogenetics and PCR screening for the BCR-ABL oncogene is undertaken in a timely manner, as outlined in the protocol. At the time of relapse it will be important to screen for kinase domain and other mutations which may be associated with the emergence of resistance to Imatinib therapy. For the purposes of screening, samples should be sent to Dr L Foroni at the Royal Free (address as above).

16.8.1 HLA typing and donor search
This should be done as soon as possible, preferably in phase I, in relation to matched sibling donors or matched unrelated donors or single haplotype matched donors. The following options should be explored in the sequence given:

1. The availability of a matched sibling donor.
2. The availability of a matched unrelated donor (MUD). Such transplants should be considered but should only be carried out in transplant centres with experience of this approach. This option should be discussed with the trial co-ordinators.

3. The availability of a related single haplotype match. Again the option should only be carried out in transplant centres with experience of this approach and should be discussed with the trial co-ordinators.

4. All remaining patients without a donor in any of these three categories are eligible for an autologous transplant.

16.8.2 *Induction Therapy* with phase I will be administered as described in section 9.2.1. Imatinib will be commenced with the start of phase II induction at a dose of 400 - 600 mg per day. The dose can begin at 400mg if necessary, but should be escalated to 600mg quickly wherever possible. Adverse events should be recorded on the case report form and serious adverse events should be reported immediately (see section 19). Cytogenetic and PCR assessment of BCR-ABL will be undertaken at the end of phase I and phase II, on bone marrow samples. There will be no further high dose methotrexate and other consolidation therapy.

16.8.3 **Definition of remission** the bone marrow aspirate should be normocellular, contain less than 5% blast cells and show evidence of normal maturation of other marrow elements or, < 5% blasts with reduced cellularity if the peripheral blood count is normalising.

16.8.4 **Consolidation therapy** using Imatinib at a dose of 400mg – 600mg/day orally, for 28 days, will then be administered to those patients achieving a hematological complete remission. The dose can begin at 400mg and should be escalated where possible to 600mg/day according to patient tolerance. Adverse events should be recorded on the case report form and serious adverse events should be reported immediately (see section 19) Adjustments to the dose of Imatinib as a consequence of toxicity should be undertaken as outlined in appendix 5. Cytogenetic and PCR assessment of BCR-ABL will be undertaken at the end of Imatinib consolidation on bone marrow samples.

16.8.5 **Imatinib may be obtained free of charge from Novartis** (see appendix 9).

**Note:** Confirmation that cytogenetic and PCR assessments of BCR-ABL have been initiated will be required before Imatinib is made available. Imatinib will be made available to named pharmacies and they will be notified of your patient’s registration.

16.8.6 **Allogeneic transplantation.** Patients in continuing remission after Imatinib consolidation will proceed to an allogeneic transplant if an appropriate donor (sibling, unrelated or haplo-identical as outlined in section 16.8.1) is available. The conditioning for a sibling transplant will use Etoposide 60mg/kg in two doses, and total body irradiation, as per section 15.6. Unrelated or haplo-identical transplants may receive conditioning therapy according to the local protocol. Supportive care is as for Ph-ve patients (section 15). **Marrow cytogenetics and BCR-ABL assessment will be undertaken every 3 months for the first year and 6 monthly after that. Peripheral blood BCR-ABL analysis will also be undertaken at the same time points.**

16.8.7 **Autologous transplantation.** Those patients without a donor are eligible for an autologous transplant. Mobilisation is recommended with Mitoxantrone 30 mg/m² on days 1 and 2 of week 15, combined with high dose Ara-C 2g/m² on days 1-3 and 1 vial of Lenograstim (rhG-CSF; 263mg) daily, followed by a stem cell harvest. Timing of stem cell harvest will be undertaken using CD34+ quantification of the circulating peripheral blood stem cells. If PBSC is technically difficult, bone marrow harvest after administration of rhG-CSF is acceptable.

16.8.8 **Minimal residual disease** will be assessed by cytogenetics and molecular biology on a sample of the stem cell harvest. Marrow cytogenetics and BCR-ABL assessment will be undertaken every 3 months for the first year and 6 monthly after that. Peripheral blood BCR-ABL analysis will also be undertaken at the same time points.
16.8.9 Maintenance post allogeneic and autologous stem cell transplantation with Imatinib.

After recovery of the white cell count and platelets to 3.0 x 10^9/l and 50.0 x 10^9/l respectively, Imatinib at a dose of 400 – 600mg/day will be commenced for patients receiving both autologous and allogeneic stem cell transplantation. Dose escalation to 600mg/day should be considered according to patient tolerance. Adjustments to the dose of Imatinib, as a consequence of toxicity should be undertaken as outlined in Appendix 5.

17. MANAGEMENT OF RECURRENCE

Second Remission Autograft

Although second remission auto or allo transplants are not officially part of this protocol, the opportunity to offer the patient either of these transplant procedures in second remission should be considered. This is one of the prime reasons for harvesting autologous marrow or PBSCs in those patients not initially randomised to early ABMT. It is envisaged that cryopreserved first remission bone marrow or stem cells may be used for patients failing in the chemotherapy arm as a second remission or first relapse autograft. Normally the cryopreserved first remission marrow or stem cells would not be used unless the patient had achieved a minimum of six months in first remission in the chemotherapy arm. For such patients, reinduction might be attempted with a similar protocol to Phase I or Phase II of the initial induction regimens.

Consolidation before a second remission autograft may be considered on this occasion with high dose cytosine arabinoside, since high dose methotrexate would have been used for the intensification in first remission. The ablative regimen for the transplant protocols will be cyclophosphamide and TBI. For patients relapsing within the first six months of achieving first remission, some investigators might not consider any transplant appropriate and others might consider that the cryopreserved marrow was inevitably contaminated with significant disease. In this case if the patient did then go on to achieve a second remission, the transplant centre might consider reharvesting the patient in second remission and using second remission autologous bone marrow or stem cells for transplant.

Further advice at this stage can be sought from the Clinical Coordinators if required.

18. STATISTICAL CONSIDERATIONS

Patient numbers

The numbers of patients required in a trial depends chiefly on the difference in survival between treatment arms that is to be detected reliably. For example, to demonstrate at $P=0.05$ a 60% improvement in five-year survival from 25% on one treatment to 40% on the other requires approximately 500 patients to have a 95% chance of detecting this difference. If, however, a smaller - but still worthwhile - 40% improvement in survival from 25% to 35% is to be detected, this would require approximately 1000 patients to have a 95% chance of detecting this difference. With only 600 patients there would be a 20% chance of missing a survival improvement of this size.

There are approximately 170 cases of ALL between the ages of 15 and 59 diagnosed each year in the British Isles. Half of these patients are aged 15-24 and only 20% aged 45-59. So, nearly all should be considered suitable for intensive chemotherapy. It is hoped that over 75% of all ALL patients aged 15-59 will be entered into the trial and that about 80% of them will subsequently achieve remission and so be eligible for randomisation between auto-BMT and chemotherapy. However, about 25% of patients will have HLA-matched donors and a further 10% may have contraindications to BMT or refuse consent to randomisation. The annual intake of patients is projected, therefore, to be about 130 registrations and about 70 randomisations. Since this trial is joint with ECOG, at least an additional 70 patients per year should be recruited, increasing the randomisation rate to about 110 per year.
Thus, if the trial proceeds successfully for 5 years, some 550 patients could be randomised, which would give a 70% chance of detecting (at a 2-tailed P-value of 0.05) an absolute difference in survival of 10% at 5 years, and a 95% chance of detecting a 15% difference. About 40 patients a year can be expected to have a donor. Thus the comparison between these patients and those without a donor will have approximately 75% power to detect an absolute survival difference of 10% and over 95% power to detect a 15% difference. The numbers would be increased substantially if SWOG and other trial groups also participate, increasing the power of the study.

Up to September 2000, the actual recruitment and randomisation rates have been approximately 140 and 38, respectively, per year. The proportion of registered patients who reach randomisation has been lower than anticipated, and this means that the target number randomised of 500 will require a total of 1880 patients to be registered.

**Data analysis**

Interim analyses of the main endpoints will be supplied approximately annually, in strict confidence, to a data monitoring committee (DMC). In the light of these interim analyses, the DMC will advise the MRC Leukaemia Steering Committee if, in their view, the randomised comparisons in the trial have provided proof beyond reasonable doubt (2P<0.001) that for all or for some types of patient one treatment is clearly indicated or clearly contraindicated. The main subsets to be analysed separately will be Ph+ve/-ve.

The main analyses will be performed using standard log-rank methods based on the intention to treat, i.e. all patients believed to be eligible at the time of randomisation will be included in the analysis, irrespective of protocol compliance, early relapse, etc. The randomisations, and subsidiary data analyses, will be stratified by age, sex, performance status, CNS involvement at diagnosis, white blood count, time to remission (<28 days, 28+ days), and Philadelphia +ve/-ve leukaemia. All analyses will assume that there may be some quantitative differences in the size of any treatment effects in different strata, but that there is unlikely to be any qualitative difference (i.e. harm in one group, benefit in another).

Final analyses will be performed when the last patient randomised has been followed up for 2 years, i.e. after all patients have finished their initial treatment.

**Statistical analysis of Philadelphia positive patients (this section has been written by ECOG)**

In the interim results from a large cooperative group trial from MRC and ECOG, (MRC UKALL XII/E2993), the 2 year failure rate was approximately 40% in the allogeneic transplant group and approximately 80% in the autologous transplant group. With Imatinib we wish to achieve a 20% reduction in failure rate in each transplant group.

A total of 140 eligible patients will be entered and followed for an additional 2 years to evaluate the primary endpoint. Of these 140, it is assumed that 75% of patients (or 105 patients) will achieve complete remission (CR). Of these 105 patients who achieve CR, approximately 10% will either refuse to continue to post-remission therapy or drop out of the study after administration of Imatinib. Thus, it is assumed that the remaining 94 patients will receive either allogeneic or autologous transplant. Of these 94, its is anticipated that about 50% of patients will be allocated to the allogeneic transplant group. This is because in this study, there will be more haplo and unrelated donor patients than in UKALL XII/E2993. With 94 patients, we will have approximately 98% power to detect a 20% reduction of the 2 year failure rate. With 47 patients in each transplant group, we will have at least 84% power to detect a 20% reduction in the allogeneic or autologous transplant group. This power calculation is based on the exact binomial distribution at 0.05 two-sided level of significance.

Feasibility: Allowing for 10% ineligibility, the overall accrual goal will be 154 patients. Based on the accrual to MRC UKALL XII and ECOG 2993 in this patient population, the projected accrual
rate is about 60 patients per year. Therefore, the accrual will be completed in approximately 2.5 years.

19. **PHARMACOVIGILANCE**

In accordance with the European Union Clinical Trials Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), it is now necessary for sponsor organisations to implement procedures for the recording, verification, reporting, analysis and management of adverse events and serious adverse events, both expected and unexpected. This section defines adverse events and reactions, details the expected events for this study and explains the process that should be followed in order to report an unexpected serious adverse event.

19.1 **Definitions**

**Adverse Reaction**

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

**Adverse Event**

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An adverse event can therefore be any unfavourable change and unintended sign (including laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Serious Adverse Event (SAE)**

A serious adverse event is an adverse event that meets one of the following criteria/outcomes:

- Death
- Life-threatening (i.e. at immediate risk of death)
- Causes in-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Requires medical intervention to prevent permanent damage

Important medical events that may not result in death, may not be life threatening or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

The recording and reporting of adverse events should continue throughout the course of the subject’s participation within the study. Events persisting at the end of the subject’s involvement in the study should be followed to resolution.

19.2 **Events and reactions not to be reported to the Chief Investigator**

For this trial, the following conditions will be excluded from requiring reporting to the chief investigator on a serious adverse event form, because they are expected in a trial of this type. Investigators should note, however, that the reporting of expected events may be necessary under certain conditions, notably single cases of expected SAEs with an unexpected outcome.
(e.g. death) or an increase in the rate of occurrence of an expected event that is judged to be clinically important.

General

Prolonged bone marrow and immune suppression are expected as a result of the combination chemotherapy employed in this protocol. Severe sepsis and bleeding may be consequences of this.

L-Aspariginase

Severe liver dysfunction, anaphylaxis, severe pancreatitis, hyperglycaemia, hypercoagulability, induced thrombophilia.

Prednisolone

Fluid/salt retention, hypertension, irritability, glycosuria, hyperglycaemia, obesity, hirsuitism.

Vincristine Sulphate

Local necrosis, jaw pain, paresis, constipation, systemic neurotoxicity, alopecia.

Daunorubicin Hydrochloride

Local necrosis, cardiotoxicity, alopecia.

Methotrexate

Neurotoxicity, mucositis, liver dysfunction.

Mercaptopurine

Liver dysfunction

Cytarabine

Nausea, vomiting, oral ulceration, fever, arthralgia

Cyclophosphamide

Stomatitis, nausea and vomiting, alopecia, haemorrhagic cystitis

Etoposide

Cardiac arrhythmias, alopecia, headache, fever, hypotension

Tioguanine

Stomatitis, diarrhea, hepatic toxicity, loss of vibration sense, unsteady gait

Dexamethasone

GI bleeding, diabetes, hypertension, hirsuitism, fluid/salt retention

Imatinib
Headache, neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhoea, dyspepsia, periorbital oedema, dermatitis/eczema/rash, muscle spasms and cramps, musculoskeletal pain, joint swelling, fluid retention and oedema.

Adverse reactions having a suspected causal relationship with Imatinib will be assessed for expectedness using the UK specific Summary of Product Characteristics for this product.

19.3 Reporting of Serious Adverse Events

SAEs not included in section 19.2 above must be reported immediately on the serious adverse event form (copies of this form are available from the CTSU website at www.ctsu.ox.ac.uk. A copy of the form is also held within Appendix 10 of the protocol – this may be photocopied in the event that the electronic version is not accessible). The form requires details of start & stop dates of the event; the grade of the event (which should be graded according to CTCAE v3.0, full details of which are available at http://ctep.cancer.gov) the causal relationship to the study drugs administered (not related, not likely, possible, probable or certain/definite); action taken and outcome. The form should be medically assessed at the site by the principal or sub-investigator (if this task has been delegated to him/her on the site participants' log) and he or she must assess the causality. The form should be faxed immediately to the Clinical Trials Service Unit on the following number 01865 743986.

A request for follow up information may be made.

The CI on behalf of the sponsor will then review and process the SAE reports accordingly; in the CI’s absence, a designee will be responsible for this task. SAEs which, in the opinion of the CI are both related to the study drug and unexpected (Suspected Unexpected Serious Adverse Reactions), will be reported to the Medicines and Healthcare Regulatory Authority.

A form has been introduced to the Philadelphia positive patient record book in order to capture any associated toxicity, particularly with the use of Imatinib. This toxicity form has not been included in the Philadelphia negative record book since it is felt that due to the significant experience with the standard chemotherapy regimen employed in these patients, it is not necessary to document any already well known associated toxicity.
Process Flow for Reporting of Serious Adverse Events

Does the event meet the definition of serious as outlined in section 19.1 of the protocol?

Yes

Is the event listed as expected within section 19.2 of the protocol?

Yes

Ph +ve

Report in record book

Ph -ve

Report in record book

No

This is an UnexpectedSerious Adverse Event requiring immediate reporting (within 24 hrs of notification of the event).

Complete an SAE form*, ensuring that all requested details are completed

Suspected relationship to Imatinib or L-Asparaginase

SAE form for Novartis or Medac must also be completed. Additional copies available from CTSU: 01865 765615

Fax form to CTSU on 01865 743986
Retain a copy of the form at site

Non-serious events (Ph positive and negative) should be recorded in the patient record book as appropriate

No

Ph +ve

Report in record book

Ph -ve

Report in record book

* SAE forms available at www.ctsu.ox.ac.uk. A copy is held within appendix 10 of the protocol
APPENDIX 1: GUIDELINES FOR THE ADMINISTRATION OF INTRAVENOUS HIGH-DOSE METHOTREXATE

Regimen for administration of high-dose methotrexate

NOTE: PATIENTS MUST NOT RECEIVE COTRIMOXAZOLE IN THE WEEK PRIOR TO THE FIRST METHOTREXATE INFUSION OR IN SUBSEQUENT WEEKS UNTIL MAINTENANCE THERAPY STARTS.

A few days before each methotrexate infusion, measure:

- Serum creatinine
- Bilirubin, AST, ALT
- Plasma sodium and potassium
- FBC

In addition, in the week before admission before the 1st and 3rd methotrexate infusions, determine GFR (measured or calculated according to local practice). If there is delayed methotrexate excretion after the first course, then repeat GFR before the 2nd infusion. Meticulous attention should be paid at all times to the GFR. The initial GFR before starting methotrexate should be well over 100 ml/min. The GFR before the third course of high-dose methotrexate should be above 50 ml/min. In the event of any query about this, delay the third methotrexate by up to a week and recalculate the GFR. Consult the Coordinators if in any doubt.

If the results are within normal limits, proceed with:

**Pre-hydration**

For at least 6 hours prior to the commencement of the intravenous methotrexate.

**Hydration fluid**

1 litre dextrose saline to which has been added 50 mmol sodium bicarbonate and 20 mmol potassium chloride.

**Infusion rate**

125 ml/m$^2$/hr.

**Check urine pH**

Adjust the sodium bicarbonate concentration to maintain the urinary pH between 7 and 8 (i.e. alkaline). A urinary pH of 7.5 or greater must be achieved before starting the methotrexate infusion.

Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable.

**HIGH-DOSE METHOTREXATE INFUSION**

**Methotrexate dose**

Methotrexate 3 g/m$^2$ with:

- 10% (i.e. 300 mg/m$^2$) given in first hour (loading dose) in 200 mls.
- 90% (i.e. 2700 mg/m$^2$) given over next 23 hours in 1 litre.

Infusion details. Dilute methotrexate in appropriate volume of saline 0.9%.

**NOTE:** The infusion of methotrexate must always stop at 24 hours even if not completed for any reason.

**Hydration during methotrexate infusion**

Give concurrent infusion at a rate of 1 litre over 8 hours equalling 3 litres in 24 hours. FOLINIC ACID RESCUE MUST START AT 36 HOURS FROM THE START OF METHOTREXATE.

The first dose of folinic acid (to be given at 36 hours after the start of methotrexate infusion) must be written up at the time of prescribing the methotrexate infusion.
Dosage of folinic acid:

- At 36 hours: Give 15 mg/m$^2$ iv.
- 36-48 hours: Give 15 mg/m$^2$ iv every 3 hours.
- From then on: Give 15 mg/m$^2$ iv every 6 hours until methotrexate level is less than 1.0 x 10$^{-7}$ M.

If the patient is not vomiting folinic acid may be given orally after the first two doses.

If the 48-hour (from start of methotrexate infusion) methotrexate level is >2 x 10$^{-5}$ M, INCREASE the dose of folinic acid iv (see below for how to calculate dose).

If the 72-hour (from start of methotrexate infusion) methotrexate level is:
- >2 x 10$^{-6}$ M, INCREASE folinic acid iv.
- ≤2 x 10$^{-6}$ M, CONTINUE folinic acid 15 mg/m$^2$ iv 6-hourly until level <1 x 10$^{-7}$ M.

Formula for calculating increased folinic acid dose:

Dose of folinic acid for next 24 hours:

\[
\text{Dose of folinic acid for next 24 hours} = \frac{\text{Usual total daily folinic acid dose}}{\text{Denominator methotrexate level that day**}} \times \text{Plasma methotrexate level for that day**}
\]

The denominator methotrexate for that day is as follows:

- At 48 hours (from start of methotrexate infusion) = 2 x 10$^{-5}$ M.
- At 72 hours (from start of methotrexate infusion) = 2 x 10$^{-6}$ M.
- At 96 hours (from start of methotrexate infusion) = 1 x 10$^{-7}$ M.

** expressed in molar (M) units.

Monitoring of plasma methotrexate levels following infusion.
Times given are from time 0 (time of starting intravenous methotrexate infusion).

The following plasma samples are required for patient's safe rescue with folinic acid:
48 hours,
72 hours, and
then every 24 hours if not completely rescued, i.e. if plasma methotrexate level not less than 1 x 10$^{-7}$ M.

Hydration regimen after completion of intravenous methotrexate infusion
Continue to infuse at a rate of 125 ml/m$^2$/hour for a minimum of 48 hours with:
1L dextrose saline 0.45% containing 50 mmol of sodium bicarbonate and 20 mmol potassium chloride.

Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable

Continue to ensure that urinary pH is above 7 by adjusting sodium bicarbonate dose.

After 48 hours from the start of the intravenous methotrexate, ENSURE a combined oral and/or intravenous intake greater than 3 litres/m$^2$/24 hours until plasma methotrexate levels <1 x 10$^{-7}$ M.

Check fluid balance at regular intervals (4-hourly) through each day, taking early action if fluid overload occurs by giving frusemide if the urine output falls below 400 ml/m$^2$ in any given 4-hour period.
Other investigations during folinic acid rescue:

Daily Creatinine, sodium and potassium.
Alternate days Bilirubin, AST, ALT, albumin, full blood count.

These investigations should also be checked at least twice during the week following the first and second methotrexate infusion to detect any toxicity that might occur.

Conversion table for methotrexate levels expressed in different units

<table>
<thead>
<tr>
<th>Molar (M)</th>
<th>µg/ml</th>
<th>ng/ml</th>
<th>µmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 10^{-3}</td>
<td>460.0</td>
<td>1013.0</td>
<td></td>
</tr>
<tr>
<td>2 x 10^{-4}</td>
<td>92.0</td>
<td>202.0</td>
<td></td>
</tr>
<tr>
<td>1 x 10^{-4}</td>
<td>46.0</td>
<td>101.0</td>
<td></td>
</tr>
<tr>
<td>2 x 10^{-5}</td>
<td>9.2</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>1 x 10^{-5}</td>
<td>4.6</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>2 x 10^{-6}</td>
<td>0.92</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>1 x 10^{-6}</td>
<td>0.46</td>
<td>460.0</td>
<td>1.01</td>
</tr>
<tr>
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<tr>
<td>2 x 10^{-8}</td>
<td>0.010</td>
<td>9.2</td>
<td>0.02</td>
</tr>
<tr>
<td>1 x 10^{-8}</td>
<td>0.005</td>
<td>4.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

To convert methotrexate level expressed in µmol to µg/l multiply by 0.454

Table for the calculation of folinic acid rescue on the basis of MTX plasma levels.

<table>
<thead>
<tr>
<th>Time after starting MTX</th>
<th>MTX plasma concentration (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48h</td>
<td>&lt;0.1 0.1 - 2 2 - 20 20 - 100 &gt;100</td>
</tr>
<tr>
<td>48h</td>
<td>None&lt;sup&gt;a&lt;/sup&gt; 15mg/m&lt;sup&gt;2&lt;/sup&gt; q6h&lt;sup&gt;b&lt;/sup&gt; 15mg/m&lt;sup&gt;2&lt;/sup&gt; q6h 10mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 100mg/m&lt;sup&gt;2&lt;/sup&gt; q3h</td>
</tr>
<tr>
<td>72h</td>
<td>None 15mg/m&lt;sup&gt;2&lt;/sup&gt; q6h 10mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 100mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 1 g/m&lt;sup&gt;2&lt;/sup&gt; q3h</td>
</tr>
<tr>
<td>96h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None 15mg/m&lt;sup&gt;2&lt;/sup&gt; q6h 10mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 100mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 1g/m&lt;sup&gt;2&lt;/sup&gt; q3h</td>
</tr>
<tr>
<td>120h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None 15mg/m&lt;sup&gt;2&lt;/sup&gt; q6h 10mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 100mg/m&lt;sup&gt;2&lt;/sup&gt; q3h 1 g/m&lt;sup&gt;2&lt;/sup&gt; q3h</td>
</tr>
</tbody>
</table>

Notes

a  No extra folinic acid is required provided MTX levels are below 0.1 µmol/l (10<sup>-7</sup>M) at 48h.

b  Dose and schedule of folic acid: q6h = every 6 hours.

c  At time points after 120h folinic acid administration should be continued as recommended for 120h.

Drug interactions

Drugs which compromise renal function eg. aminoglycosides and cisplatin can decrease clearance of methotrexate and lead to systemic toxicity. Avoid concurrent use of NSAIDs including salicylates and sulphonamides. Large doses of penicillin may interfere with the active renal tubular secretion of methotrexate. It is recommended that prophylactic co-trimoxazole be stopped one week before HDMTX therapy.
APPENDIX 2: RADIOTHERAPY GUIDELINES

1. CRANIAL RADIOTHERAPY - for CNS prophylactic treatment

(a) Megavoltage apparatus should be used, preferably a linear accelerator.

(b) All fields should be treated on each treatment day.

(c) Midplane dose 2400 cGy in 12 fractions of 200 cGy each, in 16-19 days. (Treatment may start on any day except Friday.)

(d) Lateral opposed fields are used to include all cranial meninges including those surrounding the optic nerve in the retro-orbit, and extending down the spinal cord to level of C2.

(e) Preferred technique - use of a linear accelerator will ensure that the lens dose is kept as low as possible. A technique which centres on the orbit and uses customised lead blocks minimises beam divergence and therefore reduces the lens dose.

The patient is immobilised in a supine shell and a treatment field centre is selected clinically which is symmetrical and lies 15 mm behind the cornea on each side. Using a simulator, these two points are opposed and a simulator film taken for the production of customised lead blocks. These should be designed so as to treat the cervical cord down to the level of C2 and to ensure adequate treatment to the origin of the facial nerve.

The use of this technique necessitates either the use of asymmetric jaws to block the lower part of the neck or else the use of a very large amount of lead. It may therefore not be possible at all centres, and in such cases a similar blocking arrangement using a field centred in the mid-cranium is acceptable.

A third (but less satisfactory) alternative is to use a rectangular field with one edge running parallel to Ried's baseline.

(f) Treatment to additional fields, e.g. nasal electrons to the cribiform plate, may be used at the discretion of the clinician. If such modifications are used, they should be specified on the enquiry sheet and the reason they were considered necessary given.

(g) Thermoluminescent dosimetry - it is advised that thermoluminescent dosimetry be performed and the results recorded, as it is hoped to use the data collected to study cataractogenesis in long-term survivors. Lithium fluoride chips should be placed during the treatment of all fields, and the position may be:

(i) taped on the eyelid on the front of the position of the lens,

or

(ii) taped at the outer canthus of the eye.

The position used should be recorded on the form.

Doses to the eye should be less than 10% of the midplane dose.

(h) Quality control
It is suggested that an initial simulator film is taken for planning purposes. Ideally, block positions should be checked at a second simulator session and in addition beam films should be taken on the treatment set to verify block positions. All available films will be requested for review shortly after the completion of treatment.
(i) **Interruptions to radiotherapy**

Treatment will be *interrupted* if:

(i) neutrophil count falls below $0.5 \times 10^9$/L.
(ii) platelet count falls below $50 \times 10^9$/L.
(iii) the patient is febrile.

Treatment may be *resumed* when:

(i) neutrophil count above $1.0 \times 10^9$/L.
(ii) platelet count above $75 \times 10^9$/L.
(iii) afebrile for more than 72 hours.

**CRANIO-SPINAL RADIOTHERAPY** for CNS leukaemia at diagnosis or for patients with a CNS relapse

DO NOT GIVE THIS IF YOU WANT TO PROCEED TO BMT.

(a) **CRANIUM**

Patients should be treated in a prone cast.

Dosage - 2400 cGy midplane dose in 12 fractions of 200 cGy each, starting any day except Friday.

(b) **SPINE**

(i) A direct posterior field should be used. To avoid overdose to the spinal cord at the gap, the inferior margin of the cranial field should be placed so as to parallel the divergent upper margin of the spinal field.

(ii) If the patient has had previous cranial irradiation, the gap between cranial and spinal fields should be C3, 4.

(iii) Adults, in contrast to children, may require to have the spine treated in 2 segments with an appropriate gap. The position of this gap should be altered halfway through the treatment.

(iv) Dose of 1200 Gy in 6 fractions of 200 cGy on consecutive treatment days, concomitant with the last 6 cranial fractions. The dose should be calculated at the anterior surface of the spinal cord as judged by its average depth of a lateral X-ray of the vertebral column taken in the treatment position.

(v) The width of the spinal field is usually 5 cm but may be expanded from the lower border of L4 down over the sacrum to a width of 7-8 cm to encompass the sacral roots, although this is not standard practice now in the UK.

3. **TESTICULAR DISEASE AT PRESENTATION**

(a) Megavoltage or orthovoltage apparatus may be used.

(b) The testes only are treated with lead shielding to the surrounding tissues, including the penis.

(c) A dose of 2400 cGy in 12 daily fractions of 200 cGy should be given during the first 20 weeks consecutively with cranial irradiation if the patient has been randomised to this treatment.
APPENDIX 3: GENERAL DRUG INFORMATION

N.B. The drug information and dosages quoted here are for this study only and should not be applied to other treatment protocols.

DRUGS USED IN INDUCTION (PHASES I & II)

Doses for induction are calculated using Ideal Body Weight Formula:
Female = 45.5kg + (2.3 x each inch over 60)
Male = 50kg + (2.3 x each inch over 60)

1. L-ASPARAGINASE

Asparaginase (E.coli) medac available on a named patient basis from Medac:
Contact their distributors “UDG” on 01773 510 123 who can arrange delivery within approximately 2 working days. Quote that the patient is enrolled on UKALL XII study led by Professor Goldstone. If any problems with supply, contact the National Oncology Product Manager, Lorna Livingstone:

Tel: 01786 458086
Fax: 01786 458032
Mob: 07810 752233
lorna.livingstone@medac-uk.co.uk

Asparaginase (E.coli) medac dose 5,000 iu /m² given IM in phase I induction
Asparaginase (E coli) medac dose 10,000 iu (flat dose) given IM in intensification

Formulation 10,000 units per vial.

Store protected from light at room temperature.

Mixing With 4mls of water for injection.
The water should be squirted carefully on the inner wall of the vial and not directly onto the powder for injection itself. Slowly turn around the vial (avoid shaking and formation of foam). The solution may show a very slight opalescence.

Stability The reconstituted solution must be kept at room temperature and used within six hours.

Administration By intramuscular injection. As the volume to be injected is greater than 2 mls it should be administered over 2 sites

Side-effects Anaphylaxis
Severe pancreatitis
Severe liver dysfunction
Hyperglycaemia
Hypercoagulability
Induced thrombophilia (see pages 4 and 13).

Precautions A test dose of 1000 IU intradermally should be given before treatment commences. The drug is given early in induction and there may still be thrombocytopenia. Platelets may be necessary to cover the injection, but if it is given carefully with extra local pressure they may not be needed. Where asparaginase is being given for re-induction following a CNS or other extra-medullary relapse, a test dose intradermally of 1000 units should be repeated.
2. PREDNISOLONE

N.B. Please specify clearly on the prescription charts that prednisolone and not prednisone is to be used. Please draw the attention of your junior staff and the pharmacy department to this.

Formulation 1 mg 2.5 mg (enteric-coated) and 5 mg (ordinary, soluble and enteric-coated) tablets available (25 mg, non-EC, available).

Storage At room temperature.

Administration 60 mg/m² orally daily in three divided doses after meals.

Toxicity Obesity, hirsutism, fluid and salt retention, hypertension, irritability, glycosuria and hyperglycaemia.

3. VINCRISTINE SULPHATE

Formulation 1-2 mg per ml vials or syringes each containing 1 or 2 mg concentrate 1 mg/ml in mixing solution pre-prepared: DILUTE TO GIVE IN 20 ml DOSE.

Storage At 2-8°C in refrigerator.

Stability Depends on formulation.

Administration By bolus intravenous injection (20 ml dose). Ensure that the needle is well into the vein and avoid extravasation.

Toxicity LETHAL IF GIVEN INTRATHECALLY. LABEL “FOR INTRAVENOUS USE ONLY”.

Local necrosis if extravasation occurs. jaw pain, paresis, constipation, systemic neurotoxicity and alopecia.

4. DAUNORUBICIN HYDROCHLORIDE

Formulation 20 mg powder (in vials) with 4 ml water for injection.

Storage Powder - cool, dark place.

Mixing Dissolve in 10-20 ml of sodium chloride for injection.

Stability of mixed solution At room temperature for 48 hours in darkness.

Administration 60 mg/m² (and 25 mg/m²) by slow iv infusion.

N.B. Avoid extravasation. Check dose before administration.

Toxicity (i) Local necrosis if extravasation occurs.

(ii) Cardiotoxicity.
5. METHOTREXATE

(a) Methotrexate (MTX) injection

Formulation  Ready mixed vials in the following strengths:

- 50 mg in 2 ml
- 200 mg in 8 ml
- 500 mg in 20 ml
- 1g in 10 ml
- 5g in 50 ml

N.B. Check label carefully before administration.

These vials contain sodium chloride & sodium hydroxide adjusted to a pH of 8.5; there is no preservative present.

Stability  Note expiry date on bottle. After the vial has been used, discard remaining contents as there is no preservative.

Administration  As per protocol

Labels  If for intrathecal use, this must be labelled "For intrathecal use only"

Toxicity  Neurotoxicity, mucositis, liver dysfunction, bone marrow depression.

6. MERCAPTOPURINE

Formulation  50 mg scored tablets and 10mg scored tablets.

Storage  At room temperature.

Stability  Please note the expiry date.

Administration  75 mg/m$^2$ orally taken once a day before breakfast. Note, dose in induction is 60mg/m$^2$.

Toxicity  Bone marrow depression, liver dysfunction.

N.B. Do not give allopurinol when the patient is on mercaptopurine, as the allopurinol potentiates the action of mercaptopurine.

7. CYTARABINE

Formulation  Vials containing freeze-dried powder of 100 mg cytarabine. Other preparations available.

Storage  At room temperature.

Stability  Depends on formulation.

Administration
1. **IV:** By direct iv injection 75 mg/m\(^2\) or in 100 cc 5% dextrose over 30 minutes.

2. **Intrathecal:** 50 mg by bolus in 2 ml saline.

**Toxicity** Includes bone marrow suppression, nausea, vomiting, oral ulceration, fever and arthralgia.

**Labels** If for intrathecal use, this must be labelled "For intrathecal use only"

### 8. CYCLOPHOSPHAMIDE

**Formulation** White powder for injection in vials containing 100 mg, 200 mg, 500 mg and 1000 mg. Dissolve powder in 5 ml water for injection per 100 mg.

**Storage** Stable at room temperature for 2-3 hours after reconstitution.

**Administration** IV 650 mg/m\(^2\) in 250 ml normal saline over 30 minutes.

**WARNING:** Protective clothing and eye protection to be used for reconstitution and administration.

**Toxicity** Bone marrow suppression, stomatitis, nausea and vomiting, alopecia, haemorrhagic cystitis, "floaters" in eyes during administration.

### DRUGS USED DURING CONSOLIDATION

#### 1. **LOW-DOSE ETOPOSIDE (VP16)**

**Formulation** Ampoules containing 100 mg etoposide in 5 ml.

**Storage** At room temperature.

**Mixing** Dilute to a concentration of not more than (0.4mg/ml) etoposide in sodium chloride 0.9%.

**Stability** 0.25 mg/ml stable for 6 hours at **room temperature** when diluted.

**Administration** (1) Low dose: 100 mg/m\(^2\) iv in 500 ml normal saline over 1 hour; (2) High dose: (see Appendix 4).

**Toxicity** Dose-related bone marrow suppression, alopecia, headache, fever and hypotension. (Severe hypotension may occur if the drug is given too rapidly. Avoid extravasation.)

#### 2. **TIOGUANINE**

**Formulation** 40 mg scored tablets.

**Storage** At room temperature.
Administration  Orally between meals to facilitate complete absorption. Total daily dose may be taken at one time. Dose 60 mg/m²/day.

Toxicity  Bone marrow suppression, stomatitis, severe diarrhoea, hepatic toxicity, loss of vibration sense and unsteady gait.

3. DEXAMETHASONE

Formulation  2 mg tablets.

Storage  At room temperature.

Administration  Orally in one dose after meals. Coincidental treatment with 5-HT3 antagonist may be necessary.

Toxicity  Gastrointestinal bleeding, diabetes, hypertension, hirsutism, fluid and salt retention

4. CYTARABINE (see above)

5. DAUNORUBICIN (see above).

N.B. DOSE IN THIS PHASE LOWER, i.e. 25 mg/m²

6. CYCLOPHOSPHAMIDE (see above)

DRUG INFORMATION AND PERMITTED DOSE MODIFICATIONS

PERMITTED MODIFICATIONS FOR TOXICITY

1. Induction treatment

(a) Prednisolone, vincristine, L-asparaginase, cyclophosphamide, MP, daunorubicin, cytosine arabinoside and VP16 and intrathecal methotrexate dosages are NOT to be modified for leucopenia or thrombocytopenia.

(b) L-asparaginase should be discontinued in the presence of pancreatitis (identified by raised amylase or a low serum insulin), severe liver dysfunction, life-threatening allergic reactions or thrombosis (see 9.2.1).

Previous experience suggests that 4-5% of patients will have asparaginase-related toxicity with hyperglycaemia being the commonest problem. Since hyperglycaemia may be due to prednisolone rather than L-asparaginase, serum insulin and amylase measurements should be performed before withdrawal of L-asparaginase.

(c) Vincristine should be reduced to 1 mg/m² in the presence of severe jaw pain, paresis or constipation. If the symptoms do not recur, resume full dosage. Vincristine should be withheld in the presence of ileus or foot drop. Resume at 1 mg/m² after recovery. Patients with evidence of liver dysfunction should be discussed with one of the coordinators, as vincristine dose modification may be indicated.

(d) Prednisolone should be reduced to 30% of the recommended dose if the patient develops hypertension, diabetes or mental instability - if symptoms or signs continue, or mental instability, a further reduction may be necessary.
2. CNS treatment

(a) Intrathecal methotrexate

Neurotoxic reactions.

If neurotoxicity occurs or is suspected, this requires the assessment of the CSF methotrexate level. **STOP treatment as this is a direct chemical effect.**

Systemic reactions.

Myelosuppression, mucositis etc. **DO NOT REDUCE** the dose of intrathecal methotrexate. Instead give folinic acid 15 mg (tablets or iv) 24-36 hours after the next intrathecal methotrexate.

**NEVER GIVE ON SAME DAY AS INTRAVENOUS TREATMENT**

(b) Intrathecal cytosine arabinoside in maintenance

Occasional neurotoxicity. **NEVER GIVE ON SAME DAY AS INTRAVENOUS CHEMO-THERAPY**

50 mg intrathecally in 4 ml normal saline. **Side effects:** headache if ambulatory too soon after injection.

MAINTENANCE

(a) Dose modifications during maintenance for toxicity

**Blood count depressed**

*If neutrophil count is between 0.5 and 1.0 x 10⁹/1 or platelets are between 50 and 100 x 10⁹/L, reduce mercaptopurine and methotrexate to 50% of dose. Keep at this dose till counts rise above these levels, then increase both drugs to 75% of recommended protocol dosage for 2 weeks and to 100% dose if tolerated.*

*If neutrophil count <0.5 x 10⁹/L or platelets <50 x 10⁹/L, **STOP both drugs.** Re-start drugs at 50% dose once neutrophils >1.0 x 10⁹/L and increase as above to 75% and 100% as tolerated.*

*Repeated falls in haemoglobin alone may be due to mercaptopurine intolerance; in which case, reduce mercaptopurine only as above and attempt to increase the dose gradually again as described. Methotrexate should stay at full dose.*

Sometimes the counts take longer than above to recover- consider performing a bone marrow after 2-3 weeks.

*Anaemia* occurring early in the course of continuing therapy should be treated with transfusion and the dose of mercaptopurine and methotrexate is maintained. If persistent anaemia occurs (i.e. Hb below 8 g/dl) despite reducing the dose of mercaptopurine, then the methotrexate dose should also be modified. Please contact trial coordinators for advice.

If blood counts fail to return to normal, check remission status by bone marrow aspiration.

(b) Relation of co-trimoxazole to neutropenia

In general, patients should be allowed one “trial” of cytotoxic dose adjustment, as described above. If the patient remains neutropenic after being off drugs for 2 weeks with no improvement in blood count, then stop prophylactic co-trimoxazole. Re-introduce 1 tablet three times per week once mercaptopurine or methotrexate are at >75% protocol dosage. If neutropenia recurs once co-trimoxazole is re-introduced or the patient cannot tolerate at least 75% drug dosage then co-trimoxazole should be stopped for at least two months. **The maintenance of adequate cytotoxic drug doses should take priority over continuing**
**cotrimoxazole.** If co-trimoxazole is stopped, however, it must be remembered that the patient is at increased risk of pneumocystis pneumonia and there should be a relatively low threshold for treatment of any suspected interstitial pneumonitis. Patients who do not tolerate cotrimoxazole prophylaxis and develop pneumocystis pneumonia require therapy with fortnightly aerosolised pentamidine thereafter. (Review PCP, BMJ 1990; 211-212).

(c) **Severe diarrhoea and vomiting**

STOP both drugs. RESTART at 50% of protocol dose when better and return to full dose when tolerated.

(d) **Severe methotrexate mucositis**

WITHHOLD methotrexate until improved and then re-start at full dose, or at highest tolerated dose.

(e) **Clinically significant liver dysfunction (jaundice)**

Oral methotrexate should be STOPPED until improvement occurs. RE-START at 50% of protocol dosage and increase as tolerated. If liver dysfunction recurs, contact one of the Clinical Coordinators.

(f) For maintenance modifications for those Philadelphia-positive patients receiving Imatinib (see Section 16).
APPENDIX 4: HIGH-DOSE ETOPOSIDE (VP16)

Storage: Room temperature.

Presentation: 100 mg in 5 ml ampoules.

Dose 60 mg/kg.

Reconstitution: Do NOT dilute.

Stability: Store at room temperature.

Administration: Infuse undiluted into a central venous catheter using a plastic syringe driver over 4 hours, providing drug does not remain in syringe for greater than 24 hours (see Section 15.8).

Side effects:

Short-term: Nausea and vomiting, tachycardia and arrhythmias. Hypotension, which can be reversed by slowing the infusion rate but may require fluid or colloid support.

Long-term: Alopecia, which reverses on cessation of therapy (66% patients). Leucopenia and thrombocytopenia (nadir leucocyte count at 16-21 days). Anaphylactic-like reactions are rare and respond to cessation of therapy and administration of antihistamine.

Extravasation: Etoposide is mildly irritant. Extravasation should be treated with icepacks, an intradermal injection of hydrocortisone 100 mg and twice daily hydrocortisone cream 1%, or refer to local extravasation policy.
APPENDIX 5: DRUGS USED IN PHILADELPHIA POSITIVE PATIENTS

Imatinib

Formulation: Gelatin capsules or tablets containing 100mg/400mg

Storage: Room temperature.

Administration: Gelatin capsules will be taken orally as a once daily dose with a drink and some food. Caffeine and grapefruit containing products should be avoided at the time.

Toxicity

**Contraindications:** Hypersensitivity to the active substance or to any of the excipients.

**Precautions:** Use with caution in severe hepatic or renal impairment. Monitor liver function, weigh patients regularly. Perform complete blood counts. Avoid or restrict use of paracetamol.

Drugs which may increase Imatinib plasma concentrations are: inhibitors of cytochrome P450 isoenzyme CYP3A4 activity (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin). Drugs which may decrease Imatinib plasma concentrations are: inducers of CYP3A4 activity (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or hypericum perforatum, also known as St John's Wort).

Imatinib increases plasma levels of simvastatin and may alter the plasma levels of some drugs which are CYP3A4 substrates with a narrow therapeutic window (e.g. cyclosporin or pimecrolimus). May increase plasma concentration of other CYP3A4 metabolised drugs (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG CoA reductase inhibitors, i.e. statins etc).

Patients requiring anticoagulation should receive low-molecular weight or standard heparin rather than warfarin. Systemic exposure to substrates of CYP2D6 is potentially increased when co-administered with Imatinib. There is no adequate data on the use of Imatinib in pregnancy (see full prescribing information).

**Side effects:**

*Very common:* Headache, neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhoea, dyspepsia, periorbital oedema, dermatitis/eczema/rash, muscle spasm and cramps, musculoskeletal pain, joint swelling, fluid retention and oedema.

*Common:* Anorexia, febrile neutropenia, pancytopenia, dizziness, taste disturbance, paraesthesia, insomnia, conjunctivitis, increased lacrimation, pleural effusion, epistaxis, abdominal pain, abdominal distension, flatulence, constipation, dry mouth, face oedema, eyelid oedema, pruritus, erythema, dry skin, alopecia, night sweats, pyrexia, fatigue, weakness, rigors, increased weight, tract infection, dehydration, hyperuricaemia, hypokalaemia, hyperkalaemia,

**Laboratory test abnormalities:** Cytopenias, neutropenia and thrombocytopenia, elevation of transaminases or bilirubin.
ADJUSTMENT OF IMATINIB DUE TO TOXICITY.

Dose modifications for Imatinib

1. Haematological toxicity.
   If neutrophils fall below $1.0 \times 10^9/L$, or platelets fall below $50 \times 10^9/L$.
   Stop Imatinib and recommence at half previous dose level when counts reach $1.5 \times 10^9/L$ neutrophils and $75 \times 10^9/L$ platelets.
   Patients who become anaemic should be transfused and Imatinib continued.
   If haematological toxicity persists, discuss with Professor Goldstone / Dr Chopra.

2. Non haematological toxicity.

   Grade 2 non-hepatic toxicity

   If a patient experiences Grade 2 toxicities, other than hepatic, that do not resolve despite symptomatic treatment, Imatinib should be withheld until the toxicity resolves to $\leq$ Grade 1. If the toxicity resolves to $\leq$ Grade 1 Imatinib may be continued at the same dose level. If the toxicity recurs, Imatinib should be withheld until the toxicity resolves to $\leq$ grade 1 and Imatinib may then be continued at the preceding dose level. The same cycle may be repeated but if toxicities continue to recur the patient will have to go off study.

   Grade 2 hepatic toxicity

   NCI common toxicity criteria: hepatic

<table>
<thead>
<tr>
<th>Grade</th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>AST, ALT and ALK Phos</td>
<td>WNL</td>
<td>$&gt;\text{ULN}-2.5\times\text{ULN}$</td>
<td>$&gt;2.5-5.0\times\text{ULN}$</td>
<td>$&gt;5.0-20.0\times\text{ULN}$</td>
<td>$&gt;20.0\times\text{ULN}$</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>WNL</td>
<td>$&gt;\text{ULN}-1.5\times\text{ULN}$</td>
<td>$&gt;1.5-3.0\times\text{ULN}$</td>
<td>$&gt;3.0-10.0\times\text{ULN}$</td>
<td>$&gt;10.0\times\text{ULN}$</td>
</tr>
</tbody>
</table>

   WLN: Within Normal Limits
   ULN: Upper Limit Normal

   If a patient experiences a mild Grade 2 hepatic toxicity (AST, ALT 2.5 to 3.5 x upper normal limit) continue Imatinib uninterrupted at the same dose level, however repeat AST, ALT 3 times per week until the toxicity resolves to $\leq$ Grade 1, and then weekly enzyme estimations can be resumed. If the mild Grade 2 hepatic toxicity persists, continue measuring AST, ALT 3 times per week throughout the trial. If the mild Grade 2 hepatic toxicity continues to increase (AST, ALT 3 x upper normal limit). Imatinib must be withheld until the toxicity resolves to $\leq$ Grade 1. If the toxicity resolves to $\leq$ Grade 1 Imatinib may be resumed at the same dose level. If the toxicity recurs, drugs must be withheld again until $\leq$ Grade 1, and then Imatinib may be continued at the preceding dose level. If this Grade 2 hepatic toxicity recurs after dose level reduction, the drugs must be discontinued permanently.

   If any patient experiences moderate Grade 2 hepatic toxicity (AST, ALT $\geq$ 3.5 x’s upper normal limit) withhold Imatinib until $\leq$ Grade 1. If the moderate Grade hepatic toxicity resolves to $\leq$ Grade 1, continue Imatinib at the same dose level. If the Grade 2 hepatic toxicity recurs, withhold study drugs again until $\leq$ Grade 1, and then resume at preceding dose level. If this Grade 2 hepatic toxicity recurs after dose level reduction Imatinib must be discontinued permanently.
Grade 3/4 toxicity non-haematological toxicity (including hepatic)

If a patient experiences Grade 3/4 toxicity Imatinib should be withheld until the toxicity resolves to ≤ Grade 1. Upon recovery the patient may continue treatment at the preceding dose level. If the grade 3/4 toxicity recurs after the dose reduction study drugs must be discontinued permanently. If a patient has not recovered from any toxicity within two weeks of interrupting treatment they must be discontinued from the study.
APPENDIX 6: MONITORING MINIMAL RESIDUAL DISEASE BY MOLECULAR ANALYSIS

It is becoming apparent that monitoring the level of residual disease in remission patients can in some circumstances predict clinical outcome. Advances in molecular techniques allow the assay and detection of very small amounts of residual disease (1 leukaemic cell in 104 - 105 normal cells). After the initial diagnostic tests, the UKALL XII trial has included a systematic examination of patients' bone marrow in follow-up using these molecular techniques.

These results will have important implications for future trials. It is therefore important that adequate specimens of blood and bone marrow are collected at diagnosis and despatched as specified below. Further specimens should be collected at intervals shown below or on request from the relevant laboratory.

Initial tests on Presentation Material

For this purpose, presentation material (BM preferably) must be tested to establish the nature/ molecular features of the leukaemic clone at the time of its greatest level (similar to cytogenetic analysis). Failure to provide presentation sample will impair any future MRD study for a patient as each one has a different molecular profile.

To carry out these investigations, presentation samples should be sent to the UKALL XII designated collection centre (address below). In the absence of available material, 2-4 unstained slides should be sent at least to guarantee DNA analysis.

Any fresh sample received will be tested for the identification of Philadelphia positive cases with results available within 48-72 hrs from sample being received. DNA prepared from BM samples or slides will then be used for the identification of molecular markers for MRD analysis on follow up samples.

MRD analysis of follow up samples

Samples for MRD should be sent at time specified below to maximise the value of MRD analysis as a prognostic indicator of response to therapy.

<table>
<thead>
<tr>
<th>Follow-up specimens</th>
<th>Follow-up specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-ve. patients:</td>
<td>Ph+ve patients:</td>
</tr>
<tr>
<td>1. After induction phase I*</td>
<td>1. After induction phase I*</td>
</tr>
<tr>
<td>2. After induction phase II</td>
<td>2. After induction phase II</td>
</tr>
<tr>
<td>3. After HD-MTX</td>
<td>3. After Imatinib consolidation</td>
</tr>
<tr>
<td>4. From auto PBSC harvest</td>
<td>4. From auto PBSC harvest</td>
</tr>
<tr>
<td>5. Post autograft/allograft every 3 months for first year and every 6 months during year 2 or until relapse</td>
<td>5. Post autograft/allograft every 3 months for the first year then as per Philadelphia negative patients or until relapse</td>
</tr>
</tbody>
</table>

*: when WBC count has recovered >1

Destination of specimens: (send 2.5ml BM and 10ml blood in EDTA please)

Dr L Foroni
Department of Haematology
Royal Free and UCL Medical School
Rowland Hill Street
London NW3 2PF
Tel: 0207 830 2965
Fax: 0207 830 2092
It is important to stress at this stage that the significance of finding such small numbers of leukaemic cells in a patient's bone marrow remains uncertain. An important benefit in this trial will be that a rational assessment of the importance of minimal residual disease will be derived. The trial coordinators therefore believe that once the initial diagnostic information has been provided, further information concerning the presence of minimal residual disease should be collated and released only at the end of the trial. This will allow an accurate assessment of the importance of residual disease on final outcome. Particularly important is the correlation between MRD in autologous PBSC harvest and outcome. It is therefore important that all patients receiving such a procedure be monitored with the highest priority.

### Schedule of sampling for MRD studies

**Presentation material (2 ml BM and 10 ml PB) from all patients**

**Follow up sampling:**

#### Philadelphia negative (B and T cell adult ALL)

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>post Intensification</th>
<th>end of consolidation</th>
<th>3 monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>wk4</td>
<td>wk8</td>
<td>w16</td>
<td>wk39</td>
<td>w98</td>
</tr>
<tr>
<td>2 ml BM</td>
<td>2 ml BM</td>
<td>2 ml BM</td>
<td>2 ml BM</td>
<td>2 ml BM</td>
</tr>
<tr>
<td>10 ml PB</td>
<td>10 ml PB</td>
<td>10 ml PB</td>
<td>10 ml PB</td>
<td>10 ml PB</td>
</tr>
</tbody>
</table>

#### Philadelphia positive ALL

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>post IMATINIB</th>
<th>end of consolidation</th>
<th>3 monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>wk4</td>
<td>wk8</td>
<td>w12</td>
<td>wk39</td>
<td>w98</td>
</tr>
<tr>
<td>2 ml BM</td>
<td>2 ml BM</td>
<td>2 ml BM</td>
<td>2 ml BM</td>
<td>2 ml BM</td>
</tr>
<tr>
<td>10 ml PB</td>
<td>10 ml PB</td>
<td>10 ml PB</td>
<td>10 ml PB</td>
<td>10 ml PB</td>
</tr>
</tbody>
</table>

1. In all patients: PBSC harvest for autologous transplant should be monitored for MRD
2. MRD post SCT: every three months during yr 1 and every 6 months during yr 2

Attached below are accompanying forms for both Ph negative and Ph positive Adult ALL patients. Upon receipt of presentation samples, these forms will be completed and sent to the relevant sites.
Re: MRD study of adult ALL patient on UKALLXII trial

Patient Name: .........................................................
DOB: .................................................................
UKALLXII No: ...........................................................
Treatment started: ..................................................

**Specify Immunophenotype:**

Sample type: 
- PB [ ]
- BM [ ]

Stage of treatment: 
- Induct Phase I [ ]
- Pre Phase II [ ]
- Post Phase II [ ]
- Post Intensification [ ]
- BM harvest [ ]
- Consolidation Phase N: .......... [ ]

Status: 
- 1 CR [ ]
- Relapse [ ]
- 2nd CR [ ]

BM transplant date: .........................
- AUTO [ ]
- ALLO [ ]
- MUD [ ]

Hospital: ...........................................................................................................................

Name of Consultant (**type clearly**) ..................................................................................

Sender: ...............................................................................................................................

Signed: ..............................................................................................................................

Contact tel no: ...................................................................................................................

FAX number: ....................................................................................................................

e-mail contact (please provide if available): .....................................................................
PHILADELPHIA POSITIVE ALL

LETIZIA FORONI
Reader in Haematology, MD PhD
Haematology Department
Royal Free Hospital
Rowland Hill Street
London NW3 2PF

Date ……………………
Patient Name: 
DOB
UKALLXII No:
Treatment started: …………………
Immunophenotype: …………………

Sample type
PB  [ ]
BM  [ ]

Stage of treatment:
Induct Phase I  [ ] Pre Phase II  [ ] Post Phase II  [ ]
post-Glivec:  [ ] weeks of treatment: ………… Is the patient on Glivec now:  Y  N
Post Intensification  [ ] BM harvest  [ ] Consolidation Phase ………  [ ]

Status:  1 CR  [ ] Relapse  [ ] 2nd CR  [ ]
BMT:  ALLO  [ ] AUTO  [ ] MUD  [ ] Date of transplant………/……/………………
Hospital: ……………………………………………………………………………………………………………………………
Name of Consultant (type clearly) ……………………………………………………………………………………………
Sender: …………………………………………………………………………………………………………………………………
Signed: …………………………………………………………………………………………………………………………………
Contact tel no: ………………………………………………………………………………………………………………………
Fax no: …………………………………………………………………………………………………………………………………
e-mail contact: ………………………………………………………………………………………………………………………

Affix label if available
APPENDIX 7: GUIDELINES FOR INTRATHECAL CHEMOTHERAPY.

Training:
All medical, nursing and pharmacy staff must receive training appropriate to their level of involvement in the prescribing, verification, handling, preparation and administration of intrathecal chemotherapy. Training should be undertaken by a lead Consultant in Haematology / Oncology and verified by certification.

It is essential that all staff are aware of the dangers associated with the administration of cytotoxic chemotherapy by the intrathecal route.

Prescribing:
Prescriptions for intrathecal cytotoxic chemotherapy should be written by a designated Specialist Registrar or Consultant who has received the appropriate training.

The prescription should clearly state the drug is to be administered by the intrathecal route. No abbreviations for the route are acceptable.

Intrathecal injections and injections by other routes of administration must not take place at the same time. The UKALL XII protocol has been modified to take account of this. This should be considered by the prescriber.

In-patients will not be scheduled to receive intravenous and intrathecal drugs on the same day.

In the maintenance phase intrathecal cytarabine is given TWO WEEKS AFTER IV VINCRISTINE, NEVER ON THE SAME DAY.

Preparation:
Intrathecal chemotherapy will always be prepared in pharmacy.

Labelling and packaging:
The unabbreviated route of administration will be included on the labels.

All intrathecal doses of chemotherapy will be labelled: “FOR INTRATHECAL USE”.

Vincristine doses will be labelled: “FOR INTRAVENOUS USE ONLY” Vincristine should be reconstituted in 20 mls normal saline.

Intrathecal doses will be packaged in sealed red plastic bags or use existing local policy to highlight the differences from intravenous drugs.

Delivery:
Intrathecal injections will be delivered, directly to the area where they are to be administered, in separate transport containers from cytotoxic chemotherapy to be administered by other routes.

Administration:
Units administering intrathecal chemotherapy should follow the “National Guidance on the Safe Administration of Intrathecal Chemotherapy”.

The main areas to consider are:

Patients should only receive intrathecal cytotoxic chemotherapy in designated areas where the members of staff are routinely involved in the administration of drugs by the intrathecal route. Intravenous cytotoxic chemotherapy should never be administered in the same designated area.

Intrathecal doses should be administered by designated medical staff who have received the appropriate training in the administration of intrathecal cytotoxic chemotherapy (which will have involved a supervised training period).

Prior to intrathecal administration, the doctor administering the therapy must verify the prescription and syringe details, with an appropriately trained (chemotherapy qualified) nurse and the prescription chart must be signed by both.

Intrathecal administration of cytotoxic chemotherapy must be scheduled for times when experienced staff are available to give it. It should take place during working hours and not at weekends.
APPENDIX 8: TRIAL TRANSPLANT CENTRES (2001)

Bath
Royal United Hospital, Coombe Park, Bath BA1 3NG
(0122-582-4488)

Belfast
Belfast City Hospital, Lisburn Road, Belfast BT9 7AB
(0289-032-9241)

Birmingham
Department of Haematology, Queen Elizabeth II Hospital, Edgbaston,
Birmingham B15 2TH
(0121-472-1311)

Birmingham
Department of Haematology, Birmingham Heartlands Hospital, Birmingham B9
5ST
(0121-424-2000 ext. 4243699)

Bournemouth
Royal Bournemouth & Christchurch NHS Trust, Castle Lane East, Bournemouth
BH7 7DW
(0120-230-3626)

Cambridge
Department of Haematology, Addenbrooke's Hospital, Hills Road, Cambridge
CB2 2QQ
(0122-321-6747)

Cardiff
University of Wales College of Medicine, Heath Park, Cardiff CF14 4XW
(0292-074-7747)

Coventry
Department of Haematology, University Hospitals Coventry & Warwick NHS
Trust, Clifford Bridge Road, Walsgrove, Coventry CV2 2DX
(0247-653-8866)

Dublin
St James's Hospital, PO Box 580, Dublin 8, Eire
(0035-3145-37941)

Edinburgh
Haematology Department, Western General Hospital, Crewe Road North,
Edinburgh EH4 2XU
(0131-537-1000)

Glasgow
Glasgow Royal Infirmary, Glasgow G4 0SF
(0141-211-4000)

Leeds
Leeds General Infirmary, Great George Street, Leeds LS1 3EX
(0113-243-2799)

Leicester
The Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW
(0116-258-6602)

Liverpool
Department of Haematology, Duncan Building, Royal Liverpool Hospital, Prescot
Street, Liverpool L7 8XP
(0151-706-4344) (0151-706-4311)

London
Royal Free Hospital, Pond Street, London NW3 2QG
(0207-794-0500 ext. 3257)

London
Guy’s Hospital, St Thomas's Street, London SE1 9RT
(0207-955-5000 ext. 4004)

London
University College Hospital, Gower Street, London WC1 E 6AU
(0207-387-9300 ext. 9712)

London
London Hospital Medical College, Whitechapel, London E1 1BB
(0207-377-7000 ext. 7180)

London
Medical Oncology Unit, St Bartholomew’s Hospital, West Smithfield, London
EC1A 7BE
(0207-601-7461)
London  LRF Leukaemia Unit, Haematology Department, Hammersmith Hospital, Ducane Road, London W12 0NN  (0208-383-1000)
London  Royal Marsden Hospital NHS Trust Downs Road, Sutton, Surrey SM2 5PT  (0208-642-6011 ext 3117)
London  Northwick Park Hospital, Watford Road Harrow, Middlesex HA1 3UJ  (0208-864-3232)
London  King's College Hospital, Denmark Hill, London SE5 (0207-737-4000)
Manchester  Christie Hospital, Wilmslow Road, Withington, Manchester M20 9BX  (0161-446-3748)
Manchester  Department of Clinical Haematology, Manchester Royal Infirmary, Manchester M13 9WL  (061-276-1234 Ext 4802)
Newcastle  Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP  (0191-232-5131)
Nottingham  City Hospital, Hucknall Road, Nottingham NG5 1 PB (0115-969-1169 ext. 45564)
Oxford  Department of Haematology, Level 4, John Radcliffe Hospital, Oxford 0X3 9DU  (0186-574-1166)
Plymouth  Department of Haematology, Derriford Hospital, Derriford Road, Plymouth, Devon PL6 8DH  (0175-279-2398)
Sheffield  Department of Haematology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF (0114-271-1900 ext. 3350)
Southampton  Department of Haematology, Royal South Hants Hospital, Southampton SO14 0YG  (0238-063-4288)
APPENDIX 9: ACCESS TO LENOGRASTIM AND IMATINIB

Discounted Lenograstim can be obtained from Chugai Pharma UK, Mulliner House, Flanders Road, London W4 1NN. After the patient has completed their study, contact Chugai on 0208 987 5671, and 25% of drug used will be reimbursed.

For patients with Philadelphia positive ALL, Imatinib will be supplied free of charge by Novartis.

Confirmation that cytogenetic and PCR assessments of BCR-ABL have been initiated will be required before Imatinib is made available. Upon registration of a Philadelphia positive patient, you will be sent a confirmation of entry, which will enable you to obtain Imatinib.

Once you have received confirmation please contact Novartis for supply of Imatinib. You will need patient details and proposed start date for Imatinib.

Angela Findley
Clinical Development Advisor
Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR

Tel: 44(0)1276 698590
Fax: 44(0)1276 698605

Please note: It is imperative that you inform Novartis as soon as Imatinib is stopped for any reason, including relapse of disease.
APPENDIX 10: SERIOUS ADVERSE EVENT REPORTING FORM

Attached below is a copy of the form to be used for the reporting of Serious Adverse Events for the UKALL12 study only.

This form is also available via the Clinical Trials Service Unit website at www.ctsu.ox.ac.uk

Once completed, the form should be sent by fax to the CTSU. Dependant on the nature of the event, further follow up information may be requested.

Please double click on the icon below to access the form:

Attachment 1: UKALL12 SAE Reporting Form
REFERENCES


22. Report from the International Bone Marrow Transplant Registry. Bone Marrow Transplantation 1989; 4: -221-228


29. Bennett WM. Drugs and renal disease, 2nd edition


