East Midlands Cancer Network Guidelines for the Investigation and Management of Patients with Acute Lymphoblastic Leukaemia (ALL) Treated in Adult Haematology Service (From 18 Years)

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Diagnosis

- FBC
- U&E’s
- LFT
- LDH
- Urate
- BM aspirate and trephine biopsy (to be done at Treatment Centre whenever possible to ensure MRD samples are processed as per trial requirements)
- Immunophenotype
- Cytogenetics including Philadelphia status
- Baseline MRD sample
- Mercaptopurine metabolism status sample (UKALL2003 only)
- Blood for HLA typing (if transplant candidate)
- Sperm storage to be offered

Treatment delivery

BCSH levels of care requirements:

**Level 3**
Centre must be treating more than 5 patients treated with curative intent per year.

**Also**
Filtered air single room should be available.

Clinical trial **MUST** be offered – patients should be counseled that no satisfactory ‘off trial’ therapy is available.
**Trial options**

**UKALL2011**

(UKALL2003 interim guidance will be available until trial commencement)

Please refer to the Trial protocol

- < 25 years – to be opened in Nottingham and Leicester

UKALL2011 requires:

- Paediatric liaison
- TYA MDT discussion
- Age appropriate bed
- MRD monitoring (Sheffield)

**UKALL14**

Please refer to the Trial current protocol version.

Eligibility:

- 25-60 years inclusive – open in Nottingham and Leicester
- Requires MRD monitoring (Royal Free)
- Non transplant patients will follow consolidation schedule
- Trial schema

**Summary of study aims**

**Primary**

- To determine if the addition of monoclonal antibody to standard induction chemotherapy results in improved EFS in patients with precursor B cell (aim 1B).
- To determine if the addition of nelarabine improves outcome for patients with T cell ALL (aim 1T).
Secondary

- To determine the tolerability of pegylated asparaginase in induction treatment of all patients (aim 2) and to compare anti-asparaginase antibody levels between patients in the two randomization groups from aim 1B (patients with B lineage ALL only).

- To determine whether risk-adapted introduction of unrelated donor HSCT (myeloablative conditioning in patients ≤ 40 years old and non-myeloablative conditioning in patients >40 years old) results in greater EFS for patients at highest risk of relapse (aim 3).

- To compare 2 schedules of administration (standard vs ‘collapsed’) of keratinocyte growth factor (palifermin) for efficacy in preventing the severe mucosal toxicity of etoposide/TB1 HSCT conditioning regimen (aim 4).

- To formally assess the late effects of ALL therapy for all patients on the trial whether they have received chemotherapy alone or an allograft. To identify and describe some of the adverse physical and psychosocial consequences of the disease and its treatment.

Recommended supportive care

Allopurinol should be started 24 hours prior to induction chemotherapy and should be continued for a minimum of 5 days. Rasburicase should be considered as an alternative to allopurinol if the white cell count is high i.e >100 x 109/L or the patient has bulky disease e.g. large mediastinal mass or elevated urate at diagnosis.

All patients need prophylaxis against HSV and VZV reactivation. It is recommended that patients are given acyclovir 200mg bd throughout therapy although local policies may be followed.

All patients need prophylaxis against PCP from day zero of induction. The recommended PCP prophylaxis is Septrin 960mg bd for 2 days each week, avoiding the day that methotrexate is given when the patient is on maintenance therapy. In the event of the patient being allergic to septrin local policies should be followed but alternative prophylactic agents include nebulised pentamidine or dapsone.

Antifungal prophylaxis is mandatory for all patients on ALL therapy from the time of induction. Azoles must be avoided when the patient is on vincristine. There is no clear evidence to suggest which anti-fungal prophylaxis regimen should be used in this situation but one option is to give ambisome 7mg/kg weekly. Local policies may be followed. Azoles can be used safely after phase 1 of induction.

Antifungal prophylaxis is not generally required when a patient is on maintenance therapy unless that patient is deemed to be high risk for fungal disease.
Role of L-asparaginase (abbreviated)

L-asparaginase is arguably one of the most valuable drugs in the treatment of ALL. However, it is associated with numerous toxicities including hepatic dysfunction, pancreatitis and thrombohaemorrhagic complications related to depletion of coagulation factors. An additional complicating feature of the use of L-asparaginase clinically is the development of antibodies to the enzyme that can either result in hypersensitivity reactions (IgE) or via neutralising antibodies (IgG) with decrease in enzyme activity with loss of therapeutic efficacy. Neutralizing antibodies developing in the absence of a clinical reaction is known as silent inactivation. When toxicity occurs early in treatment, therapeutic delays are often generated which can compromise the aims of therapy.

In the case of hypersensitivity to peg-asp, Erwina asparaginase should be substituted at a dose of 20,000 units/m2 IM (x6 doses) as a replacement for each scheduled dose of PEG-asparaginase.

Management of thrombosis

LMWH is the treatment of choice for the management of central line related thrombosis. In this situation, asparaginase should be suspended for that cycle but can be given with heparin prophylaxis in subsequent cycles.

The use of LMWH in patients immediately following a diagnosis of a CNS thrombosis is more contentious. All heparinised patients must be monitored using anti Xa levels or the APTT depending on the type of heparin given. It is important to note that a proportion of patients will be resistant to heparin due to the depletion of AT caused by asparaginase. In this instance replacement of AT may be indicated. This should be done after seeking specialist advice from a thrombosis and haemostasis expert. Alternatively please contact the CI or one of the clinical coordinators for advice.

Methotrexate encephalopathy management

Methotrexate encephalopathy presents with fits, focal neurological deficit or impaired consciousness and occurs within one day to about 3 weeks of exposure to IT methotrexate. Full recovery is usual.

Other causes of CNS events should be considered such as sagittal sinus thrombosis or central nervous system involvement with ALL.

Methotrexate should be discontinued whilst the patient is also receiving cytarabine systemically.

Re-challenge is possible without recurrence but if recurrence happens, the intrathecal regimen should be changed to cytarabine 50mg in association with 12.5mg hydrocortisone.

Full details of the treatment protocol must be obtained from the current version and so are not reproduced here.
**Notable management points**

Delay Hickman line insertion to day 28+ if possible

**Management of Asparaginase thrombogenicity** :-

- If fibrinogen levels are monitored and blood product replacement undertaken it must be noted that these products are a source of asparagene and may reverse the therapeutic effect of asparaginase.

- All patients with a platelet count over 50 must receive standard thromboprophylaxis especially during Peg-asparaginase therapy.

- Fungal prophylaxis during induction and consolidation should be with Ambisome/Abelcet.(see above) Azoles must not be used during any phase including Vinca alkaloids and attention must be paid to ensure that if azoles are used then these are stopped prior to any subsequent block including Vincristine.

- MRI scanning should be used for all suspected cases of AVN – plain radiographs are inadequate.

- Lumbar Puncture – the protocol states that-
  Lumbar puncture is not required at diagnosis except in the case of suspected central nervous system involvement. Otherwise, it should be avoided (in case of traumatic puncture and CNS seeding) until the first dose of intrathecal methotrexate is due at which time blasts should have been cleared from the peripheral blood. The first lumbar puncture should always be given by the most experienced operator available, to reduce the incidence of traumatic taps.

**Shared Care of Patients on National Trial**

For patients who have to travel long distances to the Trial centre the option of shared care may be considered.

1. If the local Hospital has Ethics and R&D approval care may be transferred to the local unit for the maintenance phase of care. (At present this requires full Trial ethics and R&D approval but a modified maintenance care protocol is in discussion)

2. If the local hospital does not have the Trial open then bloods may be taken and analysed locally but all clinical decisions must be taken by the Trial Centre, ie Nottingham or Leicester. (Vincristine and intrathecal chemotherapy must be given centrally)
**Principles/Standards for Shared Care during Maintenance**

- Effective communication web/fax/email
- Clearly identified consultant / CNS etc
- End of treatment summary to include virology results, infection history, TPMT genotype, intermediate maintenance dose modifications and recommended starting 6 MP dosage
- Routine BM’s unlikely to be done locally because of MRD samples unless Hospital is approved as a trial participant.
- Admissions with complications etc: DGH acceptable subject to patient preference

**UKALL14 Transplant schedule**

HLA typing needs to be commenced as soon as possible after diagnosis.

The following sections are copied from the Protocol:

**Patient eligibility for transplant**

**Inclusion criteria (transplant)**

- Completion of Phase 1 and Phase 2 treatment within the trial
- HLA-compatible sibling or unrelated donor (8/8 molecular match at A, B, C and DR. DQ mismatch is permitted.
- Two subgroups of patients will proceed to transplant:–
  - Any patient with an HLA-compatible sibling donor.
  - High Risk patients with a molecularly matched donor at HLA-A,B,C & DR.

**Eligibility for high risk arm – unrelated donor stem cell transplantation**

Any one of the factors below makes the patient high-risk:-

- Age over 40 years
- WBC ≥30 x 10^9/L (precursor-B), ≥100 x 10^9/L (T-lineage)
• Cytogenetics – any one or more of the abnormalities below:
  o t(4;11)(q21;q23)/MLL-AF4
  o Low hypodiploidy/near triploidy (30-39 chromosomes / 60-78 chromosomes
  o Complex karyotype (five or more chromosomal abnormalities)
  o Philadelphia chromosome t(9;22) (q34;q11)/BCR-ABL1 (detected by cytogenetic or molecular methods)

• High Risk Minimal Residual Disease (MRD) post phase 2 of induction.

Further details of the transplant schedule will be found in the protocol.

Relapsed Disease

Reinduction

Most patients will be treated with either FLAG IDA or Amsacrine & High Dose cytarabine. If a second remission is obtained all patients should be considered for a transplant procedure if they have not received this in CR1.

UKALL 2003 / 2011 patients will usually receive Clofarabine/ Cyclophosphamide/Etoposide reinduction (funded via CDF if necessary).

Management of Elderly Patients with ALL

UKALL60 is in development

Elderly patients may be treated in the Local Hospital Unit.

Philadelphia Positive disease patients should be managed with a TKI. Use Imatinib 600mg od or, if specifically required an IFR may be submitted for Dasatinib 140mg od.

Other patients fit for chemotherapy should be considered for UKALL X protocol or Vincristine/prednisolone if not fit enough for the more intensive arm.