Pan Birmingham NHS
Cancer Network

Guideline for the Management of Acute Lymphoblastic Leukaemia (ALL) in Adults

Version History

Version	Date	Summary of Change/Process
1.0		The UKALL trial protocol was approved as version 1.
1.1	22.07.10	First draft distributed to the Haematology Network Site Specific Group, Nicky Pettitt, Teenage Cancer Trust Clinical Nurse Specialist and Jeanette Hawkins, Lead Cancer Nurse
1.1		Circulated to Dave Hobin, Consultant Paediatric Oncologist
1.1	04.04.11	Gina Dutton, Research Network Manager, consulted re protocols
1.1	18.02.11	Discussed at Network Site Specific Group
1.2	18.04.11	Updated by Fiona Clark, Consultant Haematologist. For submission to the clinical governance subgroup.
2.0	10.05.11	Endorsed by the Governance

Date Approved by Network Governance	**May 2011**

Date for Review	**May 2014**

Revisions between Version 1 and Version 2

Version 1 was the UKALL trial protocol. Version 2 is a substantial revision, incorporating UKALL 14 and Teenage\Young Adults regimens.

1 Scope

This guidance has been produced to support:

- The management and investigation of patients suspected of having ALL
- The management of patients diagnosed with ALL

2 Guideline Background

In Pan Birmingham Cancer Network two Trusts are designated transplant centres offering level 2 - 4 care (University Hospital Birmingham Foundation Trust and Heart of England Foundation Trust). Good Hope Hospital offers level 1 care for patients

with haematological cancers. In addition to this Sandwell and West Birmingham Hospitals NHS Trust practices to level 2.

Guideline Statements

3 Referral

3.1 Patients with a combination of the following should undergo an urgent blood count and film ESR and/or c-reactive protein (+/- clotting screen):

- Fatigue
- Drenching night sweats
- Fever
- Weight loss
- Breathlessness
- Bruising / bleeding
- Recurrent infections
- Lymphadenopathy
- Splenomegaly

3.2 Patients with the above signs and symptoms should be referred **immediately** to the local haematology team for urgent investigation.

3.3 Patients with ALL may also present with:

a. Blood count / film reported as suggestive of acute leukaemia
b. Pancytopenia
c. Bone pain
d. Neurological symptoms
e. Mediastinal mass, which may cause cardiorespiratory compromise

4 Investigation and Diagnosis

4.1 Patients suspected of having ALL should undergo the following:

a. Bone marrow aspirate and trephine biopsy (unless peripheral blood blast count is high).
b. Immunophenotyping with multi-colour flow cytometry, panels to identify lineage, aberrant antigens and markers of minimal residual disease (MRD): as per British Committee for Standards in Haematology (BCSH) guideline on Immunophenotyping Acute Leukaemias (2002).
c. CT scan chest, abdomen, pelvis if evidence of lymphadenopathy, organ involvement.
d. CT or MRI head and/or spine if there are neurological symptoms or signs at presentation, if these are normal with no mass effect lumbar puncture with cerebrospinal fluid (CSF) examination for lymphoid blasts.
e. Cytogenetics and molecular genetic analysis must be performed in all cases, as well as FISH for BCR-ABL, ETV6-RUNX-1(TEL-AML1), amplification of RUNX-1 and MLL gene rearrangements.

f. If the patient is entered into a national trial, additional samples for baseline MRD and trial purposes will be required.

4.2 The marrow slides should be reported by a Haematopathologist (Histologist or Haematologist) trained in leukaemia morphology. An integrated diagnostic report should be generated, incorporating morphological, histological, immunophenotypic and molecular/genetic information, and reported as per the WHO classification 2008.

5 Primary Treatment

5.1 All patients: supportive care

5.1.1 Local, Network and BCSH guidelines should be followed for the management of the following treatments and care:
a. Blood and blood product support
b. The use of growth factors
c. Neutropenia – prevention and treatment
d. Infection prophylaxis

5.1.2 Tumour lysis should be prevented/detected early and managed proactively. This should include careful monitoring of U's and E's, potassium and urine output as well as adequate hydration, allopurinol. Rasburicase should be used where the WCC is >50, if there is biochemical disturbance (hyperuricaemia, renal impairment) or there is evidence of bulky lymphadenopathy (e.g. bulky mediastinum).

5.1.3 Where active treatment is not recommended patients may find a second opinion reassuring and this should be supported.

5.2 Philadelphia Negative ALL (age 25 - 65 years)

5.2.1 All patients should be offered a clinical trial if available. The current national trial opening 2010 will be **UKALL14**, for patients aged 25 - 65.

5.2.2 Adult patients with ALL have a 90% chance of entering first complete remission (CR) with induction chemotherapy, however leukaemia-free survival is only 30 - 40%.

5.2.3 All patients deemed fit enough to receive intensive treatment should be offered induction chemotherapy.

5.2.4 Patients following an intensive route and considered a potential transplant candidate should be HLA-typed at presentation or at the earliest opportunity and sibling typing should be performed at the earliest opportunity.

5.2.5 Patients achieving a complete remission and with an HLA-identical sibling should be referred for consideration of an allogeneic transplant in CR1, as post remission therapy.

5.2.6 Patients identified as high risk, based on risk factors identified in the UKALL XII trial, where appropriate may be referred for HLA-matched unrelated donor transplantation in CR1. Definition of 'high risk' includes: presenting WCC >30 $X10^9$/L (pre-B ALL), WCC >100 $X10^9$/L (T-ALL); cytogenetics: t(4;11), hypodiploidy, near triploidy, complex (>5 abnormalities).

5.2.7 Patients may also be eligible for unrelated donor transplantation if identified as high risk within the UKALL14 trial (based on MRD assessment after Phase II). It is imperative that early HLA-typing is performed and donor search initiated.

5.2.8 Minimal residual disease assessed by molecular IgH PCR is established in paediatric practice but should not be used diagnostically in the adult cohort outside a clinical trial, molecular MRD is incorporated into UKALL14 and UKALL2003 trial protocols.

5.2.9 Patients unable to tolerate intensive induction chemotherapy, due to physician assessment based on age >65 years, comorbid conditions, performance status: should be offered best supportive care including transfusion support. Attenuated chemotherapy may be suitable and allow patients to achieve CR with low toxicity. (Elderly, non-intensive NCRI protocol is in draft).

5.3 Teenage and Young Adults with Ph Negative ALL (age 16 - 24 years inclusive)

5.3.1 Multinational trial data has demonstrated a significant survival advantage for patients aged 15 - 19 years treated with paediatric-style regimens compared to adult protocols.

5.3.2 The NCRI trial UKALL2003 (and its anticipated successor UKALL2010) has expanded to include patients aged 16 - 24.

5.3.3 All patients aged 16 - 24 years must be treated on an age-specific paediatric protocol **and within the trial.**

5.3.4 Patients aged 16 - 18 years must be referred for diagnosis and treatment to a principal treatment centre for teenagers and young adults, (University Hospital Birmingham NHS Foundation Trust or Birmingham Children's Hospital NHS Foundation Trust – Teenage and Young Adults teams).

5.3.5 Patients aged 19-24 years must be offered referral to a principle treatment centre but if treated locally must be entered into the paediatric trial.

5.4 Philadelphia Positive ALL

5.4.1 The presence of the Philadelphia chromosome in patients with acute lymphoblastic leukaemia (ALL) confers a poor prognosis. 20-30% of adults presenting with ALL are Philadelphia chromosome positive (Ph+) with the incidence rising to ~50% in age group greater than 60.

5.4.2 Historical data suggests durable disease free survival for patients receiving chemotherapy alone in the order of 10 - 20%.

5.4.3 The Japanese Adult Leukaemia Study Group reported its outcomes for patients treated in consecutive trials for Ph+ALL. Remission induction combined with Imatinib (600mg) was associated with 96% CR rates. Patients with a matched donor underwent allogeneic transplantation in CR1. Compared to historical cohorts treated without Imatinib, there was a significant improvement in event free survival (EFS) and overall survival (OS) at 1 year, (event free survival: 60% at 1 year, 48.5% at 2 years and overall survival 76% at 1year, 60% at 2 years). The GRAAPH 2003 trial reported 45 newly diagnosed Ph+ALL patients treated with Imatinib 600mg during consolidation chemotherapy. CR rates were 96%, significantly higher compared to the historical cohort in LALA94 (71%); with 38% of patients overall achieving molecular negativity. For this study estimated disease free survival was 51% and OS 65% at 18 months follow-up.

5.4.4 It is recommended that patients presenting with Ph+ ALL receive Imatinib 600mg daily, commencing as soon as the bcr-abl Ph+ status is confirmed.

5.4.5 Patients should remain on Imatinib until transplant or disease progression.

5.4.6 Patients failing to achieve a remission (<5% blasts) after 2 cycles of chemotherapy combined with Imatinib should be considered a treatment failure and Imatinib discontinued.

5.4.7 Second generation TKI (dasatinib and nilotinib) have shown clinical activity as salvage for patients with relapsed refractory ALL but at present are not recommended outside a clinical trial.

5.4.8 Patients deemed fit for transplantation and with a suitable allogeneic donor (sibling or unrelated donor) should be referred for transplant in CR1.

5.5 Central Nervous System (CNS) disease at Presentation

5.5.1 CNS involvement is present in 5-10% of patients presenting with adult ALL.

5.5.2 CNS leukaemia is defined as unequivocal evidence of lymphoblasts in CSF cytospin (morphological +/- immunophenotypic), or cranial nerve palsies or significant neurological dysfunction.

5.5.3 Patients with CNS leukaemia should commence induction chemotherapy and also receive intrathecal therapy with methotrexate, escalated to twice per week and given at this frequency until the cytospin is clear of blasts. Such patients should also receive cranial irradiation, prior to consolidation, if they are not going to receive myeloablative allogeneic transplant. (As per UKALL 14 trial protocol).

5.6 Pregnancy

5.6.1 ALL in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother.

5.6.2 Chemotherapy in the first trimester should be avoided if possible. The option of terminating the pregnancy should be discussed with the mother. If termination is refused and the mother's life is at risk, chemotherapy should be started.

5.6.3 Where appropriate consideration should be given to early induced labour between cycles of chemotherapy.

6. Transplantation

6.1 Adult ALL has a very poor salvage rate in relapse and should be considered for transplantation early in the disease (CR1). **HLA-typing should be requested on all patients at diagnosis and siblings typed promptly**. An unrelated donor search should be instigated promptly to avoid delay to transplant.

6.2 Allogeneic transplantation is highly effective in reducing the risk of disease relapse but is associated with significant risk. Myeloablative transplant should be offered to patients with ALL in the first remission, aged <40 years and who have an HLA identical sibling donor. In patients lacking a sibling donor an unrelated transplant may be considered for those with high-risk disease.

6.3 Myeloablative conditioning should include fractionated TBI at doses not <13.2Gy and with cranio-spinal boost.

6.4 HLA-matched sibling allogeneic transplantation improves outcome in patients in second CR and should be considered the treatment of choice for younger patients who are in second remission.

6.5 Allogeneic transplants performed using reduced intensity conditioning regimens have not been assessed prospectively in trials, however registry data suggests durable DFS for patients with high-risk disease. Reduced-Intensity Conditioning allografts (RIC) for ALL should only be undertaken as part of a clinical trial and are incorporated into UKALL 14 trial.

6.6 Younger and high risk patients, may be considered for a alternative donor transplant (cord blood).

7. Follow-up

Follow-up should be as per trial requirements or in the haematology clinics at appropriate intervals e.g. 2 - 3 monthly when in complete remission after completion of all courses of induction and consolidation chemotherapy. Patients should be advised to report promptly to their GP for an urgent full blood count if they develop any signs or symptoms that might indicate disease relapse.

8. Patient Information and Counselling

8.1 All patients, and with their consent, their partners will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a Clinical Nurse Specialist who is a member of the relevant Multi Disciplinary Team. The patient should have a method of access to the Haematology team at all times.

8.2 Access to psychological support will be available if required. All patients should undergo a Holistic Needs Assessment and onward referral as required.

9. Clinical Trials

9.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

9.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network. Email: PBCRN@westmidlands.nhs.uk .

9.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

10. Palliative Care

Early links should be made to the palliative care team where the treatment intent is not curative or where the patient has symptoms that are difficult to manage.

Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the Network Site Specific Group in 2011\2012.

References

1. UKALL14 trial protocol
2. UKALL2003 trial protocol
3. How I treat acute lymphocytic leukaemia in adults *Rowe J, Blood 2007*
4. BCSH Guidelines an Immunophenotyping 2002

Authors

1 Dr Fiona Clark Consultant Haematologist

Approval Date of Network Site Specific Group	Date	February 2011
Approval Date by the Clinical Governance Team	Date	May 2011

Approval Signatures

Pan Birmingham Cancer Network Governance Committee
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Signature Date May 2011

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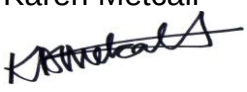

Signature Date May 2011

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UKALL Trial Schema