Manchester Cancer Haematological-Oncology Pathway Board

Guidelines for the Diagnosis and treatment of Adult Acute Lymphoblastic Leukaemia

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These guidelines should be read in conjunction with the latest National Cancer Drug Fund information and all applicable national/international guidance.

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Introduction

Acute lymphoblastic leukaemia is an uncommon haematological malignancy that can be diagnosed at any age. Survival rates now approach 90% for most children with ALL. Despite improvements in outcomes over the years, adults patients with ALL consistently have a much poorer prognosis.

Current outcomes for adults with ALL

Outcome data for patients diagnosed with ALL in the US in the 2 decades between 1980-1984 and 2000-2004 show substantial improvements in survival observed for patients less than 60 years of age (table 1). Improvements in outcome relate primarily to intensification of therapy using 'paediatric-inspired' protocols for teenage and young adult patients, the incorporation of targeted agents e.g. tyrosine kinase inhibitors for BCR-ABL1 + disease, improved patient risk stratification using minimal residual disease (MRD) assessment, and a more rational approach to allogeneic haematopoietic cell transplantation in adult ALL. Bearing this in mind, patient age, risk stratification at diagnosis, MRD response assessment during treatment and suitability for allogeneic transplantation should all be considerations in therapeutic decision making.

Table 1. Improvements in Survival for Patients with ALL[1]

Age group	5 year point estimate of survival 1980-84 (standard error)	5 year point estimate of survival 2000-04 (standard error)	Percentage increase	P value
15-19	21.5 (2.0)	33.2 (1.8)	+11.7	<0.001
20-29	41.0 (4.9)	61.1 (4.4)	+20.1	0.001
30-44	20.2 (4.8)	34.3 (3.9)	+14.1	0.002
45-59	10.3 (4.9)	24.3 (3.4)	+14.0	0.001
60+	8.4 (3.0)	12.7 (2.9)	+4.3	0.48

General principles of ALL management

- All patients should be treated with age-appropriate therapy, and treatment of patients with ALL should be undertaken where possible within the context of a clinical trial to facilitate information gathering, and access to novel therapeutics.
- Patients should be offered the opportunity to be referred to a centre where the appropriate clinical trial is open.
- As experienced specific and supportive care is required in the management of patients with ALL, the European Working Group on Adult ALL recommends that patients should be treated in centres that see at least five new patients per annum.
- In certain circumstances, it may be appropriate for patients being treated non-intensively/with palliative intent, and not eligible for clinical trial to be managed at their local centre with specialist input as required, dependent on patient/clinician preference.
- Adherence to the detail and timing of treatment schedules is important, and minimising therapeutic delays positively impacts outcome.

Initial assessment/diagnosis

1. Investigations:

Investigations at presentation should be performed according to local practice and may include the following:

- Full medical history and physical examination
- Assessment of performance status (Karnofsky/ECOG)
- Height, weight and body surface area (BSA)
- Full blood count and film
- Coagulation screen
- Biochemistry to include urate, LDH
- Liver function to include bilirubin, alkaline phosphatase, ALT or AST
- Viral serologies
- Bone marrow aspiration for the following:
    - Morphology
    - Immunophenotyping
        - Cell surface markers: CD19, CD10, CD22, CD2, CD7, CD3, CD13, CD33, CD117, CD34, CD45 and HLA-DR
        - Intracellular markers: cCD3, cCD22, cCD79a, IgM, MPO and Tdt
    - Cytogenetics (to include G- banding, and FISH for MLL rearrangement, BCR/ABL1, ETV6/RUNX1)
    - MRD assessment* (please follow individual trial protocol guidance)
- A trephine biopsy should also be sought where possible for histopathological confirmation of diagnosis

- Patients with suspected T-ALL (and B-ALL with evidence of lymphadenopathy or organomegaly) should have baseline imaging assessment with CT NTAP or CT/PET as per local protocols
- Echocardiogram
- Pregnancy test for all female patients of child bearing age. This must be performed within 2 weeks prior to starting treatment.
- HLA typing on all potentially transplant eligible patients at diagnosis

*Any testing for MRD which is used to guide treatment should be performed in an accredited laboratory. Laboratories providing molecular MRD monitoring for ALL are listed below:

Pediatric / TYA patients	Adult patients
Mr James Blackburn Genetic Technologist (VRC Registered) Sheffield Diagnostic Genetics Service Sheffield Children's NHS Foundation Trust, Western Bank, Sheffield, S10 2TH Tel: 0114 2717284 Fax: 0114 2756029 email: james.blackburn@sch.nhs.uk	**Professor Adele Fielding** Adult ALL MRD laboratory UCL Cancer Institute Paul O'Gorman Building 72 Huntley Street London, WC1E 6DD Phone: 0207 679 0719 email: allmrdlab@ucl.ac.uk

MRD sample requirements

For MRD assessment, 2-5mls bone marrow in EDTA by 1st class post is required. In the event of a dry tap at diagnosis or relapse and a high peripheral blood WCC, 20-40mls peripheral blood should be sent along with information detailing the patient's blast percentage. At all other time points, peripheral blood will be uninformative and will result in an 'inadequate sample' being reported. If the peripheral blood WCC is low, a trephine biopsy can be sent in saline (NOT FORMALIN) for MRD assessment. Where possible, samples should be taken Monday-Thursday to avoid delays in transit. If samples cannot be shipped on the same day they are taken, they should be stored at 4°C and shipped on the next working day. The treating clinician will be provided with the result of the analysis via a report and will be notified if samples are inadequate.

2. Central nervous system (CNS) disease assessment:

Guidance should be sought from individual trial protocols. In general, lumbar puncture is not mandated at diagnosis except in the case of suspected CNS involvement. Otherwise, it should be avoided until the first dose intrathecal (IT) chemotherapy administration is due (at which time the blasts should have been cleared from the peripheral blood). The first lumbar puncture should always be performed by the most experienced operator available, to reduce the incidence of traumatic tap and CNS seeding. At the time of initial IT chemotherapy dose, cerebrospinal fluid (CSF) samples should be sent for cytospin and immunophenotyping as per local laboratory practices. Subsequent CSF examination should be guided by the presence or absence of disease at diagnosis, and the patient's evolving clinical status. Whilst it is recommended to monitor for blast clearance from the CSF in patients who have detectable disease at presentation, it is not mandatory to perform cytospin/CSF immunophenotyping on CSF at every IT chemotherapy administration if a patient is not known or suspected of having CNS involvement.

CNS disease (in an atraumatic tap) can be categorised as follows:

- CNS1 <5/μl WBC in the CSF with no blasts seen on cytospin
- CNS2 – <5/μl WBC in the CSF with blasts seen on cytospin
- CNS3 – the presence of >5/μl and unequivocal lymphoblasts on CSF cytospin

If the patient has circulating blasts in the peripheral blood and the lumbar puncture (LP) is traumatic (>10 RBC/μl), there is evidence that this adversely affects treatment outcomes[2].

Clinically significant neurological deficits (such as cranial nerve lesions) and/or radiological evidence of an intracranial or intradural mass consistent with extramedullary disease should be considered to represent CNS positivity. Patients with clinical CNS involvement such as cranial nerve lesions or parenchymal brain lesions on imaging should be treated as CNS 3 positive. For the management of CNS disease, individual trial protocols should be consulted.

3. Patient risk stratification:

Initial risk stratification should be performed according to individual trial protocols.

a) Paediatric/teenage and young adult (TYA) ALL patients

Paediatric/TYA patients with ALL following UKALL2011 or UKALL2003 interim guidance will undergo treatment stratification based on age, presenting WCC and cytogenetic profile. Treatment pathways will be allocated/adjusted according to risk (see individual protocols for details):

NCI Standard Risk:

- B-cell precursor (BCP)-ALL: >1 year and < 10 years AND Highest WCC before starting treatment of <50x10*9/l

NCI High Risk:

- BCP-ALL: >10 years old at diagnosis AND/OR diagnostic WCC of >50x10*9/l
- T-ALL and LBL

In addition to the above, patients may be deemed high risk if they harbour one of the following cytogenetic abnormalities:

- MLL rearrangement
- Near haploidy
- Low hypodiploidy
- iAMP21
- t(17;19)

b) Adult patients

For adult patients being treated on the current UK national adult ALL trial protocol (UKALL14), treatment pathways may be adjusted if patients are deemed to be *'high-risk'* at diagnosis by meeting one or more of the following criteria:

Age over 40 years

WCC >30x10*9/l (BCP-ALL) or >100x10*9/l (T-ALL)

Cytogenetics:

- t(4;11)(q21;q23)/MLL-AF4
- Low hypodiploidy/near triploidy (30-39 chromosomes / 60-78 chromosomes)
- Complex karyotype (five or more chromosomal abnormalities)
- Philadelphia chromosome t(9;22)(q34;q11)/BCR-ABL1

For paediatric/TYA (on UKALL2011/UKALL2003 interim guidance) and adult patients (on UKALL14), further MRD-based risk assessment will be performed as per protocol and may impact on future treatment decisions.

Pre-treatment supportive care

Induction therapy should be administered as an inpatient until neutrophil recovery. Early treatment toxicities including febrile neutropenia, hyperglycaemia, hepatotoxicity occur commonly during induction (typically days 10-20) and can be more safely managed with close inpatient observation. Thereafter, the remainder of treatment can generally be safely administered as an outpatient but individual patient characteristics and local practices should be taken into account.

Tumour Lysis

Tumour lysis syndrome (TLS) describes the metabolic derangements that occur with tumour breakdown following initiation of cytotoxic chemotherapy. TLS usually develops within 48 hours of initiating chemotherapy and almost always within 1 week. It can lead to acute renal failure and can be life-threatening.

All patients should be adequately hydrated with intravenous fluids from the time of diagnosis and treatment commencement. Potassium should not be added to routinely to hydration fluid during induction. Allopurinol should be started prior to induction therapy and continued for at least 5 days. In patients considered to be high risk for tumour lysis syndrome (e.g. white cell count >100 x 10^9/L, renal impairment, LDH >3x ULN) rasburicase should be considered in place of allopurinol. Accurate fluid balance and twice daily weights are essential.

Antimicrobial prophylaxis

Antimicrobial prophylaxis should be dictated by trial protocol for those patients enrolled on to clinical trial. Outside of the context of a clinical trial, antiviral prophylaxis with aciclovir and pneumocystis jirovecii pneumonia prophylaxis (typically trimethoprim-sulphamethoxazole) should be continued throughout treatment (including maintenance therapy), bearing in mind that no sulpha containing drug should be given on the days that the patient is receiving methotrexate. Fungal prophylaxis should include mould coverage during induction therapy. Azole antifungals cannot be used within 48 hours of vincristine because of the risk of exacerbating vincristine-induced peripheral

neuropathy. Therefore, amphotericin-based drugs are used for prophylaxis during induction. Azoles are generally considered safe for outpatient management during consolidation therapy.

Venous access

Due to the risks of venous thrombosis associated with the administration of asparaginase in the context of high circulating disease burden, central venous access should generally be avoided where possible during induction therapy. If no contra-indication and platelet count allows, patients should also receive LMWH prophylaxis during induction.

Age-appropriate ALL treatment

16 to 25-year-old patients

Patients less than 16 years of age should be referred for specialist paediatric management.

All patients aged 16-18 should be referred for notification and treatment at their local designated TYA centre. All patients aged 18-25 should be referred to their designated TYA MDT for notification, and offered treatment at their TYA centre. Such patients may choose to complete treatment in their designated adult haemato-oncology centre experienced in the management of ALL, but may benefit from outreach TYA support. All patients between 16-25 years of age should be offered the opportunity to enter the current UK national randomised study, UKALL2011.

Philadelphia chromosome (Ph) positive patients aged 16-18 should be treated as per the UK Interim Recommendations for Treatment of Children with Philadelphia Positive ALL, based on the amended EsPhALL protocol (Protocol Amendment 3, UK version 5, 10 February 2010) until such time as a new study incorporating the treatment of Ph positive 16-18 year old patients becomes available in the UK. Ph positive patients aged ≥19 years and over (≤65) are eligible for the current UK national randomised adult ALL clinical trial, UKALL14. All protocols for Ph positive ALL should incorporate tyrosine kinase inhibition therapy alongside chemotherapy.

25 to 65-year-old patients

Patients aged 25-65 years with both Ph positive and Ph negative disease should be referred to, and treated at a centre offering entry on to the current UK national randomised adult study, UKALL14. Where possible, clinicians should be discouraged from treating patients according to trial protocol without patients being entered onto the study.

Patients aged 65+ years or 55+ years and unfit for UKALL14

Ph positive and Ph negative ALL patients should be considered for the current UK national elderly patient ALL study, UKALL60+. Outside of the context of a clinical trial, patients should be treated according to age, performance status, comorbidities, and patient wishes. Those

patients deemed fit enough for induction chemotherapy should receive 2 cycles of induction (including intrathecal chemotherapy administration where feasible), followed by CNS intensification with high dose Methotrexate (dose dependent on renal function and clinical status). It is generally advisable for asparaginase to be omitted in treatment protocols for this age group, in view of increased risks of toxicity.

Those considered not fit for consolidation should be placed directly onto maintenance chemotherapy thereafter. Ph positive patients being treated outside of the context of a clinical trial should all receive tyrosine kinase inhibitor (TKI) therapy with Imatinib at a dose of 600-800mg per day, in addition to their chosen chemotherapy treatment regime.

Relapsed ALL

The treatment of a patient with relapsed ALL should take into consideration relapse localisation, patients age and clinical status, timing of relapse, previous history of allogeneic transplantation and the patients wishes. Despite improvements in first line therapy, results for the treatment of relapsed adult ALL demonstrate consistently poor prognosis, with median overall survival rates at 5 years after relapse of <10%[3]. Remissions with chemotherapy alone are generally not durable and allogeneic transplantation is at present the only known curative approach[4-6]. Average rates of second complete remission (CR) with standard combination chemotherapy regimens range from 20-80%, with rates of salvage for second and subsequent relapse, or relapse post haematopoietic cell transplantation (SCT) being significantly lower.

16-25 year olds

Where available, patients should be offered the opportunity to enter a clinical trial. Patients aged 16-18 should be considered for treatment on the current UK national paediatric relapsed ALL study (IntReALL) if available. Otherwise patients should be considered for treatment on the previous ALLR3 paediatric relapse trial protocol.

Between the ages of 18-25, patients who have not previously undergone allogeneic transplantation should be offered intensive salvage chemotherapy with intention to proceed to total body irradiation (TBI)-containing myeloablative SCT in second CR. There are no clear data to suggest superiority of one re-induction regimen over another. FLAG-Ida is a commonly used and is appropriate choice of re-induction in this circumstance. For CNS relapse, regimens incorporating intensive CSF directed therapy as well as systemic therapy (e.g. HDMTx/HiDAC, or FLAG-Ida with additional intrathecal chemotherapy) are required. Nelarabine is licenced as salvage treatment for relapsed T-cell ALL/lymphoblastic lymphoma and can be used as a single agent[7], or in combination[8] as an appropriate choice for re-induction in this setting. It is currently available via the cancer drugs fund for relapsed T-ALL as a bridge to transplantation.

Those patients with B-ALL who are refractory to re-induction chemotherapy should be considered for current CD19 CAR T-cell approaches if available. Such patients should be

discussed with the appropriate study PI prior to administration of further chemotherapy, as eligibility for CAR T-cell therapy may be influenced by prior chemotherapy treatment, and novel immunotherapeutic strategies (e.g. Inotuzumab, Blinatumomab) may be more appropriate as a bridge to CAR T-cell therapy if available.

25+ years old

All patients should be considered for entry into a clinical trial if available.

Outside of a trial, consideration of intensive salvage chemotherapy strategies is appropriate in patients who are deemed fit enough to proceed with allogeneic transplantation in second CR. If the patient has already received a SCT, a second allogeneic transplantation is rarely appropriate.

As above, FLAG-Ida is an appropriate re-induction regimen for those who are fit and suitable for intensive chemotherapy followed by SCT. Nelarabine should be considered for relapsed T-ALL/lymphoblastic lymphoma either as a single agent or in combination. For CNS relapse, intensive CSF directed therapy and systemic therapy (e.g. HDMTx/HiDAC, or FLAG-Ida with additional intrathecal chemotherapy) can be considered, followed by TBI-containing myeloablative (patients <40 years) or reduced intensity conditioned (RIC) allogeneic SCT with additional craniospinal radiotherapy.

For those patients not suitable for consolidation with allogeneic transplantation, outcomes with intensive chemotherapy are not clearly superior to those with non-intensive approaches, and are likely to confer additional treatment related morbidity and mortality. In such circumstances, it may be appropriate to adopt a palliative approach.

Relapsed Ph positive ALL

At relapse, bone marrow samples should be sought and analysed for the presence of additional cytogenetic abnormalities, and mutations in the BCR-ABL1 kinase domain (TKD) to guide subsequent choice of TKI. TKD mutational screening should be sent to the following address:

West Midlands Regional Genetics Laboratory

Birmingham Women's Health Care NHS Trust

Edgbaston

Birmingham

B15 2TG

genetics.lab@bwhct.nhs.uk

Dasatinib is available via the cancer drugs fund for Imatinib refractory or resistant disease, and should be offered when there is no contra-indicating kinase domain mutation. Dasatinib is also useful in the presence of CNS disease, as has been shown to penetrate the CSF[9].

Other specific sub-groups

B-other ALL

Approximately 30% of B-ALL patients will meet the criteria for 'B-other' ALL, and be identified as harbouring ABL class or JAK family activating alterations that may be amenable to targeted therapies with either tyrosine kinase inhibitors[10-12], or JAK inhibitors[13]. B-ALL patients with no overtly poor genetic risk factors (see below) and an inexplicably bad response to conventional chemotherapy (induction failure, or MRD positive at week 14) should be considered for genetic screening, as should T-ALL patients showing poor response to chemotherapy.

B-other ALL is defined as B-cell precursor ALL without one of the following:

- t(12;21)(p13;q22)/ETV6-RUNX1
- High hyperdiploidy (51-65 chromosomes)
- t(9;22)(q34;q11.2)/BCR-ABL1
- KMT2A (MLL) rearrangement
- t(1;19)(q23;p13)/TCF3-PBX1
- t(17;19)(q23;p13)/TCF3-HLF
- Near-haploidy (<30 chromosomes)
- Low hypodiploidy (30-39 chromosomes)
- Intrachromosomal amplification of chromosome 21 (iAMP21)

Local cytogenetic laboratories should screen such patients with commercially available FISH probes for PDGFRβ. If positive, the national leukaemia research cytogenetics group (LRCG) should be notified and sent fixed cells to discriminate PDGFR/CSF1R involvement, and identify partner genes. If there are initial FISH or cytogenetic pointers to ABL1 or ABL2 involvement (unexplained extra ABL1 signal identified by FISH with BCR-ABL1 dual colour

fusion probe, or cytogenetically visible translocation involving 1q25), LRCG should be notified and sent fixed cells for further analysis to identify potential partner genes.

Lymphoblastic Lymphoma

Currently there is no 'gold standard' approach to treating adult acute lymphoblastic lymphoma (LBL) in the UK. Within the WHO classification, acute lymphoblastic leukaemia and lymphoblastic lymphoma are classified as the same disease, separated by a cut-off of 25% bone marrow involvement. Whilst LBL patients historically were treated as per non-Hodgkin lymphoma protocols, it is now well recognised that patients with LBL have better outcomes when treated on ALL-type protocols (incorporating both systemic and CNS-directed therapy)[14]. Most patients with T-cell LBL have significant mediastinal tumours at presentation, and initial diagnostic work-up should include baseline imaging (CT NTAP or PET/CT as dictated by local protocols) as well as follow-up imaging at the end of induction to assess disease response. Whilst many centres in the UK use PET scanning in LBL to determine response, the use of PET scanning in this disease has not been evaluated in any prospective adult trial. The current UK national paediatric and adolescent ALL trial (UKALL2011) defines CT response as >35% reduction in tumour volume at the end of induction (day 29). Those patients who have not achieved >35% reduction in tumour volume at this time point are taken off study. In this situation it would be appropriate to consider salvage treatments including further intensive chemotherapy (e.g. FLAG-Ida; nelarabine-based regimens) the potential role of radiotherapy, and suitability for allogeneic SCT. Currently there are no studies suggesting superior results from SCT as compared to chemotherapy alone in responding patients with LBL.

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