Clinical Guidelines for Lymphoid Diseases – Acute Lymphoblastic Leukaemia (ALL)

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Version History

Version	Date Issued	Brief Summary of amendments	Owner's Name:
1-7	Historical		Dr N Morley
8	May 2016	Updated trials and drug regimens	Dr N Morley
9	Jan 2017	Updated diagnostic workup for younger patients with sub-optimal response or relapse	Dr N Morley
10	Feb 2018	Addition of Blinatumomab for relapsed/ refractory disease. Changes to management of CNS disease due to loss of availability of Depocyte.	Dr N Morley
11	March 2019	Addition of Inotuzumab for relapsed/ refractory disease.	Dr N Morley
12	May 2019	Addition of CAR T cell therapy	Dr N Morley
13	July 2019	Addition of WGS to diagnosis section	Dr H Barker
14	Aug 2019	Addition of Blinatumomab for MRD	Dr N Morley

(Please note that if there is insufficient space on this page to show all versions, it is only necessary to show the previous 2 versions)

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Treatment of Acute Lymphoblastic Leukaemia

1. General

Scope includes patients with Acute Lymphoblastic Leukaemia and Lymphoblastic Lymphoma.
All patients should be referred centrally to Sheffield to Dr N.J.Morley or Dr J.G.Wright in his absence.
PCP prophylaxis is required with either Septrin or monthly nebulised pentamidine.
Antifungal prophylaxis should follow existing local antifungal protocols.

2. Diagnosis

Diagnostic samples should be sent to HODS for confirmation.

Where ALL is suspected and there are circulating blast cells in the peripheral blood a sample should be sent to flow cytometry to establish the lineage so that appropriate marrow samples can be sent.
Ideally patients should be referred to Sheffield to have their diagnostic marrow samples.

Samples required include;

Morphology
Immunophenotyping
Cytogenetics (standard G-banding and FISH for ETV6-RUNX1, amplification of RUNX1, BCR-ABL and MLL)
MRD (sample in ACD for patients to be treated on a paediatric protocol, EDTA for patients to be treated on an adult protocol)

Please also bear in mind samples to meet trial requirements (e.g. MRD) for patients who may be treated on a clinical trial.

For patients under 25 years samples should be sent TPMT testing pre-transfusion.

Patients treated on a Paediatric Regimen with a sub-optimal response to course 1 (Induction failure/ Day 29 MRD>1%) or with relapsed disease, should have further work-up on their initial diagnostic samples to look for ABL-class fusions.

Whole Genome Sequencing (WGS)

Currently the following patients are eligible for WGS

- All patients (adult and paediatric) with acute lymphoid leukaemia (ALL)
- All patients (adult and paediatric) with acute leukaemia of ambiguous lineage

The samples can be at diagnosis or at relapse for each of the above. Tumour DNA will be obtained from bone marrow or peripheral blood with > 40% blasts collected in EDTA. When a patient is confirmed with a diagnosis of ALL the treating clinician will be informed and requested to send patient consent including record of discussion and to obtain a germline sample. The part of the WGS order form pertaining to the germline sample should be completed by the clinician/SpR or Clinical Nurse Specialist taking the germline sample. For germline DNA samples the following are considered:

- Saliva post treatment (following 2 courses of anthracycline chemo in AML or post confirmation of no blasts by morphology for ALL)
- Cultured fibroblasts from a skin puncture biopsy , the sample of choice
- Uncultured skin puncture biopsy

Send germline samples to Sheffield HODS laboratory for onward dispatch to SDGS at SCH

3. Intensive Chemotherapy

Patients aged 16 -25yrs should be encouraged to enter the UKALL2011 trial whilst it is open.
Off trial, standard treatment should follow the protocol without randomisations i.e. standard dexamethasone in Induction, Regimen allocation directed by Day 29 MRD, Interim maintenance/Escalating Capizzi for course 3, a single Delayed Intensification and Intrathecals and Pulses in Maintenance.

Adults aged 25 – 65yrs should be encouraged to enter the UKALL14 trial. Off trial therapy for patients >25yrs is the UKALL14 trial protocol without randomisations i.e. no Rituximab or Nelarabine.

All patients should be tissue typed since allograft in first or second remission may be appropriate. For those off trial the decision to transplant or not should be made on a case by case basis.

Patients with Philadelphia positive ALL should receive Imatinib concurrently with chemotherapy and should be transplanted in first remission where possible.

Blinatumomab should be considered for patients with Philadelphia chromosome negative CD19 positive disease with minimal residual disease of at least 0.1% in first complete remission. (**NICE TA589**).

4. Older patients

Older patients should be encouraged to enter the UKALL60+ study which has Registration, Non-intensive, Intensive, Intensive+ and Philadelphia +ve arms.

Off trial patients,

Fit, informed and willing. Consider UKALL14 Phase I Induction.
Less fit, older or uncertain. Intensive or Non-intensive arm of UKALL60+ study off trial.
Elderly or frail. Consider standard maintenance.
CNS prophylaxis may be considered on a case-by-case basis.

5. Treatment of refractory or relapsed disease

Relapsed/refractory ALL has a poor prognosis and decisions should be made on an individual basis with discussion at the MDT.

Consider screening for RAS mutations to determine eligibility for the Seludex study.

For those who are potentially eligible for allogeneic transplant in second remission,

B-ALL Inotuzumab (Blueteq registration required) (**NICE TA541**)
Blinatumomab (Blueteq registration required) (**NICE TA450**)
Clofarabine + cyclophosphaimde + etoposide. (Blueteq registration required)
FLAG +/-Ida
Repeat UKALL14 Induction Phase I for later relapses

T-ALL Single agent Nelarabine (Blueteq registration required)
Nelarabine + cyclophophamide + etoposide. (Blueteq registration required)
FLAG +/-Ida

CNS prophylaxis should also be considered on an individual basis depending on potential transplant conditioning.

6. Relapsed/refractory Ph+ve cases

Check for BCR-ABL binding site mutations.
Consider single agent Imatininb or Imatinib in combination with chemotherapy.
Patients resistant to Imatinib may receive Ponatinib (Blueteq registration required) (**NICE TA451**).
Those relapsing with CNS disease should receive Dasatinib.
CNS prophylaxis must be considered in the context of the treatment schedule agreed at the MDT.

7. CNS Relapse

If available consider Depocyte fortnightly for 5 doses +/- Palliative radiotherapy.
If Depocyte is not available then either Triple Intrathecals or single agent Intrathecal Methotrexate may be used.

8. CAR T cell for Relapsed ALL

For those patients relapsing after allogeneic stem cell transplant or after second line treatments consider referral for CAR T cell therapy.

NICE TA554 Tisagenlecleucel (Kymriah) therapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years.

9. Summary of treatment regimens

Regimen	Indications
UKALL14 Regimens	First line >25yrs age on or off trial, Late relapse
UKALL 14+ Imatinib	First line ALL Ph+ve on or off trial
UKALL2011 Regimens	First line ALL <25yrs age on or off trial
UKALL60+ Regimens	Older unfit patients.
Clofarabine/cyclphosphamide/etoposide	Relapsed or refractory B-ALL
Blinatumomab	Ph-ve, MRD+ve CD19+ve B-ALL in CR1 Relapsed or refractory B-ALL
Inotuzumab	Relapsed or refractory B-ALL
Tisagenlecleucel	Relapsed or refractory B-ALL, patient <25years
Nelarabine/cyclophosphamide/etoposide	Relapsed or refractory T-ALL

FLAG +/- Idarubicin	Relapsed or refractory disease
Vincristine/Prednisolone	Palliative/ Ad-hoc
Maintenance chemotherapy	Palliative/ Ad-hoc
Imatinib monotherapy or in combination	Ph+ve ALL palliative or relapsed disease.
Dasatinib monotherapy or combination	Ph+ve ALL with CNS disease.
Ponatinib monotherapy	Ph+ve ALL relapsed disease.
Depocyte	Treatment of CNS ALL