Pan-London Haematology-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms
Part 1: Acute Lymphoblastic Leukaemia

January 2020
Contents

Pan-London Haemato-Oncology Clinical Guidelines

Acute Leukaemias and Myeloid Neoplasms Part 1: Acute Lymphoblastic Leukaemia

Contents

1 Introduction

2 Referral Pathways

   2.1 Children, teenagers and young adults

3 Investigation and Diagnosis

   3.1 BMAT. Fertility

   3.2 Peripheral blood film

   3.3 Bone marrow aspirate

   3.4 Flow cytometry

   3.5 Cytogenetics

   3.6 Bone marrow trephine

   3.7 Imaging

   3.8 Pathology

   3.9 Lumbar puncture and CSF examination

   3.10 Bone marrow aspiration and trephine (BMAT)

4 Patient Information/Support

5 Treatment

   5.1 Initial management considerations

   5.2 Clinical trials

   5.3 Specific therapeutic problems

   5.4 Allogeneic stem cell transplantation

   5.5 Patients not wishing to enter a clinical trial

6 Management of Disease and Treatment-related Complications

   6.1 Anaemia

   6.2 Severe neutropenia

   6.3 Neutropenic sepsis

   6.4 Severe thrombocytopenia

   6.5 Thrombosis/haemostasis

   6.6 Haemostasis and thrombosis

   6.7 Hyperleukocytosis/hyperviscosity syndrome
Lead Authors 2020:
Professor Adele Fielding, University College London Hospitals NHS Foundation Trust
Dr Emma Nicholson, The Royal Marsden NHS Foundation Trust
Dr Bela Wrench, Barts Health NHS Trust
Dr Renuka Palanicawandar, Imperial College Healthcare NHS Trust
Dr Sandra Easdale, The Royal Marsden NHS Foundation Trust
Stephanie Kirschke, Imperial College Healthcare NHS Trust

2018 Edition:
Professor Adele Fielding, University College London Hospitals NHS Foundation Trust
Dr Eduardo Olavarria, Imperial College Healthcare NHS Trust

Disclaimer
These guidelines should be read in conjunction with the latest NICE guidance, and all applicable
national/international guidance. The prescribing information in these guidelines is for health professionals
only. It is not intended to replace consultation with the Haematology Consultant at the patient’s specialist
centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing
information. While great care has been taken to see that the information in these guidelines is accurate, the
user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance
provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of
guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the
healthcare practitioners using them to adapt them for safe use within their institutions and for the individual
needs of patients.

Contact us
The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing
group, please contact us through the following link: Pan London Blood Cancer (or via
uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email
addresses.
1 Introduction

Acute lymphoblastic leukaemia (ALL) is an uncommon malignant disorder in adults. It represents approximately 15% of all leukaemias in adults. Patients diagnosed with ALL and treated with intensive protocols should be cared for in a British Committee for Standards in Haematology (BCSH) Level 3 haemato-oncology unit which participates in clinical trials for patients with ALL.

Treatment for ALL is primarily based around clinical trials, which are quite regimented and driven by well-defined protocols. This guideline does not recapitulate these clinical trials but sets out a general guide to treatment strategies for new and relapsed patients.

The main considerations are:

- ALL is an eminently curable disease in young patients that becomes harder to treat as the patient ages. Fewer patients are cured as age advances and therapeutic complications become increasingly common.
- All patients should be treated with age-appropriate therapy.
- Since the disease is rare and treatment is complicated, there are many areas of controversy where best practice is not defined. Patients should be treated within a clinical trial wherever possible.
- Experienced specific and supportive care is required. For example, a European Working Group on adult ALL recommends that patients should be treated in centres which see at least five new patients a year.
- Adherence to the detail and timing of scheduled schemes of treatment is important. Minimising therapeutic delays has a positive impact on outcomes. Recognising complications of therapy quickly and being aware of which complications require treatment cessation and which do not are also vital.
- Allogeneic bone marrow transplant is currently a common element of patient management for patients aged 25 years and over. Hence, all patients and siblings aged 25 and older should be tissue-typed at diagnosis and an unrelated donor search carried out if there are no sibling donors. In practice, this means informing the appropriate transplant centre about all age-appropriate new diagnoses of ALL. Currently, those aged between 25 and 65 years old, and all patients who are Philadelphia-positive (Ph+), should be considered as possible transplant candidates at diagnosis.
- Appropriate specimens should always be taken before therapy is started. Cytogenetic testing is the standard of care. Minimal residual disease (MRD) assessment is standard practice. This requires a diagnostic specimen to be sent centrally to the adult MRD laboratory at the UCL (for patients enrolled into UKALL14 or UKALL60+ clinical trials), or the paediatric MRD laboratory at Great Ormond Street Hospital (GOSH; for UKALL2011 clinical trial).
2 Referral Pathways

See Annex 1: Acute Leukaemia Patient Pathway.

Patients with suspected ALL should be referred to a haematologist for assessment on the same day on a 2 week wait pathway.

Patients with severe neutropenia, thrombocytopenia or blasts in peripheral blood picked up on a routine blood test via the laboratory and suspected ALL should be urgently referred to an A&E department or directly to a haemato-oncology inpatient unit which treats ALL (BCSH Level 3).

All new patients should be referred to the multidisciplinary team (MDT) for confirmation of diagnosis, prognosis and management plan, taking into account their performance status, needs and co-morbidities. Planning for an allogeneic stem cell transplant should begin at the time of diagnosis in conjunction with the transplant centre. A joint approach with elderly care physicians and palliative care teams may be appropriate in patients with poor prognosis disease and who are not eligible for transplant.

MDT discussions should be had for:

- all new patients with ALL in order to confirm the diagnosis and treatment plan
- all patients where a new line of therapy needs to be considered
- all patients with a restaging assessment of response to treatment
- all patients for whom an allogeneic stem cell transplant is a consideration.

Information to be captured and documented prior to or during the MDT should include:

- demographic information
- referring physician and/or GP
- performance status
- an indicator of co-morbidities (e.g. co-morbidity score)
- any relevant history
- pertinent positive and negative findings on physical examination (splenomegaly, rashes, etc)
- FBC, haematinics, LFTs, U&E, LDH, urate, SPEP, peripheral blasts
- bone marrow aspirate and trephine histology
- bone marrow aspirate immunophenotyping
- cytogenetic, Ph/MLL/ Ph like gene rearrangements IgH/TCR (critical for MRD assessment)
- specific diagnostic ALL sub-type by WHO 2008
- relevant imaging (e.g. CT staging)
- risk score
- availability of a clinical trial/research study and if the patient is eligible
- management and treatment plan
- clinical nurse specialist/key worker
- named consultant.
The MDT outcome form should be sent to the GP (by email, or preferably by fax) within 24 working hours of the MDT discussion.

Patients with ALL should be discussed at an MDT meeting within two weeks of diagnosis – it is expected that treatment would have commenced prior to the MDT discussion.

New patients should be discussed with the MDT ALL lead or the MDT lead at presentation for urgent agreement on the management plan prior to formal MDT discussion.

2.1 Children, teenagers and young adults

Children below the age of 16 years with a diagnosis of ALL or suspected ALL must be referred to the paediatric oncology team at the principal treatment centre (PTC) and must not be managed exclusively by adult site-specific teams.

- The joint PTC for children aged below 16 years for South Thames is The Royal Marsden (Sutton)/ St George’s Hospital.
- The PTC for North Thames (including North West London) is Great Ormond Street Hospital/ University College London Hospitals.
- All patients <1 year from both North and South Thames should be referred to Great Ormond Street Hospital.

Teenagers aged 16–18 should be managed at a PTC for teenage and young adult (TYA) cancers. Young adults aged 19–24 should be given the choice of being managed at a PTC or TYA designated hospital.

- The PTC for TYA for South Thames is The Royal Marsden (Sutton).
- The PTC for North Thames (including North West London) is University College London Hospitals.

All patients within this age range, regardless of place of care, should be referred to the TYA MDT at the relevant PTC.
3 Investigation and Diagnosis

Patients may present with B-symptoms, bone pain, central nervous system (CNS) symptoms and/or cytopenias with or without lymphadenopathy/hepatosplenomegaly. When a diagnosis of ALL is suspected, appropriate tests should be undertaken (see Annex 2).

An FBC should be performed in elderly patients presenting with symptoms of anaemia, infection or bruising/bleeding. At specialist centres, a blood film, bone marrow aspirate and trephine (BMAT) with immunophenotyping and cytogenetics can be undertaken to assess for a clonal abnormality. Where a bone marrow is declined by a patient, peripheral blood immunophenotyping/cytogenetics/FISH/molecular testing may be informative.

- FBC, differential and film
- Coagulation screen and D-dimers
- Blood group and antibody screen
- U&Es/LFTs/Ca and phosphate
- Glucose
- LDH/uric acid
- CRP
- Serum immunoglobulins/SPEP
- HLA typing
- HBV (HBV sAg, HBV sAb, HBV cAb), HCV, HIV, CMV serology
- TPMT genotype
- G6PD screen
- ECG
- CXR
- CT neck/chest/abdomen/pelvis
- ECHO/MUGA
- Creatinine clearance

3.1 Fertility

Consideration of fertility preservation should be made for those of reproductive age (men below the age of 55 and women below the age of 40).

3.2 Peripheral blood film

It is recommended that a film be examined routinely in conjunction with the BMAT for blasts and any other atypical features, e.g. evidence of haemolysis.
3.3 Bone marrow aspirate

It is recommended that at least 400 cells are evaluated in order to assess leukaemic blast percentage. The presence of leukaemic blasts ≥20% is diagnostic of ALL.

3.4 Flow cytometry

This is a mandatory test as it will identify the leukaemic clone and be valuable for MRD detection. Flow cytometry laboratories need to make sure all patients with B-lineage ALL have CD19, CD20 and CD22 analysed at diagnosis.

3.5 Cytogenetics

G-banding and FISH analysis is usually done on a bone marrow aspirate sample, although they may also be undertaken on peripheral blood if marrow is not available. At least 20 metaphases should be evaluated for non-random chromosomal abnormalities and reported. Cytogenetics and molecular diagnostics including high-risk abnormalities: Philadelphia chromosome/t(9;22)/BCR-ABL, IAMP21 (RUNX1 amplification), t(17;19)(q22;p13)/TCF3(E2A)-HLF, MLL rearrangement, and low hypodiploidy/near triploidy (‘Ho-Tr’).

Interphase FISH may supplement standard analysis and is particularly useful where conventional G-banding fails. It can detect targeted chromosomal abnormalities such as BCR-ABL or c-myc.

The presence of the Philadelphia translocation should be established urgently so that targeted treatment can be initiated as early as possible.

Baseline assessment for IgH and TCR rearrangements/quantification should be undertaken and followed for MRD. These should be sent to the trial centre (UCL or GOSH) or to the SIHMDS if the patient is not on a clinical trial.

Screening for ABL-class gene mutations is recommended in all TYA patients. In B-lineage ALL, these abnormalities are mutually exclusive of other primary genetics abnormalities and testing can be restricted to patients that lack ETV6-RUNX1, high hyperdiploidy (51-65 chromosomes), t(9;22)(q34;q11.2)/BCR-ABL1, KMT2A rearrangement, t(1;19)(q23;p13)/TCF3-PBX1, t(17;19)(q23;p13)/TCF3-HLF, near-haploidy (<30 chromosomes), low hypodiploidy (30-39 chromosomes) or intrachromosomal amplification of chromosome 21 (iAMP21). In T-ALL screening is recommended in all cases.

ABL class fusions are quite rare in adults. However, screening for ABL-class fusions is very strongly recommended in all adult patients with a suboptimal response to therapy namely high level MRD or overt therapy resistance.

Whole genome sequencing will be available for acute leukaemia patients alongside standard of care testing. The proposed go live date is 2020. Further information on consent and sample requirements for this test should be obtained from local SIHMDS laboratories.

3.6 Bone marrow trephine

This test will assess marrow cellularity, topography and blasts and immunocytochemistry for lineage markers to complement immunophenotyping/morphologic assessment on the aspirate. Pathologists need to make sure all patients with B-lineage ALL have CD19, CD20 and CD22 analysed at diagnosis.
Table 3.1: Immunological classification

| B-lineage lymphoblastic leukaemia |  |
|----------------------------------|  |
| Pro-B-cell ALL                   | No further differentiation markers |
| c-ALL                            | CD10+ |
| Pre-B-cell ALL                   | CD10+/-, cytoplasmic IgM+ |
| Mature B-cell ALL                | CD10+/-, surface IgM+ |

<table>
<thead>
<tr>
<th>T-lineage lymphoblastic leukaemia</th>
<th>TdT+, cytoplasmic (cy) or surface (s) CD3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early T-cell ALL</td>
<td>cyCD3+, CD7+, CD5+/-, CD2+/-, CD1a-</td>
</tr>
<tr>
<td>Cortical T-cell ALL</td>
<td>cyCD3+, CD7+, CD1a+, sCD3+/-</td>
</tr>
<tr>
<td>T-cell ALL</td>
<td>sCD3+, CD1a-</td>
</tr>
<tr>
<td>Early T cell precursor (ETP) ALL</td>
<td>CD7+ CD1a-CD8- CD5-(or weak+), positive for 1 or more of myeloid/stem cell markers CD34, CD117, HLA-DR, CD13, CD33, CD11b or CD54, CD2+/- and cCD3 +/−</td>
</tr>
</tbody>
</table>

Table 3.2: World Health Organization (WHO) classification (2016)

<table>
<thead>
<tr>
<th>B Lymphoblastic leukaemia/lymphoma, NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with t(9;22)(q32;q11.2); BCR-ABL1</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with t(12;21)(p12;q22); TEL-AML1 (ETV6-RUNX1)</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with hyperdiploidy</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); IL3-IGH</td>
</tr>
<tr>
<td>B Lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)</td>
</tr>
<tr>
<td>B-ALL with intrachromosomal amplification of chromosome 21</td>
</tr>
<tr>
<td>B-ALL with translocations involving tyrosine kinases or cytokine receptors (“BCR-ABL1-like ALL”)</td>
</tr>
<tr>
<td>T-cell lymphoblastic leukaemia/lymphoma (T-ALL)</td>
</tr>
</tbody>
</table>

3.7 Imaging

Patients with T-ALL should have a baseline CT neck/chest/abdomen/pelvis. Imaging can be helpful in B-ALL as clinically indicated.

The utility of PET CT in T-ALL is unclear but centres who can obtain CT-PET may find it helpful to do it.
Patients with neurological symptoms at diagnosis (or during treatment) should undergo MRI brain (with gadolinium) and whole spine.

3.8 Pathology

Careful attention must be paid to the labelling of forms and samples before sending to the SIHMDS and trial centre. Samples are unlikely to be processed unless clearly and correctly labelled.

BMAT:

- Slides for morphology to SIHMDS lab
- 2-5ml in EDTA for immunophenotyping with a slide
- 2-5ml in EDTA for molecular genetics
- 2-5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH
- Trephine for histopathology.
- 2-5 ml in EDTA for MRD testing centrally

3.9 Lumbar puncture and CSF examination

- Normally, each clinical trial will have instruction on how and when to perform a lumbar puncture and CSF examination together with an intrathecal chemotherapy strategy.
- As a general rule, patients should have a diagnostic CSF sample sent for cytomorphology, flow cytometry, cytogenetics/FISH as soon as the risk of contamination of the CSF by circulating ALL blasts has been minimised.
- Patients with signs or symptoms of CNS involvement at presentation by their ALL should have a lumbar puncture and CSF examination as soon as possible. An intrathecal dose of chemotherapy (AraC, methotrexate and steroids) should be given at the same time.

3.10 Bone marrow aspiration and trephine (BMAT)

- Slides for morphology to SIHMDS lab
- 5ml in EDTA for immunophenotyping with a slide
- 5ml in EDTA for molecular genetics, IgH/TCR rearrangements
- 5ml in heparin (PFH or lithium heparin) for cytogenetics/FISH
- Trephine for histopathology.
4 Patient Information/Support

If the diagnosis of ALL is certain, patients should be informed that ALL is a cancer of the blood, bone marrow and immune system. Their prognosis based on the bone marrow cytogenetics, when available, and other co-morbidities should be discussed along with possible treatment options.

All patients must have access to a key worker. This is usually (but not always) the clinical nurse specialist (CNS).

The CNS/key worker should be present at diagnosis and at any significant discussion where treatment changes and outcomes are discussed. In the absence of the CNS, a senior nurse may deputise who must ensure that all conversations are documented in the patient’s notes and on the electronic patient record (EPR). Where it is not possible for the CNS or a deputy to be present, patients should be given the CNS’s contact numbers. The clinician leading the consultation should advise the CNS, who should then arrange to make contact with the patient.

The CNS should ensure that all patients are offered a Holistic Needs Assessment (HNA) at key pathway points, including within 31 days of diagnosis, at the end of each treatment regime and whenever a person requests one. Following HNA, the patient should be offered a written care plan, which should be developed with the patient and communicated to all appropriate healthcare and allied health professionals.

Information booklets from Bloodwise and Macmillan Cancer Support are good sources of patient information at diagnosis. Patient leaflets are available for all treatment options and are also available for download on the following websites:

https://bloodwise.org.uk/
www.macmillan.org.uk/Cancerinformation/Cancerinformation.aspx
5 Treatment

See Figure 1: Treatment algorithm.

5.1 Initial management considerations

See Annex 2.

If ALL is suspected or definitively diagnosed, the patient must be transferred immediately for treatment to a BCSH Level 3 haematology-oncology unit. This can be discussed with the ALL lead or MDT lead in the haematology MDT if needed. The transfer must be undertaken as soon as ALL is suspected so that the patient can have appropriate Level 3 nursing and supportive care, and so that appropriate clinical trials can be considered and enrolment/treatment can occur in a timely fashion. Ideally, a BMAT should be undertaken at the leukaemia unit after transfer, if clinically appropriate.

Treatment for ALL follows strict protocols and most patients are enrolled in the current national ALL clinical trials (see section 10: Research/Clinical Trials). The clinical trial protocols will not therefore be outlined in this guideline. All patients should be offered entry into appropriate national trials. In view of superior results for young adults treated on paediatric protocols, it is recommended that adults up to age 25 are treated according to the current adolescent ALL trials – this should be agreed at the TYA MDT. Initial cytoreduction with dexamethasone.

Formal written consent should be obtained for all patients before starting any cytoreductive therapy.

For patients with high WBC counts, with symptoms (or at risk) of leukostasis, urgent leukapheresis can be undertaken if the high lymphoblast counts are causing pulmonary infiltrates, hypoxia, CNS changes, renal failure, cardiac ischaemia, priapism, severe retinopathy). In addition, treatment with dexamethasone should be started as a matter of urgency until definitive cytoreductive chemotherapy can be administered (pre-phase of 5–7 days is currently allowed on UK adult trial* but not for TYA study). Treatment should be started with dexamethasone 6mg/m²/day PO (or as allowed per current trial protocol) to aim for rapid reduction of blasts together with rasburicase (see Annex 4) administered as a once-daily 30-minute intravenous infusion in 50ml of a sodium chloride 0.9% solution (or allopurinol 300mg/day PO if rasburicase is contraindicated, e.g. G6PD deficiency), and adequate hydration. If rasburicase cannot be used, saline hydration with additional bicarbonate to alkalinise urine may be instituted, with forced diuresis if necessary, to reduce the symptoms of leukostasis and to reduce the adverse effects of tumour lysis. Aggressive supportive measures (as indicated by the patient’s performance status prior to the diagnosis of leukaemia) are advised. This may include ventilatory and dialysis support until definitive cytoreduction can be accomplished, and thereafter as deemed appropriate.

If patients are given hydroxyurea/hydroxycarbamide as initial debulking/ cytoreductive therapy, they may be ineligible for a clinical trial.
5.2 Clinical trials

Studies listed below are currently actively recruiting patients. The National Cancer Research Institute (NCRI) haemat-oncology clinical study group (ALL subgroup) aims for a strategy whereby once a study has closed to recruitment for a specific patient group, a new study will open to allow patients frontline access to trial treatment. Interim guidance will be offered in between trials.

5.2.1 Patients aged 0–65 years

Patients aged 25 and under should be offered the opportunity to enter a clinical trial. There is no current national clinical trial currently open for patients under 25 in the UK so patients are currently being treated as per UKALL 2019 Interim guidelines. These interim guidelines do not include patients under the age of 25 with Philadelphia positive (Ph+) disease. Hence, if patients of this age group have Ph+ disease they need to receive imatinib as soon as possible and they must be considered for allogeneic transplant. Such patients are being treated as per the UKALL14 protocol currently but off trial as the trial has now closed.

Patients aged 25–65 years are currently being treated on UKALL14-registration-only arm protocol - please register patients to this non-interventional study wherever they consent - until which time the UKALL15 study is open to recruitment. Between the ages of 60 and 65, some patients will not be considered suitable for intensive therapy; this should be assessed on a case-by-case basis.

Rituximab has been combined first line treatment for CD20+ B-ALL and has been used in combination with BFM based regimens or in combination with intensive paediatric regimens. Dosing schedules utilized vary and total number of doses are not standardised but the published data suggests an improvement in complete remission rates, increase in probability of achieving MRD negativity post consolidation and reduction in relapse rates.

The GRAALL 2005 trial showed a survival benefit to adding 16-18 doses of rituximab to patients

Only patients with CD20 expression on >20% of blasts and those with Ph neg ALL participated in this study so we cannot extrapolate the benefit to others. If the centre permits, rituximab should be added to standard of care for such patients

The UKALL 14 trial randomised all patients regardless of Ph or CD20 status to received Rituximab or no Rituximab during induction when Rituximab was administered at 375mg/m2 for 4 weekly doses. The results of this study are awaited but consideration of addition of Rituximab delivered as per this protocol could be considered although this treatment is not currently available on the NHS.

See section 5.3.2 for use of blinatumomab in MRD positive ALL

5.2.2 Patients aged 65 and over or those aged 55 and over who are not fit for UKALL14

Patients should be offered treatment as per the UKALL60+protocol for older patients. There is currently no trial open to recruitment in the UK in this age group. This protocol allows the clinician to assess the patients fitness/clinical status and select the intensity of the treatment from 3 possible treatment pathways for Ph Negative patients (Intensive, Intensive plus or Non Intensive) or 2 possible treatment pathways for Ph+ positive patients (intensive or non intensive).
If patients are not fit for consolidation therapy they should be placed directly on maintenance therapy. All patients being treated with curative intent should receive at least six doses of methotrexate intrathecally, if tolerated.

See section 5.3.2 for use of blinatumomab in MRD positive ALL

5.3 Specific therapeutic problems

5.3.1 Relapsed ALL

Relapsed ALL is a difficult therapeutic situation to manage. The treatment of any patient with relapse should involve consideration of what the maximum potential benefit for the patient could be, and this should be balanced against the risk of treatment-related morbidity and mortality. The only curative approach to the treatment of relapse is allogeneic stem cell transplant. The achievement of a complete remission (CR) is a prerequisite for this.

B precursor ALL

Blinatumomab is NICE approved for treatment of relapsed Ph negative CD19 positive B-ALL. Intotuzumab is approved for treatment of relapsed Ph negative CD22 positive B-ALL and Ph positive CD22 positive B-ALL who have had at least one prior Tyrosine Kinase Inhibitor. There is no head to head comparison of either treatment in the relapsed setting but both agents have a higher overall response rate, increased rates of MRD negativity and increase median overall survival compared to salvage chemotherapy and also increase the probability of receiving subsequent allogeneic stem cell transplant.

The incidence of VOD post HSCT in patients who have received prior Intotuzumab is high and therefore if the aim is to proceed to HSCT following remission induction then it would be recommended to select Blinatumomab as first salvage in Ph Negative CD19 positive B-ALL.

Allogeneic stem cell transplantation is the only known curative therapy for relapsed ALL and aggressive approaches should have the overall aim of achieving complete remission so that the patient can receive a stem cell transplant. If the patient has already received a stem cell transplant, a second transplant will rarely be appropriate and consideration should be given to entering phase 1 and 2 trials of novel therapy.

In patients up to age 25 with refractory disease or relapse post allogeneic stem cell transplant or relapsed/refractory disease after 2 of more lines of systemic therapies may be eligible for treatment with Tisagenlecleucel (Kymirah).

In patients aged 25 or above with second or subsequent relapse of B precursor ALL or those ineligible for blinatumomab or Intotuzumab should be offered the opportunity to enter a clinical trial wherever possible (see section 10: Research/Clinical Trials).

Outside a trial, in some situations (early relapse, very poor performance status, patient choice) it may be appropriate to take a palliative approach. In other situations, aggressive therapy will be appropriate.

Where chemotherapy is proposed, FLAG or FLAG-Ida are commonly recommended.
The rate of second complete remission with intensive chemotherapy is approximately 50%. There are no data to indicate the best choice of re-induction regimen. If patients are ineligible for, or do not wish to enter, a trial, FLAG-IDa is a commonly used and appropriate choice of re-induction regimen for those who are fit.

For older patients or any patient where an allograft or clinical trial is not available, the local palliative care team should be involved with end-of-life planning.

**Relapsed T-ALL**

Nelarabine is licensed for the treatment of relapsed T-ALL. It can be used as a single agent or in combination with Etoposide and Cyclophosphamide (NECTAR protocol) and can be a reasonable choice for re-induction. Neurotoxicity can be a significant issue in relapsed ALL – this is usually not reversible so patients should be carefully informed of the risks and in some cases this can be fatal. Where chemotherapy is proposed for salvage, FLAG or FLAG-IDa are commonly recommended.

**5.3.2. MRD positive, Philadelphia Negative, CD19 expressing B-ALL** – Blinatumomab is NICE approved for use in MRD positive patients with Ph Neg B-ALL in first complete remission with MRD positivity of ≥ 0.1% (10^-3) or greater). Patients who are MRD positive undergoing allogeneic stem cell HSCT have higher risk of relapse post HSCT than those who are MRD negative so blinatumomab could be used pre allograft in MRD positive patients to try to achieve MRD negativity prior to HSCST, although this approach has not been tested in a clinical trial.

**5.3.3 Central nervous system relapse or other isolated extramedullary relapse**

Extramedullary relapse is invariably associated with subsequent bone marrow relapse, even if the two are not concomitant. If treatment is with curative intent, systemic therapy needs to be given as well as local therapy. In the case of CNS relapse, intrathecal therapy should be given until blasts are no longer detectable in the CSF. The choice of agent depends upon the clinical situation. Central nervous system irradiation is also an important component of therapy, but should not be given in conjunction with MTX. MTX should always be given prior to CNS irradiation to avoid severe encephalopathic effects. For this reason, cytarabine and steroid may be the appropriate choice immediately following CNS relapse. CNS irradiation carries a potential for cognitive impairment and this needs to be discussed with the patient and family as appropriate.

**5.3.4 Relapsed Philadelphia-positive ALL**

In the case of Ph+ disease, paradoxically, relapse may be easier to treat, at least in the short term. A specimen should be sent to determine whether there are any mutations in the BCR-ABL kinase domain (tests can be carried out at Imperial College Healthcare NHS Trust (ICHNT) or by the Wessex Genetics Service), to guide choice of subsequent TKI. p210 quantification and p190 quantification is available in the MRD laboratories of ICHNT and UCL. Nilotinib and Bosutinib have no licence in Ph+ ALL. Ponatinib is currently the only subsequent generation TKI available via the CDF so this is the main agent on offer at most NHS organisations. Dasatinib should play a role – in particular, it is the only TKI to penetrate the CSF, so should be strongly considered in the presence of CNS disease. Second generation TKI’s should be offered to patients with relapsed Ph+ ALL.
where there is no contraindicating mutation in the BCR-ABL kinase domain but this is often precluded by funding circumstances.

5.4 Allogeneic stem cell transplantation

For young adults on the UKALL2011 clinical trial, recommendation for stem cell transplantation (SCT) is according to MRD results.

For adults treated as per the UKALL14 protocol, SCT is recommended for all patients in first complete remission with a matched sibling donor and all patients with any one of the following high-risk features and 8/8 matched unrelated donor:

- age over 40 years – this may not be automatic if there are no other high risk features
- WBC >30 x 10^9/l (B-lineage), >100 x 10^9/l (T-lineage)
- t(4;11) (q21;q23)/MLL-AF4
- low hypodiploidy/near triploidy (30–39/60–78 chromosomes; ‘Ho-Tr’)
- complex karyotype (5 or more chromosomal abnormalities)
- Philadelphia chromosome t(9;22) (q34;q11)/BCR-ABL
- any level of persistent MRD post-phase 2 of induction.

Patients with high risk disease in whom a 8/8 donor match is not available can proceed to transplant with 7/8 matched unrelated donor or umbilical cord unit(s) in the following circumstances

- high risk cytogenetics
- positive minimal residual disease (MRD) after phase 2 induction

Myeloablative versus Reduced intensity Conditioning

Adults age 40 or under should be treated with a myeloablative conditioning (as per UKALL14 protocol). All adults aged 40-65 should be considered for alloSCT, but if they have standard risk disease and achieve an MRD negative status after two phases of treatment, alloSCT may not be mandatory. If alloSCT is being carried out, it should be treated with a reduced intensity conditioning. Patients should be offered the opportunity to enter the RIC ALL study, (CI Professor David Marks).

ALL-RIC trial office, CRCTU, Centre for Clinical Haematology, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2TH. Tel: 0121 371 4365. Fax: 0121 371 7874. Email: ALL-RIC@trials.bham.ac.uk

SCT from any available donor is recommended for all patients in second complete remission (CR2).

5.5 Patients not wishing to enter a clinical trial

All patients should be strongly encouraged to enter a clinical trial wherever possible because of the potential direct benefit in receiving novel therapies and the importance of gathering appropriate information in areas of controversy given the rarity of the disease.
It is inappropriate that a patient is not offered treatment on a clinical trial simply because the trial is not open at the presenting centre. Patients should always be offered the opportunity to be referred to a centre where the appropriate clinical trial is open.

It is strongly discouraged for the protocols described in clinical trials to be followed without the patients entering the trial concerned. If patients do not wish to enter the currently available trials, or their physicians think that these are inappropriate, an individual treatment decision should be made taking into account the patient’s age, immunophenotype, cytogenetics and initial treatment response by minimal residual disease.

Specific advice on individual patients who do not wish to enter clinical trials having had the opportunity to do so can be provided by:

- Prof Adele Fielding ([a.fielding@ucl.ac.uk](mailto:a.fielding@ucl.ac.uk)) at UCL. If Adele Fielding is unavailable, individual advice may be obtained from other members of the UK National Cancer Reseach Institute (NCRI) Adult ALL Group.

- Dr Rachel Hough (UCLH) and Dr Clare Rowntree (Cardiff) can provide specific advice on the management of young adults and adolescents.

- Prof David Marks (Bristol) can provide advice on the treatment of adults with ALL and particularly on issues relating to bone marrow transplantation.
**Figure 1: Treatment Algorithm ALL**

*Excluding Burkitt lymphoma – ALL L3*

Consider all patients for entry into clinical trials

Not eligible for trials

Start supportive treatment

Ensure MRD sample taken prior to starting any cyto reduction or steroids.

Emergency cyto reduction with dexamethasone +/- chemotherapy (dex pre-phase 5–7 days)

Sperm cryopreservation

Patient fit for aggressive chemotherapy

Induction chemotherapy (as per UKALL 14 protocol in 25-60 and 18-25 year Ph Positive. UKALL19 Interim Guidelines should be followed for 18-25 years Ph negative B-ALL.

Use tyrosine kinase inhibitor per protocol if Ph+

Tissue type siblings

Remission

Continue on protocol

Allogeneic Stem Cell Transplant indicated in 25 years and older if matched sibling donor or MUD transplant if has high risk features (see above).

MRD guided strategy for selection of patients for allogeneic stem cell transplant in 18-25 year old

Refractory

Fit for salvage chemotherapy

Yes

Re-induction (FLAG+/-IDA, Blinatumumab, Inotuzumab, newer agents)

No

Refractory

Patient not fit for aggressive chemotherapy

Ph positive

Supportive care +/-

Tyrosine kinase inhibitor

 +/-

Cytoreductive chemotherapy (e.g. vincristine, prednisolone, etoposide, 6MP)

Ph negative

Supportive care +/-

Corticosteroids or

Cytoreductive chemotherapy (e.g. vincristine, hydroxy carbamide, etoposide, clofarabine)
6  Management of Disease and Treatment-related Complications

See Annex 2: Acute Lymphoid Leukaemia Checklist.

6.1 Anaemia

Appropriate blood transfusion support should be provided for patients with ALL. Red cell transfusions should be avoided if there is any risk of leukostasis. Irradiated blood should be given if the patient is going to proceed to an allogeneic stem cell transplant within the month, or if regimens with fludarabine, clofarabine, cladribine or bendamustine are used. Please see section 7.1: Transfusions.

6.2 Severe neutropenia

Patients with ALL may be neutropenic on presentation and this worsens with initiation of therapy. The standard neutropenic precautions regarding infection control, use of single rooms as well as prophylaxis, are mandatory (see section 7: Supportive Care). All healthcare professionals should employ the highest level of infection control.

The use of granulocyte colony stimulating factor (G-CSF) is highly dependent upon the context of the disease and the chemotherapy protocol in which it is being used. G-CSF should not be used for neutropenia due to the disease itself in ALL. Please see the section below on neutropenic sepsis.

6.3 Neutropenic sepsis

The use of G-CSF is highly dependent upon the context of the disease and the chemotherapy protocol in which it is being used. G-CSF is used to hasten recovery of the neutrophil count, decrease risk of infection and reduce hospital stay. Evidence supporting improved outcomes (quicker progression between cycles, fewer episodes of sepsis) when G-CSF is used has been published – some of the evidence stems from large randomised phase 3 trials. Many of the major international study groups recommend G-CSF throughout active therapy. Consideration should be given to administration of G-CSF throughout active therapy. If this is not possible in all patients, it should certainly be used in those with prolonged cytopaenias or repeated problems with sepsis.

Patients with neutropenic pyrexia or sepsis should be treated according to local protocols for neutropenic sepsis (and following National Institute for Health and Care Excellence (NICE) guidance)

In addition, for haematology oncology patients the following are mandatory:

- urinalysis
- midstream specimen of urine
- chest X-ray
- sputum and stool culture
- swabs: throat (bacterial and viral), CVAD site if present and any other focal lesions as appropriate
- CMV, EBV, Adeno PCR if indicated.
References


6.4 Severe thrombocytopenia

Platelets should be transfused when the platelet count is ≤10 x 10^9/L, or ≤20 x 10^9/L in the setting of sepsis. If the patient is bleeding, aim for higher platelet counts, depending on extent and site of blood loss. Platelets should be ≥50 x 10^9/L for a lumbar puncture. When a platelet transfusion programme is initiated, use single-donor apheresis platelet products only in order to avoid platelet refractoriness/allo-sensitisation, unless in an emergency. HLA-typing should be done prior to starting treatment in order to address donor status if transplantation is appropriate for the patient, and in case HLA-matched platelets become necessary during treatment (as often occurs in women who have had children). Irradiated blood products should be requested for patients on protocols containing fludarabine, cladribine, clofarabine or bendamustine, and for the one month prior to a planned stem cell transplant.

Consider tranexamic acid in order to maintain haemostasis in patients who have bleeding that is difficult to manage only in cycles of treatment which do not contain L-asparaginase (and if the urine dipstick is negative for blood). Please see section 7.1 on transfusions.

6.5 Thrombosis/haemostasis

All patients with a platelet count >50 x 10^9/L should receive thromboprophylaxis with low molecular weight (LMW) heparin during induction therapy. Therapeutic dose LMW heparin (in split BD dose for those with low platelet count) is the treatment of choice for management of DVT, with platelets maintained >50 x 10^9/L by transfusion, with consideration of unfractionated heparin IV for patients with renal failure or at high risk of bleeding. In the case of CNS thrombosis, anti-coagulation must be monitored (by anti-Xa level for LMW heparin or APTT for unfractionated heparin). Anti-thrombin levels must be monitored as anti-thrombin supplementation may be indicated. Also see section 7: Supportive Care.
6.6 Haemostasis and thrombosis

Ensure that patients have good control of blood pressure (if they are known to be hypertensive) and do not suffer from constipation – if not appropriately managed, both conditions can increase the risk of severe life-threatening haemorrhage.

For low fibrinogen during L-asparaginase therapy, the use of FFP and cryoprecipitate to keep the fibrinogen >1.0 is no longer advised due to ineffectiveness and the risk of replenishing asparaginase from the pool within the product: follow chemotherapy/trial protocols. Thromboprophylaxis is required during phase 1 induction (see section 7: Supportive Care).

Avoid aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) and intramuscular injections (unless platelets >50 x 10⁹/L if IM L-asparaginase is to be used). Avoid arterial blood gases unless absolutely necessary – ensure platelets >50 x 10⁹/L.

A proton-pump inhibitor (PPI) should be administered during corticosteroid-containing treatment phases.

6.7 Hyperleukocytosis/hyperviscosity syndrome

Hyperleukocytosis/hyperviscosity syndrome is hyperviscosity due to an elevated leukaemic blast cell number in the peripheral blood circulation. The increased viscosity causes leukostasis within vulnerable capillary regions and ischaemia of tissues, with occasional infiltration of leukaemic cells into the tissues themselves, causing organ compromise. Symptoms of leukostasis occur at different blast cell count thresholds, depending on the leukaemic sub-type. In ALL, typically the blast count is greater than 100 x 10⁹/L when symptoms occur. Urgent leukapheresis can be undertaken if high counts are causing symptoms of hyperviscosity. Cytoreductive therapy must be initiated or optimised simultaneously. Transfusion should be avoided in patients with hyperviscosity syndrome and aggressive hydration should be instituted.

6.8 Leukapheresis

The need for leukapheresis is determined by symptoms and risk stratification. A high leucocyte count is not in itself an indication for urgent leukapheresis. Patients with features (even very early) of leukostasis (e.g. pulmonary infiltrates, hypoxia, CNS changes, renal failure, cardiac ischaemia, priapism, severe retinopathy) should undergo leukapheresis as an emergency.

6.9 Hyperuricaemia and tumour lysis syndrome (TLS)

Patients with hyperuricaemia should be treated with allopurinol or rasburicase according to local protocols and patient-specific factors (e.g. renal failure, WBC count, level of LDH/uric acid). All patients should be well hydrated and receive allopurinol 100–300mg daily (depending on renal function). This should continue for at least the first two phases of induction treatment, unless allergy develops. Allopurinol should be re-initiated for relapsed disease.

Patients with aggressive disease may already be in tumour lysis prior to the initiation of chemotherapy. Tumour lysis is indicated by a high LDH, uric acid, hyperkalaemia, hyperphosphataemia, hypocalcaemia and renal failure (see Annex 3). The mainstay of treatment is avoidance by aggressive IV hydration from diagnosis and especially at the start of cytoreductive therapy, rasburicase as per protocol (if G6PD is normal) followed by allopurinol. If TLS does occur, patients undergoing intensive therapy must be supported with appropriate fluid and electrolyte
management and, if necessary, ICU transfer with haemofiltration until TLS resolves and renal function improves.

6.10 Central nervous system symptoms
Patients with ALL may present with CNS involvement. A typical presentation is ‘Numb-chin Syndrome’ or ‘Submental/Mental Neuropathy’. Such patients should have an urgent MRI brain and whole spine and LP with CSF for protein glucose/microbiology and cytology with immunophenotyping. Intrathecal chemotherapy should be administered at the same time as the first LP (see section 5: Treatment). Dexamethasone should also be administered if the patient is not already receiving it.

6.11 L-asparaginase-related complications
L-asparaginase is associated with numerous toxicities including hepatic dysfunction, thrombo-haemorrhagic complications, pancreatitis, hyperlipidaemia and hypersensitivity, including anaphylactic reactions. Amylase, clotting screen and fibrinogen should be monitored daily during treatment. Although previous protocols indicated that fibrinogen should be kept >1.0, current trial protocols do not advise such strict guidance – VTE prophylaxis is recommended during phase 1 induction (see above).

6.11.1 Methotrexate encephalopathy
Methotrexate encephalopathy typically presents with fits, focal neurological deficit, rapid personality change or impaired consciousness within 1–21 (average 3) days of exposure to IT methotrexate. Other CNS events such as venous sinus thrombosis or CNS involvement by ALL should be considered in the differential diagnosis. Methotrexate should be discontinued while the patient is also receiving cytarabine systemically. Re-challenge (after recovery) is possible without recurrence but this can be an anxiety-provoking experience for patient and staff, so if an event is severe, consideration of no further MTX is not unreasonable. If recurrence happens, the intrathecal regimen should be permanently changed to cytarabine 50mg and preservative-free hydrocortisone 12.5mg.
7 Supportive Care

Supportive care is very important for all patients with ALL. There are many aspects to consider and they are carefully documented in current clinical trial protocols. These protocols are available for download and should be consulted for precise details of appropriate supportive care, even if patients are not entering the clinical trial.

Patients should ideally be nursed in isolation rooms with appropriate protocols to prevent infections. Clean, neutropenic diets should be instituted and appropriate infection control measures should be undertaken. Prophylaxis and treatment of infection from presentation should be instituted based on local protocols with antibiotic choice largely dependent on local microbiological flora. For patients who will undergo intensive treatment schedules, a central venous access device should be inserted as soon as is safely possible.

Supportive care may include the following.

7.1 Transfusions

See section 6: Management of Disease and Treatment-related Complications. Transfusion triggers should be chosen in advance for patients, depending on co-morbidities. For patients with no co-morbidities or bleeding risk, and in those who do not lead active lifestyles, it would be reasonable to aim for a target Hb > 80g/dL although some hospitals have now adopted a lower threshold of Hb >70g/dL.

Red cell transfusions should be avoided if there is any risk of leukostasis.
Platelets should be transfused when the platelet count is <10 x 10^9/L, or <20 x 10^9/L in the setting of sepsis.
All platelet products should be single donor collections in order to limit the risk of allo-sensitisation. HLA-typing should be done prior to starting treatment in order to address donor status if transplantation is appropriate for the patient, and in case HLA-matched platelets become necessary during treatment (as often occurs in women who have had children). Irradiated blood products should be requested for patients on protocols containing fludarabine, cladribine and clofarabine and for at least one month prior to a planned SCT.

7.2 Hyperviscosity syndrome

See Management of Disease and Treatment-related Complications, section 6.7.

7.3 Hyperuricaemia

See Management of Disease and Treatment-related Complications, section 6.9.

7.4 Infection prophylaxis

During intensive treatment regimens in induction, intensification and consolidation, patients should receive routine prophylaxis for PCP (co-trimoxazole), HSV/VZV reactivation (acyclovir), bacterial and fungal infections (usually with an extended triazole such as posaconazole or itraconazole) or, during regimens containing vincristine, with non-azole antifungals (see below according to local flora and sensitivities and as per local protocols on neutropenic sepsis (and following NICE
guidance). G-CSF is used to hasten recovery of the neutrophil count, decrease risk of infection and reduce hospital stay. However, evidence supporting improved survival with G-CSF is lacking.

For neutropenic sepsis, use G-CSF to encourage neutrophil recovery; G-CSF can be used prophylactically in those patients with recurrent septicaemia. In order to avoid infective complications, constipation should be avoided. Rectal examination, suppositories and enemas should not be undertaken in neutropenic patients or those otherwise immunocompromised.

A neutropenic diet should be followed until counts recover. Patients should be nursed in a neutral-pressure or positive-pressure isolation room with appropriate air and water filtration systems during inpatient stays and at least during phase 1 induction.

Co-trimoxazole must be stopped one week prior to, and during, high-dose methotrexate intensification. Avoid co-trimoxazole on the day that methotrexate is given when the patient is on maintenance therapy. In the event of allergy to co-trimoxazole, local policies should be followed with an alternative prophylactic agent, such as nebulised pentamidine, oral dapsone or oral atovaquone.

Antifungal prophylaxis is mandatory for all patients on ALL therapy from phase 1 induction. **Azoles must be completely avoided during induction chemotherapy and when the patient is receiving vincristine due to potentiating of neurotoxicity which can be severe and life-threatening**, i.e. during induction phase 1 and in some parts of consolidation and maintenance periods. Non-azole (liposomal amphotericin or equinacandins) prophylaxis is recommended when vincristine is being used during phase 1; there is evidence from a randomised control clinical trial (only presented in abstract form so far) regarding prophylactic high-dose liposomal amphotericin (5mg/kg twice per week) showing that it is not more efficacious than placebo. However, the use of lower daily doses (1mg/kg/day) could be considered, given amphotericin’s risk of nephrotoxicity. Antifungal prophylaxis is not generally required during maintenance therapy, except for patients considered to be at high risk for fungal infection. Azoles should be stopped one week prior to, and subsequent to, vincristine administration. This is a risk for services which split patients between wards and ambulatory care/outpatient care as azoles as medications to take away can be prescribed by junior medical staff who are not fully aware of the next part of the protocol patients will receive. A "no azole in ALL" policy can be a consideration.

7.5 Mouth care

Mouthwashes should be used as per local protocols in susceptible patients.

7.6 Control of menstruation

In young menstruating females undergoing induction, intensification and consolidation, norethisterone 5mg PO TDS should be administered in order to prevent normal menses and bleeding complications. Breakthrough bleeding should be allowed once intensive treatment is completed and platelets have recovered. Alternatively, progesterone pessaries 200–400mg daily can be used if LFTs are deranged to suppress menstruation OR use of both if there is breakthrough bleeding OR consider increasing dose of norethisterone. Continue medication until platelets >100 x 10^9/L with recovery.
7.7 Breathlessness
- Any inpatient showing signs of respiratory distress should be assessed by a physician with knowledge of treatment for patients with ALL and, if appropriate, referred for respiratory physiotherapy assessment in accordance with local on-call guidelines, unless of overt metabolic cause.
- Any patient showing signs of non-acute breathlessness should be assessed by a physician with knowledge of treatment for patients with ALL. Referral for respiratory physiotherapy assessment and intervention should always be considered.
- Ongoing breathlessness management strategies can be provided by occupational therapy or physiotherapy.

7.8 Weight loss
- A screening tool for the assessment of dietary issues should be completed weekly for inpatients and, if issues are identified, a referral should be made to a specialist dietitian.
- Referral for specialist dietetic input should be made in the following instances:
  - Any patient with neutropenia should be provided with information and education on the neutropenic diet and be referred to a specialist dietitian.
  - If artificial feeding is being considered, a referral to the specialist dietitian should be made.
  - Any patient with mucositis should be referred for dietetic assessment, as well as for specialist speech and language assessment.
  - Weight loss/malnutrition should be identified through weekly screening of inpatients.

7.9 Pain
People reporting pain should be considered for non-pharmacological intervention including, but not limited to, TENS (transcutaneous electrical nerve stimulation), complementary therapy and psychological intervention such as mindfulness.

7.10 Complex symptom management
Discuss with specialist palliative care team for advice on symptom management (e.g. pain, mucositis) when there is no/poor response to standard interventions. If appropriate, referral can be made to the specialist palliative care team.
8 End-of-treatment Information

The MDT outcome form and clinic letters will serve to communicate new lines of treatment to the GP. End of treatment is defined as the end of primary remission induction therapy and/or when there are any significant changes in treatment.

8.1 Treatment summary and care plan

There are two related but distinct documents which patients should be given at the end of treatment.

- A treatment summary provides a summary of the cancer treatments received by the end of the first treatment, planned follow-ups (including mechanisms for these), and signs and symptoms of which to be aware. Their aim is to provide information not only to the patient, but also to the GP about possible consequences of cancer and its treatment, signs of recurrence and other important information.

- A care plan is generated as a result of an HNA and is the agreed plan between the patient and healthcare professional about how the identified areas of concern will be addressed. This may cover provision of information (e.g. through an information prescription), onward referral for specialist assessment and intervention (e.g. breathlessness management), or things which the patient themselves can do (e.g. contact their HR department about graduated return to work options).

**Recommendation**

An end-of-treatment consultation should be offered to every patient. This should include an end-of-treatment HNA and associated written care plan, and should also include the discussion and provision of a comprehensive treatment summary.

9 Follow-up Arrangements

Patients on treatment will need inpatient admission, usually during phase 1 induction, and often for some part of phase 2 and intensification. When discharged, frequent monitoring is required and is dependent on the therapeutic phase of treatment and the degree of supportive care required.

Patients may have shared care between a specialist site and the local treating hospital. These arrangements must be clearly outlined so that the patient knows where to attend in an emergency and understands the pathways of communication between the sites.

Patients who have completed chemotherapy will be followed up every three months in the first two years, then every four months in the next two years, and six-monthly in the final year. After five years of follow-up, patients may be followed in ‘long-term monitoring clinics’/‘secondary effects of chemotherapy clinics’, annually.
10  Research/Clinical Trials

All patients should be considered for a clinical trial wherever possible.

For patients with long distances to travel to the trial centre, the option of shared care may be considered:

- If the local hospital has Ethics and R&D approval, care may be transferred to the local unit for the maintenance phase of care.
- 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.

For those centres wishing to participate in shared care, clear documentation of shared care arrangements must be undertaken with communication to centres, the GP and the patient.

11  End-of-life Care

For older patients and in those with high-risk disease, discussions about prognosis and treatment options should also include discussions of end-of-life care. These discussions are to facilitate transitions between active disease-modifying therapy and clinical trials to supportive care only, at the time of disease progression/non-response. Care may be required from specialist palliative care teams, which are available in all the cancer centres and units.

The named clinical nurse specialist/key worker, patient, family members and palliative care teams, as well as members of the inpatient ward team, may be involved. Clear documentation of the discussion with guidance to the treating teams is helpful in communicating these discussions and outputs to the wider team that may care for the individual.

12  Data Requirements

Accurate data collection is essential to monitor outcomes, and the collection of this information, particularly clinical data, remains the responsibility of the members of the multidisciplinary team with support from a data manager. Haematology services are required to submit data to nationally mandated datasets for all patients diagnosed with haematological cancer.
Annex 1: Acute Leukaemia Patient Pathway

Treatment of acute leukaemia is usually urgent and occasionally presents as a medical emergency. Therefore, treatment discussions and decisions are generally made before the MDT meeting takes place. However, the treatment decision and long-term management is discussed and approved at the next MDT meeting. (Urgent case pathway depicted in red arrows.)

1. **GP 2 week wait referral**
2. **1st OPA**
3. **Investigations e.g. BM**
4. **Haematology MDT meeting: Decision to Treat**
5. **Diagnosis confirmed – 2nd OPA**
6. **High dose therapy & stem cell transplant**

---

**Internal referral/A&E**

---

**Laboratory open access service**

---

**Decision to Treat**

---

**ADMISSION TO HAEMATO-ONCOLOGY UNIT**

---

**WITHIN 2 WEEKS**

---

**Chemotherapy/clinical trial/palliation**

---

**Radiotherapy**

---

**PLANNING**
Annex 2: Acute Lymphoid Leukaemia Checklist

Once diagnosis suspected:
☐ Virology [HIV, HCV, HBV (Ag, Ab, core), CMV Total Antibody, HSV, EBV]
☐ Haematinics / LDH / uric acid / blood film / PT, APTT and fibrinogen
☐ G6PD & TPMT level (prior to any red cell transfusion)
☐ Blood products:
   ☐ Fill out special products form and send to transfusion laboratory
   ☐ Single donor (apheresis) PLTS
   ☐ Irradiated products if patient for fludarabine
☐ BMAT (check if any samples needed for clinical trials/studies):
   ☐ 4–5 pulls to get samples: smears, immuno, CGN, molecular, Minimal residual disease/trials/studies
   ☐ Request quick stain on at least 1 aspirate smear to confirm diagnosis
   ☐ Call immunophenotyping laboratory to let them know sample is coming and need diagnosis confirmed
   ☐ Let cytogenetics laboratory know that suspect all and need urgent results (and if suspect Ph chromosome or c-myc, etc).
☐ Transfer patient to haematology unit, isolation room
☐ Antibiotics – I.V. if patient unwell or CRP raised; oral prophylaxis otherwise
☐ Put patient on MDT
☐ Testicular/breast examination
☐ Full neurological examination at baseline

Once diagnosis confirmed:
☐ Give information booklets: ALL, neutropenic diet, clinical trials information
☐ HLA-typing (patient and any siblings)
☐ Book Hickman line or PICC line as appropriate
☐ Baseline ECG
☐ Baseline CXR
☐ Echo (urgent)
☐ Creatinine clearance (urgent)
☐ Full staging CT n/c/a/p
☐ If any suspicion of neurological disease:
   ☐ MRI head/spine
   ☐ Do lumbar puncture – send CSF for cytology/immuno and give it MTX +/- steroid
☐ Fertility discussion/sperm banking if applicable (ensure PLT transfusion prior)
☐ Contact clinical trials coordinator/nurse
Annex 3: Guideline for the Management of Tumour Lysis Syndrome

To be read in conjunction with Annex 4: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients.

Tumour Lysis Syndrome (TLS) is life-threatening. Rapid lysis of tumour cells leads to the release of cellular contents into circulation resulting in hyperkalaemia, hyperphosphataemia, hyperuricaemia and hypocalcaemia which may lead to acute oliguric renal failure and cardiac arrhythmias. TLS can occur spontaneously in tumours with a very high proliferative rate, and/or during induction treatment. It can be classified as laboratory TLS (no clinical manifestations) or clinical TLS (life-threatening clinical abnormalities). Symptoms during TLS/rasburicase include fever, haemolysis, headaches, vomiting, diarrhoea, rash and hypersensitivity reactions.

Prevention of TLS

1. Standard care is hydration and allopurinol and these help prevent TLS
2. Check urate, renal function and LDH prior to starting chemotherapy and hydrate with 3L/m² over 24 hours
3. For high risk patients rasburicase should be considered

Management (see separate rasburicase protocol): Rasburicase is to be used immediately prior to and during treatment-induction for the indications below and when authorised by a consultant haematologist.

TLS Screen is to be ordered 1–4 times per day according to patient's clinical condition until resolves: urea, creatinine, uric acid, phosphate, potassium, corrected calcium and LDH (FBC if AML/ALL/CML/MPN).

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Diagnosis</th>
<th>Preventative Strategies</th>
</tr>
</thead>
</table>
| High       | Burkitt lymphoma  
Burkitt-type ALL  
AML or ALL with WBC >100 x 10⁹/L | 1. IVF (~3L/m²/day, to maintain UOP >100ml/m²/hr) or aggressive hydration as per chemotherapy protocols.  
2. Rasburicase* as per rasburicase protocol |
| Moderate   | AML with WBC > 50 x 10⁹/L  
Other ALL  
High grade NHL with bulky disease  
CML accelerated/blast phase, or where rapid response to therapy expected | 1. IVF (~3L/m²/day, to maintain UOP >100ml/m²/hr) or aggressive hydration as per chemotherapy protocols.  
2. Rasburicase* as per rasburicase protocol |
| Minor      | Other AML  
Myeloma  
Other lymphoma/CLL  
Other CML and MPN | Use allopurinol.  
Use rasburicase* where clinically indicated (high risk):  
High LDH (>ULN)  
Renal failure  
High proliferation index  
High uric acid (>420 umol/L or 7mg/ml) |

* No dose adjustment in renal/hepatic impairment. Ensure normal G6PD level prior to rasburicase (if low, use aggressive hydration & allopurinol).
References


Annex 4: Guidelines for Use of Rasburicase in Adult Haematology and Oncology Patients

Criteria for use
Rasburicase may be used only for the following indications, when authorised by a consultant haematologist or oncologist.

Urate oxidase (rasburicase) is an enzyme which catalyses the oxidation of uric acid to allantoin, which is more easily excreted in the urine.

**Used in the treatment of:**
- hyperuricaemia associated with high grade haematological malignancies
- prevention of complications of tumour lysis syndrome

**Indications (see also separate guideline):**
- Induction or salvage therapy of AML, ALL, high grade lymphoma, high grade multiple myeloma with
  - High LDH (>ULN)
  - Renal failure
  - High proliferation index (Ki67>80%; consider if Ki67>50%)
  - High uric acid (>420 umol/L or 7mg/ml)

Further to the above, consider using rasburicase in those patients unable to tolerate aggressive hydration.

**Protocol for use:**
1. Ensure patient (male or female) is G6PD negative prior to use (if positive, use aggressive hydration with allopurinol – consider higher doses based on risk of TLS and creat level).
2. Ensure aggressive hydration as per chemotherapy protocols.
3. At initiation of treatment, for uric acid levels of:
   a) < 420 umol/L (7mg/L), give a single 3mg dose of rasburicase.
   b) >420 umol/L (7mg/L), give a single 6mg dose of rasburicase.
4. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
5. Start allopurinol as per protocols the morning after rasburicase given.
6. Measure uric acid levels as per tumour lysis (TLS) protocols and at least daily until TLS resolved.
7. During TLS monitoring, if uric acid levels >20 umol/L (>0.3 mg/L), or renal failure worsens, give another 1.5–6 mg rasburicase, as indicated by level and clinical parameters of TLS.
ANNEX 4: GUIDELINES FOR USE OF RASBURICASE IN ADULT HAEMATOLOGY AND ONCOLOGY PATIENTS

References


Special warnings and precautions for use

Allergic reactions may occur with this product, patients should be closely monitored and full resuscitation facilities should be at hand. Should any serious allergic or anaphylactic reaction occur treatment should be immediately discontinued and appropriate resuscitation given.

Caution should be exercised in patients with a history of atopic allergies.

Administration of rasburicase decreases serum uric acid to below normal levels, but has no direct effect in reversing hyperphosphataemia, hyperkalaemia and hypocalcaemia. If severe these abnormalities should be corrected following standard treatment guidelines.

There are limited data available to recommend the sequential use of rasburicase and allopurinol.

To ensure accurate measurement of uric acid plasma level during treatment with rasburicase, a strict sample handling procedure must be followed to minimise ex vivo degradation of the analyte. Local policies should be followed with regard to collecting blood samples and laboratory monitoring.
## Annex 5: Oral Chemotherapy Patient Education Checklist

### Oral anti-cancer patient and carer education checklist

<table>
<thead>
<tr>
<th>Prior to first cycle:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>This checklist must be completed with the patient/carer at the point of handing the medication to the patient, either in conjunction with or following a pre-treatment consultation.</em></td>
</tr>
</tbody>
</table>

**Tick ✓ if discussed with the patient/carer**

### Instructions for taking

- **Explain how and when to take the medicine, including any treatment breaks.**
- **If the patient is unable to swallow tablets or capsules or has a feeding tube, please refer to the oral systemic anti-cancer therapies (SACT) counselling handbook to dissolve or open capsules (if appropriate for the oral anti-cancer medicine).**
- **Missed doses can be taken if near to the scheduled time. Otherwise, do not try and catch up or double the next dose. Wait until the next dose is due.**
- **In case of vomiting after taking a dose, do not repeat the dose. Take the next dose at the normal time. If this occurs again, contact the chemotherapy team/24-hour advice line.**
- **Check that the patient is aware of side effects and has received written information. Any side effects should be reported to your chemotherapy nurse or doctor.**
- **If the patient is taking any prescribed/over-the-counter medicine/supplement – the patient should inform their medical team.**
- **Return any unused oral anti-cancer medicine to the hospital pharmacy. Do not flush or throw them away (for high-cost drugs see the counselling handbook).**

### Storage and handling

- **The oral anti-cancer medicine should not be handled by anyone who is pregnant or planning a pregnancy (except on the advice of medical team).**
- **If the carer is giving the anti-cancer medicine, they should not handle the medicine directly but wear gloves or push the medicine out of the blister pack (if applicable) directly into a medicine pot.**
- **Store the tablets/capsules in the container provided.**
- **Store the tablets/capsules in a secure place, away from and out of sight of children.**
- **Wash hands thoroughly after taking/giving the oral anti-cancer medicine.**
- **Check that the patient understands how to take the treatment, by asking them to repeat back their instructions.**
ANNEX 5: ORAL CHEMOTHERAPY PATIENT EDUCATION CHECKLIST

<table>
<thead>
<tr>
<th>Written information provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Taking an oral anti-cancer medicine’ patient information sheet</td>
</tr>
<tr>
<td>Diary for taking your oral anti-cancer medicine (if applicable)</td>
</tr>
<tr>
<td>For swallowing difficulty only – give relevant factsheet if appropriate for the oral anti-cancer medicine and an oral anti-cancer pack with disposables (e.g. oral/enteral syringes)</td>
</tr>
<tr>
<td>Dissolving oral anti-cancer tablets safely</td>
</tr>
<tr>
<td>Opening oral anti-cancer capsules safely</td>
</tr>
<tr>
<td>Giving an oral anti-cancer medicine through a feeding tube</td>
</tr>
<tr>
<td>Giving an anti-cancer syringe by mouth</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient name</th>
<th>Counselling/educated by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital number</td>
<td>Pharmacist/Pharmacy technician/Nurse/Interpreter</td>
</tr>
<tr>
<td>Signature and date</td>
<td>Signature and date</td>
</tr>
</tbody>
</table>

**Before all subsequent cycles:**

Check that the patient has understood the checklist above and repeat if necessary.

Check that any side effects experienced with their previous cycle were discussed with their medical team.

If a dose adjustment has been made, check that the patient is aware why their dose has been changed and how many tablets/capsules they should now take.

Check that the patient had no problems taking their previous cycle.

Check that the patient understands how to take the treatment, by asking them to repeat back their instructions.

Please retain a copy and/or endorse the prescription/electronic patient record as evidence counselling took place at each cycle.
Annex 6: Monitoring of Long-term Survivors of Chemotherapy

Haematopoietic Stem Cell Transplantation (HSCT), Acute Leukaemia, Lymphoma

Survivors of childhood and adult leukaemias/lymphomas have increased risks of secondary cancers, CVS disease and other chronic illnesses, largely secondary to therapy.

**For adult survivors of leukaemia (especially those treated in childhood):**

- A treatment summary from the treating haematologist should be requested.
- If cranial radiotherapy was a component of treatment, there is an increased risk of secondary tumours, stroke, growth hormone deficiency, ocular & neurocognitive defects.
- Check BMI, BP & lipids – survivors of ALL have ↑ risk of obesity and metabolic derangements.
- Consider gonadal assessment (FSH/LH/testosterone) & referral to fertility specialist.
- Consider DEXA scan – peak bone density reduced after childhood exposure to high-dose steroids and other therapies.
- Screen for LV dysfunction in survivors who received anthracyclines, especially if patient received a high cumulative dose or treated before the age of 5 years.
- Screen for transfusional iron overload – commence venesection programme if ferritin >1000 and patient is male or non-menstruating female.
- Consider ophthalmology review annually for assessment of early cataract formation.
- Dental pathology is common and survivors should have annual check-ups.

**For haemat-oncology survivors after the 5 year ‘cure’ milestone of follow-up:**

Patients should undergo annual review for complications of chemotherapy which should consist of:

- Thorough review of systems & physical examination.
- Ensure appropriate monitoring for secondary cancers is being undertaken (skin, breast, cervical, uterine/ovarian, prostate, colorectal, haematologic, sarcomas).
- Monitor for secondary effects and refer back to GP as appropriate:
  - LDL/HDL, TG, Glc, HbA1c, TSH, AIS & ESR, Igs & SPEP, FBC/film, LFTs, U&Es.
- For those who received anthracyclines or involved field radiotherapy to the chest area, check ECHO every 5 years and ECG annually.
- For those who received radiotherapy to the chest (e.g. IF Mantle RT) below age 30, screening at local Breast Screening Service (use dedicated referral form) to commence at age 30 or 8 years post RT, whichever later:
  - Age 30–39 Annual MRI
  - Age 40–49 Annual MRI +/- Mammo
  - Age 50+ Annual Mammo +/- MRI.
- For those who received steroids, consider DEXA scan – every 3–5 yrs.
• For those who received cranial XRT, assess for early cataracts at least once every 5 years.
• Lifestyle advice (stop smoking, EtOH/stress ↓, fitness, protection against sun exposure, etc).
• All survivors of HSCT should receive endocarditis prophylaxis for dental procedures.

References

