Manchester Cancer

Guidelines for the Diagnosis and Treatment of Adult Acute Lymphoblastic Leukaemia

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Date of issue: January 2020

Version number: v1.0

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

Contents

Introduction

Acute lymphoblastic leukaemia (ALL) 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, adult 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 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 in whom clinical trial options are not considered appropriate, 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

Initial assessment should include a full medical history and physical examination, assessment of performance status (Karnofsky/ECOG), height, weight and body surface area (BSA).

Baseline investigations

Investigations at presentation should follow local practice and include the following:

- Full blood count and film
- Coagulation profile
- Biochemistry to include urate, LDH
- Liver function to include bilirubin, alkaline phosphatase, ALT or AST
- TPMT genotyping
- Viral serology
- CXR
- 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) and screening for targetable kinase alterations where appropriate and to be reported by day 15 of induction*
- UK Copy number Alteration (CNA) Classifier is required in the forthcoming Paediatric/TYA upfront ALLtogether study. Recommendation is to use SNP-array based testing to detect changes in ploidy, iAMP21, and deletions involving BTG1, CDKN2A/B, EBF1, ETV6. IKZF1, PAX-5, RB1, PAR-1 (leading to rearrangement of CRLF2).
- SNP array testing may be available from your regional genomic Hub Laboratory linked to your SIHMDS service or nationally from Newcastle Genetics Laboratory, Central Parkway, Newcastle upon Tyne, Tyne and Wear, NE1 3 BZ (0191 2418703) (cancer.cytogenetics@nuth.nhs.uk) – results should be reported before D71 of therapy.
- Whole genome sequencing is to be made available by NHSE and Genomics England for all adults with any acute leukaemia and all Paediatric Cancers with a possible start date in April 2020. Information on the roll out of this diagnostic test which will run in parallel with the above standard of care tests is available from your Regional Genomic Hub Laboratory. Tumour and germline (skin or saliva) samples will be needed.
- MRD assessment**

- 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 additional 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

**Screening for targetable tyrosine kinase alterations*

The genetic characterisation of ALL has revealed a number of alterations which result in tyrosine kinase activation[2,3]. Typically these rearrangements involve the fusion of a kinase gene (e.g. ABL1, ABL2, CSF1R or PDGFRB) to a wide variety of activating genes (e.g. PAX5, EBF1, NUP214, ZMIZ1 etc.) and are all referred to as ABL-class fusions. Although the majority of ABL-class fusions occur within B-cell precursor ALL, it is well known the NUP214-ABL1 amplification and other ABL class rearrangements can occur in T-ALL[4]. There is growing evidence that patients harbouring one of these fusions will respond to treatment with a tyrosine kinase inhibitor (TKI)[5-7]. Whilst these lesions are uncommon in the older adult population, they can occur more frequently in adolescents and young adults with ALL. Currently we would recommend upfront screening for ABL-class fusions (ABL1, ABL2, PDGFRA, PDGFRB, CSF1R) in all patients with T-ALL, and all 'B-other' patients as defined as B-cell precursor ALL without one of the following sentinel cytogenetically visible lesions:

- 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)

If ABL-class fusion is identified, TKI therapy should be incorporated into upfront treatment strategies.

***MRD assessment**

Any testing for MRD which is used to guide treatment should be performed in an accredited laboratory. Accredited 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 Tel: 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.

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) at diagnosis is traumatic (>10 RBC/μl), there is evidence that this adversely affects treatment outcomes[8]. 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 CNS3 positive. For the management of CNS disease, individual trial protocols should be consulted, but in general patients should receive enhanced intrathecal treatment (1-2 x per week until blast clearance, then less frequently thereafter) if there is no contraindication, alongside systemic chemotherapy protocols.

Fertility preservation

Where possible, all male patients should be offered the opportunity for semen cryopreservation prior to the initiation of chemotherapy. A full virology work-up should have been sent as part of the initial patient assessment and is required prior to referral for fertility preservation. Due to the nature of this disease, patients will often present acutely unwell and require prompt medical management/initiation of anti-leukaemia therapy. For women of childbearing age, there is often insufficient time to allow for a safe exploration of fertility preservation methods. Issues relating to the impact of chemotherapy on patients fertility should be discussed with all at the outset prior to starting chemotherapy treatment.

Patient risk stratification

Initial risk stratification should be performed according to individual trial protocols where available, or following the principles as outlined below:

Paediatric/teenage and young adult (TYA) ALL patients (≤25 years of age)

Paediatric/TYA patients will undergo initial risk stratification based on age, presenting white blood cell count (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 of age 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 $>50x10^9/L$
- All T-ALL and lymphoblastic lymphoma (LBL) cases

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

- MLL (KMT2A) rearrangement
- Near haploidy

- Low hypodiploidy
- iAMP21
- t(17;19)(q22;p13)

Adult patients (>25 years of age)

For adult patients, 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 all patients (paediatric/TYA and adult) further response assessment / MRD-based risk stratification will be performed following induction/as directed by individual trial protocols and be utilised to guide treatment decisions.

Pre-treatment supportive care

During induction therapy, early treatment toxicities including febrile neutropenia, hyperglycaemia and hepatotoxicity occur commonly (typically days 10-20) and can be more safely managed with initial close inpatient observation, with local policies applying in relation to timing of discharge. After cycle 1 of therapy, the remainder of a patient's treatment can generally be safely administered as an outpatient but individual patient characteristics and local practices should be taken into account.

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) usually develops within 48 hours of initiating chemotherapy - almost always within 1 week, 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 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 local practices or individual trial protocol where applicable. In general, antiviral prophylaxis with aciclovir and pneumocystis jirovecii pneumonia prophylaxis (typically trimethoprim-sulphamethoxazole or alternative) should be continued throughout treatment (including maintenance therapy), bearing in mind that

sulpha containing drug should not 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, consideration should be given to patients receiving low molecular weight heparin (LMWH) prophylaxis during induction, unless on a trial protocol that mandates otherwise.

Age-appropriate ALL treatment

16 to 24-year-old patients

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

All patients aged 16-24 years of age should be notified to the regional TYA MDT for discussion within the specialist service based at the principal TYA treatment centre (PTC, The Christie Hospital, Manchester). Patients aged 16-18 years of age should be referred to and receive their treatment at the regional PTC at The Christie Hospital. Those aged 18-24 years of age should all be offered a choice of where they wish to receive their treatment - either at their regional principal TYA treatment centre or at one of the regional TYA designated hospitals experienced in the management of ALL. If a patient chooses to be treated at a TYA designated hospital rather than the PTC, they will be offered specialist outreach TYA support from the services at The Christie Hospital. All TYA-aged patients should be offered the opportunity to partake in available paediatric/TYA frontline ALL clinical studies.

25+ year-old patients

To date, patients aged 25+ years have followed frontline UK adult ALL trial protocols rather than intensified paediatric approaches. However, age limits for future frontline ALL treatment protocols may vary, and need to be taken into account when considering appropriate treatment. Where possible, clinicians should be discouraged from treating patients according to a particular trial protocol but 'off study', if there is an actively recruiting frontline trial available.

General upfront treatment principles

- Outside the context of a clinical trial, ALL patients aged 16-25 years of age will be treated following existing intensified, paediatric inspired treatment guidelines. Where possible, Philadelphia chromosome (Ph) positive patients aged 16-25 years should be entered onto a frontline clinical study. If no study is available, consideration should be given to treating such patients as per adult Ph positive guidelines.
- Off trial, patients aged >25 years will follow existing adult guidelines.
- Treatment for both age groups will take into account upfront risk assessment, performance status, co-morbidities, MRD responses and patient wishes.

Patients being treated intensively/with curative intent

Induction chemotherapy: Philadelphia chromosome negative disease

In general, initial treatment for Philadelphia chromosome (Ph) negative patients who are deemed fit enough for an intensive/curative approach should consist of 2 cycles of induction chemotherapy:

- Initial 4 drug induction including daunorubicin, vincristine, steroids and pegylated asparaginase plus IT chemotherapy
- Second cytarabine-based induction/consolidation with additional IT chemotherapy

Disease response assessment will be undertaken as per protocol and will dictate future treatment.

Induction chemotherapy: Philadelphia chromosome positive disease

All patients with demonstrable Ph positive disease (t(9;22)(q34;q11)/BCR-ABL1) should be identified at diagnosis. Outside of the context of a clinical study, patients should have tyrosine kinase inhibitor (TKI) therapy incorporated into upfront chemotherapy treatment strategies. Imatinib, Dasatinib and Ponatinib are all licenced treatments for patients with Ph positive ALL, with Imatinib being routinely available as part of front-line therapy for this indication, and Ponatinib being available for patients in whom imatinib is not clinically appropriate, or in whom the T315I gene mutation is present, with funding via CDF. There is growing evidence that when TKI therapy is delivered concurrently alongside induction chemotherapy, excellent response rates are achievable even with lower intensity chemotherapeutic approaches. Data from the French GRAAPH-2005 study demonstrated fewer induction deaths, and higher rates of complete remission in patients receiving reduced intensity chemotherapy plus Imatinib as compared to standard intensive chemotherapy/TKI approaches (CR rate 98% versus 91% respectively). Furthermore, major molecular response rates were similar in both arms (66% versus 64%) and 5 year EFS and OS rates were estimated at 37.1% and 45.6% respectively, without difference between the arms, validating a reduced intensity chemotherapy plus TKI approach to induction[9]. Based on such data, de-intensification of current induction protocols for Ph positive ALL may be appropriate However, approaches to de-intensify therapy beyond induction in Ph positive ALL remain experimental and should only be undertaken in the context of a clinical study.

Response assessment and the role of haematopoietic cell transplantation

BM biopsy (including CG and MRD assessment) should be performed upon count recovery from the first and second cycles of chemotherapy. Patients with bulky mediastinal or extramedullary disease at presentation should have disease re-evaluated by imaging (either CT or PET) according to local protocols after both cycles 1 and 2.

- Outside of a clinical trial, 16-24 year old patients being treated on intensified paediatric protocols, and demonstrating a sufficient molecular response to initial therapy, will be treated with continued intensive chemotherapy approaches, with no

specific patient group being routinely scheduled for allogeneic haematopoietic cell transplantation (HSCT) in first complete remission (CR1).

- For older adults (>40 years of age), or patients >25 years of age with either high risk features at diagnosis (see initial risk stratification), or demonstrating insufficient molecular response to therapy following 2 cycles of induction - allogeneic transplantation is recommended in CR1, and individual patients suitability for HSCT approach should be carefully evaluated in conjunction with the regional transplant centre.

- For patients being considered for allogeneic HSCT – CNS intensification with high dose IV methotrexate should be administered to all patients who will proceed with reduced intensity transplant conditioning approaches. Those destined to receive TBI-based full-intensity conditioning may not require CNS intensification prior to allograft.

- There is currently no established role for autologous transplantation in the management of patients with acute lymphoblastic leukaemia.

For standard risk patients demonstrating a sufficient molecular response to upfront chemotherapy approaches, and not destined for allograft, chemotherapy alone treatment should continue - incorporating additional CNS-directed intensification (high dose IV methotrexate), consolidation/delayed intensification, and maintenance chemotherapy, with disease re-assessment as indicated by individual treatment guidelines/local protocols.

Treatment of minimal residual disease

Monitoring of minimal residual disease (MRD) is considered routine clinical practice for all patients with ALL being treated with curative intent. MRD monitoring has proven to be a fundamental tool to guide therapeutic decision making. The most standardized methods to study MRD in ALL are multiparametric flow cytometry (MFC) of leukaemia-associated

immunophenotypes (LAIP) or more frequently, polymerase chain reaction (PCR) amplification-based methods that use leukaemia-specific (fusion gene transcripts) or patient specific (immunoglobulin/T-cell receptor gene rearrangements (Ig/TCR)) molecular markers, with the aim of detecting and quantifying residual tumour cells beyond the sensitivity level of cytomorphology[10-15]. MRD assays for ALL should allow for detection of one leukaemic cell among 10,000 normal cells or more, and as such, form the basis of accurate, sensitive and reliable disease response assessment, with MRD being the strongest predictor of continuous complete remission and overall survival[16].

Patients demonstrating slow molecular responses to induction therapy are deemed 'high risk' and eligible for consideration of intensified approaches to treatment. Outside of the context of a clinical study, adult patients (>25 years of age) who remain MRD positive (>$1x10^{-4}$ by PCR amplification-based methods) at the end of 2 cycles of induction therapy should be considered as to their suitability for allogeneic transplantation in first complete remission. Whilst MRD positivity at this time point can be utilised to stratify those patients that are likely to have improved outcomes with transplantation[17], MRD status of such patients at the time of transplant is strongly predictive of outcome post-transplant, with MRD positivity (>10^{-4}) being associated with inferior event free survival rates and higher cumulative incidence of relapse post allograft, regardless of type of conditioning or intensity of the chosen transplant protocol[18]. As such, additional treatment targeting MRD prior to allogeneic transplantation should be considered, with an aim of achieving an MRD result of at least <10^{-3} (ideally <10^{-4}) prior to transplant where possible.

Blinatumomab is the only licenced therapy available (via CDF) for the treatment of $CD19^{+}$ B-ALL with minimal residual disease (MRD) of at least 0.1% or 10^{-3} (as measured using a validated assay with minimum sensitivity of 10^{-4}) for Ph negative patients (on-label) or Ph positive patients (off-label) following first line induction (up to 4 cycles). The multicentre phase 2 BLAST study demonstrated 78% complete MRD responses (<10^{-4}) following 1 cycle of blinatumomab, with achievement of complete (versus incomplete) MRD response being associated with improved relapse free survival (RFS) and overall survival (OS). Of those treated on study, 67% of patients were able to progress to allogeneic transplantation in

continuous complete molecular remission. Blinatumomab was well tolerated, with low rates of grade 3-4 neurological toxicity or cytokine release syndrome (CRS)[19].

Considerations for patients >65 years of age

Patients aged >65 years should be treated according to performance status, comorbidities, and patient wishes. For less fit individuals with significant comorbidities or impaired performance status, lower intensity upfront chemotherapy approaches should be considered. Those 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. Allogeneic transplantation for patients aged 65-70 years may be appropriate in certain circumstances, and should be discussed on an individual patient basis with the regional transplant centre. For those individuals who are not considered transplant eligible, chemotherapy should continue after initial induction, with consolidation and maintenance. Those 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 TKI therapy with Imatinib at a dose of 600-800mg per day, in addition to their chosen chemotherapy treatment regime.

Management of relapsed/refractory ALL

It remains true that a significant proportion of adult patients who achieve CR1 will ultimately relapse[20]. Relapsed/refractory ALL presents a difficult clinical challenge. Until recently, salvage chemotherapy followed by allogeneic HSCT for those achieving second complete remission (CR2) with a suitable performance status and appropriate allogeneic donor option, has provided the only possible route to cure. Even with such salvage approaches, 5-year OS rates are consistently poor, with long term survival achieved only in a minority of patients[20-22]. The best outcomes are achieved in TYA patients who relapse following completion of treatment, who have been shown to have a 5-year OS of 52%[23]. Studies have repeatedly demonstrated that patients who are refractory to treatment, or who relapse whilst on treatment do very badly. In long-term data from TYA patients treated according to the UKALL2003 protocol, no patient with B cell ALL sustaining an on-treatment relapse was alive at the end of the study period[23].

Primary refractory disease/induction failure

All patients who fail to remit with initial induction chemotherapy should follow recommendations for the treatment of relapsed/refractory ALL (see below) unless individual trial protocols dictate otherwise. Furthermore, all 'b-other' and T-ALL patients demonstrating induction failure should be screened (if not already done so) for ABL-class fusions (ABL1, ABL2, PDGFRA, PDGFRB, CSF1R) order that TKI therapy can be incorporated into treatment strategies where appropriate.

Relapsed disease

Investigations are largely similar to those undertaken at diagnosis. The possibility of therapy-related acute myeloid leukaemia (AML) should be excluded. Flow cytometry should be undertaken to confirm relapse status, identify an individual patient's leukaemia associated immunophenotype (LAIP), and evaluate for the presence of targetable cell surface markers on leukaemic blasts (CD19, CD20 and sCD22). Cytogenetics should be repeated in all patients to assess for clonal evolution. Repeat samples should be sent for MRD monitoring. For Ph positive patients, mutations in the BCR-ABL1 kinase domain (TKD) should be looked for to guide subsequent choice of TKI. TKD mutational screening can be sent to the following address unless performed locally:

West Midlands Regional Genetics Laboratory

Birmingham Women's Health Care NHS Trust

Edgbaston

Birmingham

B15 2TG

genetics.lab@bwhct.nhs.uk

As for primary refractory disease, all 'b-other' and T-ALL patients are to be screened (if not done previously) for ABL-class fusions, with the incorporation of tyrosine kinase inhibitor therapy in to salvage strategies. CSF should be re-evaluated and neuro-imaging performed in patients where there is concern regarding potential CNS involvement by leukaemia. In patients with extramedullary disease, this should be evaluated by appropriate imaging modalities as at diagnosis, before the start of salvage treatment.

Treatment options for relapsed/refractory ALL

With the advent and availability of targeted immunotherapies, a greater range of treatment options now exist for ALL patients who are refractory/at the point of relapse. There is optimism that immunotherapeutic approaches will allow for achievement of better, deeper remissions and potentially improved long-term outcomes for patients who relapse following standard upfront chemotherapeutic approaches. Patients who have not undergone HSCT in CR1 should be considered for their suitability for HSCT in CR2 if achieved. HLA typing of a patient and their siblings should take place if not already performed, and for those that do not have an available sibling donor, unrelated donor search and alternative stem cell sources should be considered (including cord blood and haploidentical approaches).

Treatment of a patient with relapsed ALL should take into consideration relapse localisation and disease specific features, patient's age, performance status, timing of relapse, previous history of HSCT and the patient's wishes. In all cases, consideration should be given to the availability of an appropriate clinical trial.

Available therapies

Blinatumomab

Blinatumomab is a bispecific CD19-directed CD3 T cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells, leading to re-directed cell lysis of leukaemic blasts. Currently, NHSE permits the use of Blinatumomab for treating $CD19^+$ Ph negative relapsed or refractory (R/R) B-ALL, with re-imbursement via the cancer drugs fund (CDF). In accordance with guidelines, patients with R/R B-ALL may have 2 cycles of treatment and those in CR may then have up to 3 additional cycles of consolidation treatment.

In the pivotal phase 3 TOWER study, R/R B-ALL patients aged 18-80 years treated with Blinatumumab demonstrated improved overall response rates as compared to conventional

salvage chemotherapy (44% vs. 25% respectively), with 76% of responders with blinatumomab achieving MRD negativity, and a favourable toxicity profile demonstrated. Side effects of note reported in the TOWER study included cytokine release syndrome (CRS, grade ≥3, 5%, and neurological events (grade ≥3, 9%)[24]. As compared to standard salvage chemotherapy approaches, superior responses were seen with blinatumomab irrespective of age, prior transplant and BM blast percentage. However, patients with a BM blast percentage of < 50% showed better responses with blinatumomab than those with a higher BM blast percentage[24], and Blinatumomab-related toxicity was greater among patients with a higher tumour burden[25]. Overall survival was improved with blinatumomab as compared to conventional chemotherapy with median overall survival rates of 7.7 months in the Blinatumomab group and 4.0 months in the chemotherapy group[24].

Blinatumomab is delivered as a continuous infusion over 28 days per each 6 week cycle. Local protocols should be followed in relation to delivery of the therapy/patient monitoring of Blinatumomab-associated toxicities, but in general therapy is delivered on an inpatient basis for the first 9 days of cycle 1, and for the first 2 days of subsequent cycles. There is limited experience with blinatumomab in patients with documented active ALL in the CNS or CSF. However, patients have been treated with Blinatumomab in clinical studies after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy). Therefore patients planned to receive Blinatumomab should have CSF evaluation prior to the initiation of treatment. CNS-directed therapy should be administered if required, and once the CSF is cleared, treatment with Blinatumomab may be initiated. CNS-directed prophylaxis should be administered in between cycles to confer protection against leukaemic involvement.

Inotuzumab ozogamicin

Inotuzumab ozogamicin is a humanised CD22 monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic. After binding to sCD22, Inotuzumab is rapidly internalised into lysosomes, where calicheamicin is released to bind the minor DNA groove, leading to double-strand cleavage and subsequent apoptosis[26].

NHSE permits Inotuzumab as an option for treating relapsed or refractory Ph positive or negative $sCD22^{+}$ B-ALL. Those with Ph positive disease should have had failed at least 1 tyrosine kinase inhibitor.

In the pivotal phase 3 INO-VATE ALL trial, more patients achieved CR/CRi with Inotuzumab than with standard of care (87.7% versus 28.8% after 1 cycle of treatment respectively), with 78.4% of responders achieving MRD negativity. When used as a first or second salvage treatment in patients with B-ALL aged 18-79 years, median overall survival was increased to 7.7 months from 6.2 month with salvage chemotherapy, with 36 month overall survival of 20.3% versus 6.5% with Inotuzumab and chemotherapy respectively (doi: 10.1002/cncr.32116), with best outcomes achieved for those patients that were able to progress to allo-HSCT following Inotuzumab salvage. Inotuzumab was effective irrespective of age, salvage status, prior transplant, and disease burden, and allowed 3.8 x more patients to bridge to allogeneic transplant on study. Grade ≥3 adverse events were more common in patients >55 years old. 11% of patients experienced VOD (of all grades) with VOD being more common in those patients receiving Inotuzumab and proceeding to allogeneic transplantation (18/79, 23%). In a multivariable analysis of factors affecting risk of VOD/SOS, elevated pre-HSCT bilirubin levels and dual alkylator conditioning therapy were independent variables associated with the development of VOD[27]. As such, Inotuzumab may be inappropriate for those with pre-existing hepatic dysfunction, and careful consideration of appropriate transplant conditioning protocols should take place for those that are proceeding with allograft following inotuzumab salvage.

Inotuzumab is administered in 3- to 4-week cycles with a recommended maximum of 2/3 cycles given before consolidation with HSCT. A patient may have a maximum of 3 cycles if CR is not achieved. For patients not proceeding to SCT, a maximum of 6 cycles may be administered. CNS-directed prophylaxis should be administered in between cycles to confer protection against leukaemic involvement.

CAR-T cell therapy

Chimeric antigen receptor T cell therapy (CAR-T cell therapy) is a potent form of cellular immunotherapy that has the ability to utilize and enhance the normal capacity of a patient's immune system. It involves genetic modification of healthy T-cells to express a CAR specific for a tumour antigen, followed by ex-vivo cell expansion and patient infusion. Clinical studies to date have demonstrated promising results for patients with often heavily pre-treated relapsed/refractory B cell acute lymphoblastic leukaemia. Currently, NHSE provides access to CD19 positive CAR-T cell therapy for a minority of patients with relapsed B-ALL via CDF (see below). For all other patients not meeting these criteria, access to CAR-T cell therapy may be possible via an available clinical study. Patients who are being considered for CAR-T cell therapy at relapse should be discussed with their regional CAR-T cell centre lead early, in order that a co-ordinated response to salvage treatment can be achieved.

Tisagenlecleucel

Tisagenlecleucel is an anti-CD19 CAR T-cell therapy. NHSE permits the use of Tisagenlecleucel via CDF, for the treatment of patients up to 25 years of age with B-ALL that is refractory, in relapse post-transplant or in second or subsequent relapse who meet the conditions in the managed access agreement. The ELIANA Phase II multicentre global registration study, demonstrated potent activity of Tisagenlecleucel in paediatric and young adult patients with R/R CD19 positive B-ALL. Responses (CR/CRi) were seen in 81% of patients within 3 months of therapy. Patients on study were heavily pre-treated with a median of 3 prior therapies, with 61% having received a prior SCT. Relapse free survival of 59% was achieved at 12 months, and a median OS of 19.1 months[28]. Significant toxicities included cytokine release syndrome (CRS) in 46.67% of patients (grade ≥3), and neurological events (grade ≥3) in 13% of patients. CAR-T therapy has been shown to have better rates of remission and event free survival than Inotuzumab or Blinatumomab in cases of ALL relapsing post SCT[29]. For patients where CAR-T cell therapy is being considered, early discussion should take place with regional CAR-T centre, with particular attention to choice of therapy prior to receipt of CAR-T cells.

Salvage chemotherapy

Whilst now largely superseded by immunotherapies, standard chemotherapeutic approaches may still be considered for patients who are deemed unsuitable for salvage with the above listed agents. A broad range of regimens have been utilized in this context (including FLAG-Ida; HDAC; HDMTx; clofarabine-based) with the majority of intensive chemotherapy approaches achieving CR rates of ~30-50%. Choice of salvage chemotherapy regimen should take in to account type of disease (B or T-ALL), site of relapse, prior treatment-related toxicities or comorbidities, and aims of salvage therapy.

Nelarabine is licenced as salvage treatment for relapsed/refractory T-cell ALL/lymphoblastic lymphoma and can be used as a single agent[30], or in combination[31] as an appropriate choice for re-induction in this setting. It is currently available via the cancer drugs fund (CDF) for use as a single agent for the treatment of relapsed T-ALL as a bridge to transplantation.

Clofarabine is also licenced and available via CDF for treatment of relapsed/refractory ALL when used as a bridge to allogeneic transplantation[32].

Other specific disease sub-groups

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)[33]. 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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