ACUTE LYMPHOBLASTIC LEUKEMIA

Evidence-Based Practices from RIOHCT

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Tahereh Rostami

Acute Lymphoblastic Leukemia: Evidence-Based Practices from RIOHCT

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Research Institute for Oncology, Hematology and Cell Therapy (RIOHCT)

RIOHCT is the leading cancer research center at Tehran University of Medical Sciences. It plays a unique and vital role in the fight against leukemia by conducting high-quality research, advocating for cancer-related issues, providing information and services to the public and individuals with leukemia, and raising funds for cancer programs. This handbook is funded by the Tehran University of Medical Sciences (TUMS) research budget. To make a donation to help combat leukemia, please visit riohct.tums.ac.ir or call +98-21 88203797.

Note to readers

This book serves as a comprehensive and reliable guide for diagnosing, classifying, and treating acute lymphoblastic leukemia based on the latest scientific evidence available at the time of publication. However, it is important to recognize that information regarding cancer—encompassing diagnosis, treatment, and prevention—is continuously updated by medical professionals and the research community. Therefore, readers and treating physicians are strongly encouraged to consult the most recent local or international practice guidelines and verify the information presented here with additional sources to ensure the best possible decision-making.

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To those who fight cancer tirelessly
&
To the undying spark within us that keeps us going against all odds
The Authors

To all our colleagues, contributors, trainees, and patients who have taught us so much
The Authors

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Preface

This book has been created to assist medical oncologists and specialists in leukemia treatment in enhancing their understanding of the diagnostic and therapeutic approach to acute lymphoblastic leukemia, commonly referred to as ALL. The context is well aligned with our resources and infrastructure as a university-affiliated, tertiary treatment center operating in a low-middle income country setting.

Leukemia is a cancer that originates in the white blood cells, and acute leukemia refers to the rapid and aggressive progression of the disease, necessitating immediate treatment. Acute lymphoblastic leukemia (ALL) is classified based on underlying genetic abnormalities and clinical features, presenting a significant therapeutic challenge for hematologists. This book offers a comprehensive overview of the key aspects of ALL, providing a concise guide to epidemiology, etiology, clinical manifestations, classification, diagnosis, risk stratification, and the latest advances in therapeutic approaches for this disease. The "RIOHCT's Handbook of Acute Lymphoblastic Leukemia" serves as an essential resource for readers seeking insights into the outlook for patients with ALL, and it has been meticulously edited and authored by renowned experts in the field.

We trust that this information will provide you with a solid working knowledge about ALL or reinforce what you already know. We hope you will keep this book close at hand and consider it a valuable guidance tool when treating your patients in a professional manner. Medicine is an ever-evolving field of science, and new information or treatments may have been published or approved since this book went to print. We also acknowledge that this text may not be entirely error-free, and we welcome any feedback you may have so that we can ensure we fulfill our responsibility of providing accurate and up-to-date information to the best of our abilities.

The Authors

Introduction 1

Acute lymphoblastic leukemia (ALL) is a malignant clonal disease of the bone marrow characterized by the proliferation of early lymphoid precursors known as lymphoblast. As the abnormal lymphoblasts spill into the peripheral blood, they can also infiltrate other organs, including the reticuloendothelial system, testicles, and central nervous system (CNS). ALL is the most common type of cancer and leukemia in children, accounting for nearly three-fourths of pediatric leukemia cases, with a median age at diagnosis of 17 years.

In adults, ALL is less prevalent than acute myeloid leukemia (AML), with an estimated 5-year survival rate of approximately 70%. This favorable survival rate is largely due to the high cure rates observed in children. However, prognosis worsens with increasing age, and the median age at death is 59 years. The global prevalence of ALL is approximately 2.1 per 100,000 in men and 1.6 per 100,000 in women, with a noted annual increase of around 1% in B-cell precursor ALL cases in Europe.

A review of the genetics, cell biology, immunology, and epidemiology of childhood leukemia has shown that B-cell precursor ALL has a multifactorial etiology, characterized by a two-step process involving genetic mutations and infection exposure. The first step occurs in utero, where the formation of fusion genes or hyperdiploidy leads to the development of a covert, pre-leukemic clone. The second step involves the postnatal acquisition of secondary genetic changes that drive the progression to overt leukemia. Notably, only 1% of children born with a pre-leukemic clone go on to develop leukemia. This second step is often triggered by infections, particularly in children whose immune responses are abnormally regulated due to a lack of exposure to infections in the early weeks and months of life. Insufficient exposure to these early infections, which help prime the immune system, is more common in societies that prioritize hygiene. This phenomenon may help explain why pediatric ALL is predominantly observed in industrialized nations.

Less is known about the etiology of ALL in adults, compared with AML. Most adults with ALL have no identifiable risk factors. Although most leukemias occurring after exposure to radiation are AML rather than ALL, an increased prevalence of ALL was noted in survivors of the atomic bomb irradiation. A genome-wide association study of susceptibility to ALL in adolescents and young adults identified significant susceptibility loci

in various genes and increased risk of ALL in association with polymorphisms of others.

Patients with acute lymphoblastic leukemia (ALL) may present with a variety of signs and symptoms, which can be broadly categorized into two groups:

- Signs and symptoms related to direct infiltration of the bone marrow or other organs by leukemic cells
- Signs and symptoms related to the decreased production of normal blood cells

One of the most common signs is fever. Patients with ALL often have decreased neutrophil counts, regardless of whether their total white blood cell (WBC) count is low, normal, or elevated. As a result, these individuals are at an increased risk of infection, especially when the absolute neutrophil count is less than 500 × 10^9/L. Symptoms of anemia are also common and may include fatigue, dizziness, palpitations, and dyspnea upon even mild exertion. Some patients may present with bleeding or disseminated intravascular coagulation (DIC), leading to hemorrhagic or thrombotic complications. Other clinical manifestations can arise from the infiltration of leukemic cells into various organs, such as:

- Hepatosplenomegaly
- Lymphadenopathy
- Central nervous system involvement, causing headaches, cranial nerve palsies, or altered mental status
- Testicular involvement, leading to testicular enlargement or a testicular mass

Early recognition of these signs and symptoms is crucial for prompt diagnosis and initiation of appropriate treatment for patients with acute lymphoblastic leukemia.

Some patients present with palpable lymphadenopathy. Infiltration of the marrow by massive numbers of leukemic cells frequently manifests as bone pain. Splenomegaly is present in 10-20 percent of cases. While patients may exhibit symptoms of leukostasis—such as respiratory distress and altered mental status—due to the presence of a high number of lymphoblasts in the peripheral circulation, leukostasis is much less common in ALL compared to AML. It typically occurs only in patients with significantly elevated WBC counts, often in the range of several hundred thousand cells per microliter. Additionally, involvement of the central nervous system and testicles is also common in patients with ALL, contributing to the various clinical manifestations of the disease. Early recognition of these symptoms is essential for timely diagnosis and treatment.

Rate of new cases per 100.000

1.6

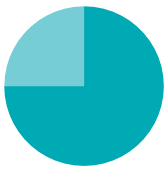
2.1

54% of patient are under 20 years

25% of patient are under 4 years

0.2% of all Cancer deaths worldwide

0.3% of all new cancers worldwide



75% of adults have B-ALL
25% of adults have T-ALL

Diagnosis and Evaluation 2

2-1. History and Physical Exam

For every patient with suspected ALL, the following diagnostic workup is essential to document the patient‘s baseline status and identify any extramedullary manifestations of the disease.

The clinical presentation of ALL is highly variable, with symptoms that may arise either insidiously or acutely. The presenting features typically reflect both the degree of bone marrow failure and the extent of extramedullary spread of the disease. Many patients present with fever, which can indicate an underlying infection or may simply be associated with leukemia itself. Common manifestations of anemia in ALL patients include fatigue, lethargy, and, in some cases, dyspnea or lightheadedness.

Bone pain or arthralgia is common in patients with ALL, particularly in children and those with marrow necrosis. In some cases, patients may present with life-threatening complications, such as severe infections or bleeding events, including intracranial hematomas. Intracranial hemorrhage is more likely to occur in patients with an initial leukocyte count exceeding 400×10^9 /L.

In rare instances, ALL may present without any noticeable signs or symptoms, and the disease may be detected incidentally during routine examinations. Liver, spleen, and lymph nodes are the most common sites of extramedullary involvement, and the degree of organomegaly is more pronounced in children than in adults (**Table 1**). You should look for symptoms of cough, dyspnea, stridor, cyanosis, facial edema, and sometimes syncope which may reflect the presence of an anterior mediastinal (thymic) mass, particularly in children, leading to superior vena cava syndrome. Other uncommon presenting features include ocular involvement (leukemic infiltration of the orbit, optic nerve, retina, iris, cornea, or conjunctiva); subcutaneous nodules (leukemia cutis); enlarged salivary glands (Mikulicz syndrome); cranial nerve palsy; and priapism.

Epidural spinal cord compression at presentation is a rare but serious finding that requires immediate treatment to prevent permanent paraparesis or paraplegia. In some pediatric patients, infiltration of tonsils, adenoids, appendix, or mesenteric lymph nodes leads

to surgical intervention before leukemia is diagnosed.

Overt testicular disease is relatively rare and is typically observed in infants or adolescents with T-cell leukemia and/or hyperleukocytosis. If patients present typical signs, such as the recent emergence of a painless swelling of the testicle(s) without any symptoms or signs of inflammation or infection, a sonographic examination of both testes is mandatory. Although initial testicular involvement is not primarily included in the risk stratification process, biopsy-proven testicular leukemia that persists beyond induction therapy should be managed according to a high-risk treatment strategy.

Table 1. Presenting clinical and laboratory features in children and adults with acute lymphoblastic leukemia

Feature	Children (%)	Adult (%)
Fever	57	56
Bleeding	43	33
Cell Lineage B-Cell T-Cell	 85 15	 75 25
Lymphadenopathy > 3 cm	15	11
Marked splenomegaly	17	uncommon
Testis involvement	1	0.3
Leukocytosis > 100×10^9/L	12	16
Hemoglobin < 8 g/dL	72	54
Platelet < 50×10^9/L	46	52
Central nervous system CNS1 CNS2 CNS3	3 67-79 5-24 3	8 95 - 5

2-2. Initial Workup

CNS assessment. Lumbar puncture (LP) at diagnosis is an essential part of the initial evaluation of patients with ALL. Cerebrospinal fluid (CSF) examination should be carried out prior to starting cytoreductive therapy or even corticosteroids with concomitant first intrathecal chemotherapy. Even hyperleukocytosis (WBC > 100 × 109/L), under condition of effective hemostasis, good general standing and absence of severe infection, is not a contraindication for LP, however it is better be performed by an experienced clinician. Traditionally, CNS involvement is defined by the presence of at least 5 leukocytes/μL of CSF (with leukemic blast cells apparent in a cytocentrifuged sample or by

flow cytometry) or by the presence of cranial nerve palsy (**Table 2**). However, with the omission of prophylactic cranial irradiation in contemporary clinical trials, the presence of any leukemic blast cells in the CSF is associated with increased risk of CNS relapse and is an indication to intensify intrathecal therapy. In case of proven or suspected CNS disease, cranial magnetic resonance imaging (MRI) with contrast should be requested.

Along with abnormalities that are usually present at the onset of ALL, increased uric acid levels and lactate dehydrogenase (LDH) are also common in these patients and correlate with large tumor burden. Coagulopathy and organ dysfunction due to leukemic infiltration may also be seen in ALL patients. Therefore, the following laboratory features should be measured at diagnosis: Complete blood count (CBC), creatinine, liver function tests (LFTs), disseminated intravascular coagulation (DIC) panel including d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT), tumor lysis syndrome (TLS) panel including LDH, uric acid, potassium, calcium, and phosphorus.

Recognizing carriers of the hepatitis B virus (HBV) is crucial, as prompt antiviral therapy can prevent virus reactivation. Therefore, an infectious evaluation for specific agents, including hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV), should be conducted before initiating therapy. Additionally, it is beneficial to assess patients for other pathogens, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and toxoplasma.

Abdominopelvic ultrasonography can help determine spleen size and evaluate for any organomegaly. A chest X-ray is also necessary to identify thymic enlargement, mediastinal masses, or pleural effusions.

A comprehensive cardiac assessment, including electrocardiography and echocardiography, should be performed, particularly for adult patients with additional comorbidities. Other initial evaluations may include computed tomography (CT) scanning or positron emission tomography (PET) if there is a suspicion of extramedullary lymphomatous involvement.

Table 2. Central nervous system status

CNS1 (negative)	• No clinical evidence of a CNS disease, including cranial nerve palsy that would be unequivocally attributable to leukemia. • No imaging (CT/MRI) evidence of a CNS abnormality that would be unequivocally attributable to leukemia. • Normal fundoscopic finding. • Blast-free CSF along with absence of any other evidence of CNS leukemia.

CNS2 (negative)	• WBC < 5/μL with presence of lymphoblasts in a non-traumatic sample. • If RBC/WBC ≤ 100 on cytospin preparation of CSF, sample is non-traumatic, and CSF uncontaminated with blood. • If RBC/WBC > 100 on cytospin preparation of CSF, sample is traumatic, and CSF contaminated with blood.
CNS3 (positive)	• A mass lesion in the brain and/or meninges on CT/MRI. • Cranial nerve palsy unrelated to other causes, even if the CSF is blast-free, or no circumscribed space-occupying lesion could be demonstrated within the neurocranium on imaging. • Pure retinal involvement, i.e., with a blast-free CSF, and no mass on MRI/CT scan. • A non-traumatic CSF sample with cell count of ≥ 5/μL and presence of blasts on the cytospin slide. • If contamination with blood is doubtful, the diagnosis of CNS involvement can still be made based on either of the following: • Cell count > 5/μL; presence of blasts; RBC/WBC ≤ 100 • Cell count > 5/μL; higher percentage of blasts in CSF than peripheral blood

CNS, Central nervous system; CSF, Cerebrospinal fluid; CT, Computed tomography; MRI, Magnetic resonance image; RBC, Red blood cell; WBC, White blood cell.

Pregnancy status should be clarified before treatment and fertility counseling and preservation be discussed with patients of reproductive age. A thorough cardiac assessment by electrocardiography and echocardiography should be performed especially for adult patients with other comorbidities. Other initial evaluations may incorporate computed tomography (CT) scanning or positron emission tomography (PET) in case of suspected extramedullary lymphomatous involvement. Early transplant evaluation consists of HLA typing and donor search and should be strongly considered.

2-3. Diagnosis

Examination of a bone marrow aspirate is recommended for the diagnosis of ALL because up to 10% of patients may lack circulating blasts at the time of diagnosis. Additionally, higher concentrations of marrow blasts are more suitable for genetic studies. However, bone marrow aspiration (BMA) can sometimes be challenging due to densely packed marrow, which may necessitate a bone marrow biopsy (BMB). In cases of marrow necrosis, multiple aspirations or biopsies may be required. Ultimately, the diagnosis is based on the microscopic and pathological evaluation of the bone marrow.

Cytomorphology. Morphological assessment of Wright-Giemsa-stained bone marrow aspirate is essential for differentiating ALL from AML and ALL from lymphoblastic lymphoma. Cytochemistry reactions can provide additional information:

- Myeloperoxidase (MPO) is always negative in ALL, except in cases of mixed-phe-

notype acute leukemia (MPAL), which may show low, dim, or strong levels of expression, particularly in B-myeloid cases.

- For a diagnosis of ALL versus lymphoblastic lymphoma, the presence of >25% lymphoid blasts in the bone marrow is required.

Cytomorphology also allows for the recognition of L3 (Burkitt-type) subsets of ALL, which exhibit distinct blast characteristics compared to L1 and L2 subtypes:

- L3 blasts have intensely basophilic cytoplasm, prominent nucleoli, and the presence of cytoplasmic vacuoles.
- In contrast, L1 and L2 lymphoblasts are relatively small, measuring 1 to 2 times the size of small lymphocytes. They exhibit scant, often light-blue cytoplasm, and have a round or slightly indented nucleus with fine to slightly coarse and clumped chromatin, along with inconspicuous nucleoli.
- Some lymphoblasts may contain amphophilic cytoplasmic granules, unlike the deep purple granules seen in myeloid cells. (**Figure 1**).

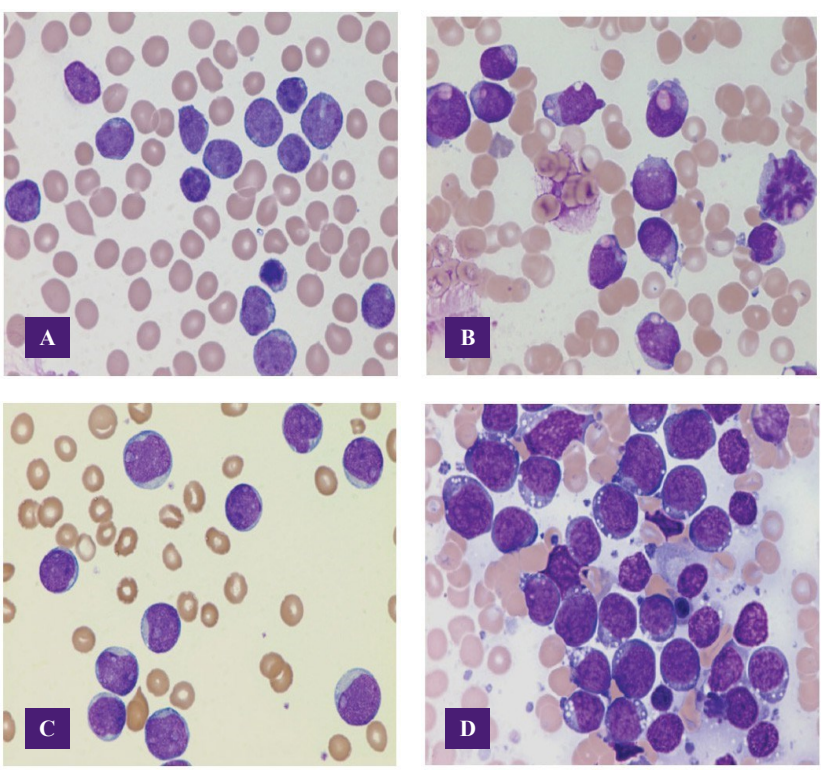


Figure 1. A. Typical lymphoblasts with scant cytoplasm, fine chromatin, and indistinct nucleoli. B. Cytoplasmic granules in acute lymphoblastic leukemia. Fuchsia granules are negative for myeloperoxidase and myeloid-pattern Sudan black B staining. C. ALL with large blasts showing prominent nucleoli. D. Lymphoblasts in Burkitt-like ALL are characterized by in strongly basophilic cytoplasm, and cytoplasmic vacuolation. (Wright-Giemsa stain; ×1000 magnification).

Immunophenotyping. Immunophenotyping is a crucial component of the diagnostic evaluation for ALL. Multicolor flow cytometry (MFC) with at least 8 colors plays a central role, as it not only establishes lineage affiliation and differentiation but also defines aberrant phenotypes for minimal residual disease (MRD) monitoring. Additionally, it can identify target antigens for immunotherapy.

- **B-lymphoblastic leukemia/lymphoma:** B-lineage markers: CD19, CD79a, CD22 (minimal requirement); TdT, CD10, CD20, cIgM, sIg (kappa or lambda)
- **T-lymphoblastic leukemia/lymphoma: T-lineage markers:** CD7, CD3 (minimal requirement); TdT, CD1a, CD2, CD5, CD4, CD8, TCR (α/β or γ/δ)

Myeloid-associated antigens may be aberrantly expressed on otherwise typical lymphoblasts, with variable frequencies ranging from 5% to 30% in children and 10% to 50% in adults. A subset of cases co-express both lymphoid and myeloid markers but do not cluster with T-cell, B-cell, or acute myeloid leukemia in gene expression profiling; These are referred to as mixed phenotype leukemia. Generally, these cases are responsive to ALL-directed induction treatments. While the presence of myeloid-associated antigens does not have prognostic significance in contemporary treatment programs, it can be valuable for immunologic monitoring of patients for MRD.

Although ALL can be further subclassified based on the recognized stages of normal maturation within the B-cell or T-cell lineage pathways (**Figure 2**), the only distinctions of therapeutic importance at present are those between T-cell, mature B-cell, and other B-cell lineage immunophenotypes (**Figure 3**).

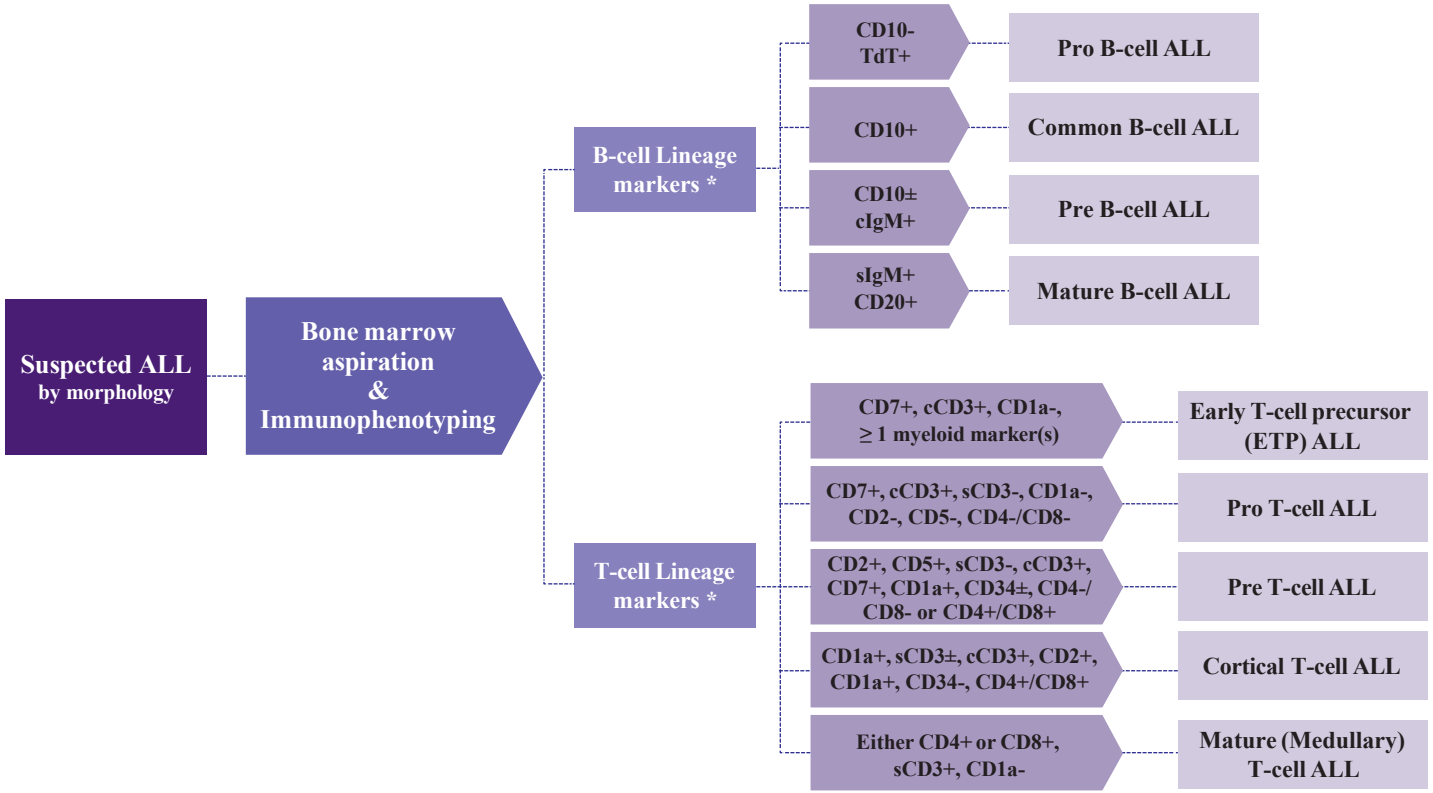


Figure 2. ALL lineage recognition through immunophenotyping.
- CD19, CD22, CD79a.
- Cytoplasmic and surface CD3 (c/s CD3), CD7.

ALL: Acute Lymphoblastic Leukemia; LBL: Lymphoblastic Lymphoma; sIgM: surface Immunoglobulin M; cIgM: cytoplasmic Immunoglobulin M.

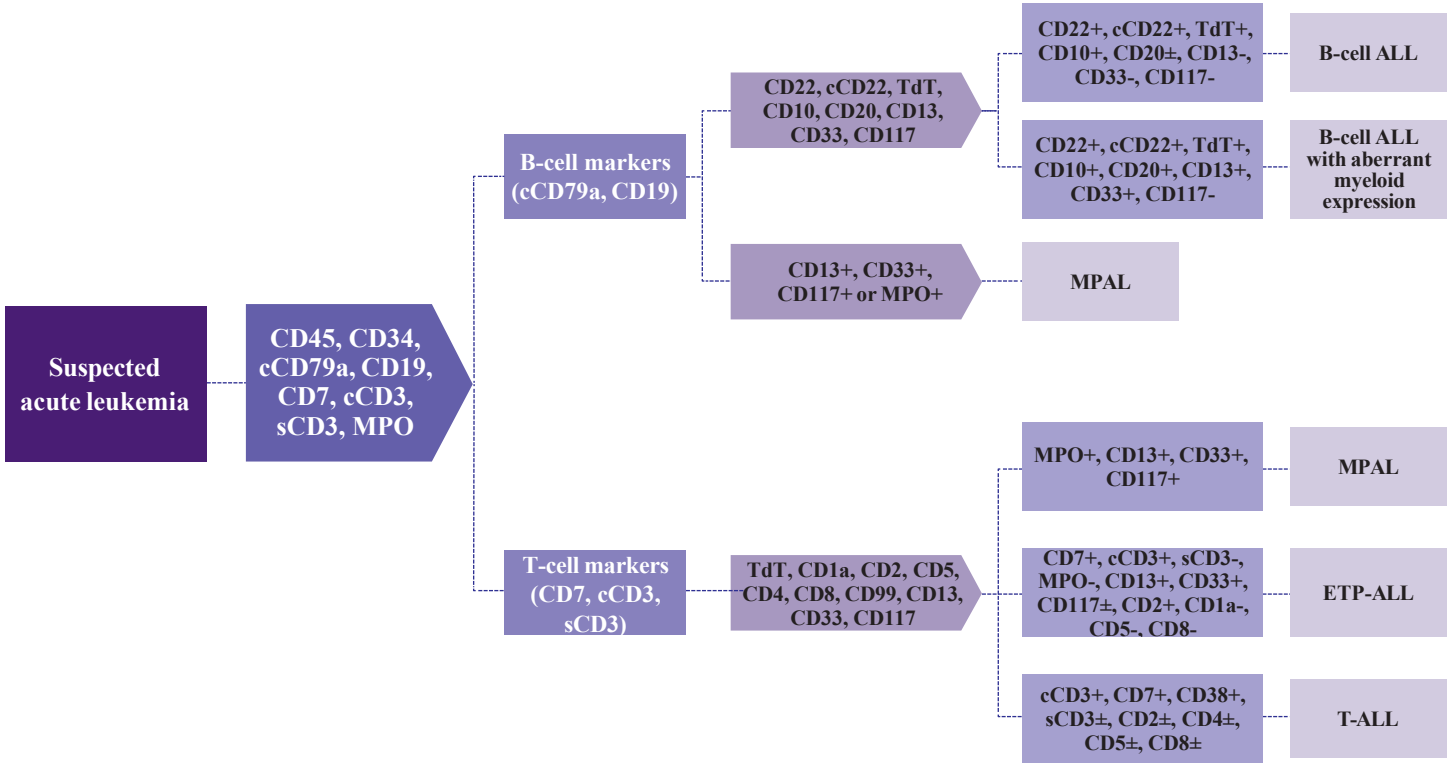


Figure 3. Our practical flowchart for ALL immunophenotyping at RIOHCT.
ETP-ALL: Early T-cell precursor lymphoblastic leukemia; MPAL: Mixed-phenotype acute leukemia

Chromosomal analysis in B-ALL. The karyotype is necessary for classification according to WHO; however, the prognostic assessment of the cytogenetic findings is even more important. In particular, cytogenetic aberration with t(9;22) or t(4;11), which are defined as unfavorable prognostic factors in the GMALL study group, has therapeutic relevance in B-ALL. Patients with hypodiploid karyotype also have an unfavorable prognosis, whereas hyperdiploidy is associated with a good prognosis (**Table 3**).

Fluorescence In Situ Hybridization (FISH) can detect the presence of a BCR:ABL1 or KMT2A rearrangement within 24 hours. Furthermore, FISH is often used in addition to classical chromosome analysis to confirm detected aberrations and to establish a baseline for follow-up to detect residual disease under therapy.

Table 3. Ploidy groups in ALL (according to Heim & Mitelman 2015

Ploidy group	Chromosome Number	Phenotype
Near haploidy	25-29	c-ALL, Pre-B ALL
Low hypodiploidy	30-39	c-ALL, Pre-B ALL
High hypodiploidy	42-45	B-ALL
High hyperdiploidy	51-65	c-ALL, Pre-B ALL

c-ALL: Common ALL

The so-called “chromosome painting” with 1-3 or 24 colors (24-color FISH) on metaphase chromosomes is performed in addition to classical chromosome analysis if the karyotype cannot be unambiguously clarified by chromosome analysis after Giemsa banding. This is often the case in complex aberrant karyotypes.

Molecular genetics in B-ALL. Molecular genetics allows, among other things, the identification of high-risk groups with t(9;22)(q34;q11) or t(4;11)(q21;q23) by detection of the corresponding fusion transcripts BCR:ABL1 or KMT2A:AFF1 (formerly: MLL:AF4). Furthermore, transcriptome analysis (RNA-Seq) can be used to characterize the gene expression profile, such as in the BCR:ABL1-like subgroup, thereby enabling the identification of therapeutically targetable structures.

More than 60% of BCR:ABL1 positive B-precursor ALL or BCR:ABL1-like ALL additionally have an IKZF1 deletion, leading to an even less favorable prognosis. Another prognostically unfavorable factor, especially when both alleles are affected, are mutations in the TP53 gene. These are most frequently observed in ALL with a low hypodiploid chromosome set or MYC rearrangements (**Table 4**).

Table 4. ELN 2024 classification
Molecular subgroups in adult ALL: incidence, prognosis, and molecular findings

Subset	Prevalence (%) Prognosis	Related aberrations
B-Lineage ALL		
BCR:ABL1/t(9;22)(q34;q11.2) (Ph^+)	20-50 Improved by TKI	
Ph-like	25-27 Unfavorable	Expression profile like Ph^+ but without BCR:ABL1 rearrangement
TCF3:PBX1/t(1;19)(q23;p13)	10-15 Favorable	
KMT2A(MLL):AFF1/t(4;11)(q21;q23.3) KMT2A-rearranged/t(v;11q23.3)	~5 Unfavorable	
IGH:MYC/t(8,14)(q24;q32)	1-5 Unfavorable	
TCF3:HLF/t(17;19)(q22;p13.3)	<1 Unfavorable	
iAMP21	~2 Inter/Unfavorable	
14q32 translocations	<5 Inter/Unfavorable	IGH fusion with partner genes CRLF2, ID4, CEBP, BCL2, EPOR, LHX4, IL-3
9p13 deletions/translocations	25 No impact	PAX5 fusion with partner genes ETV6, ELN, POM121, PML, FOXP1, MLLT3, JAK2, C20orf112, AUTS2, CHFR, SOX5, POM121C
7p12.2 focal deletions/mutations	50 (80 in Ph^+/Ph-like) Controversial	Deletions of IKZF1
DUX4-rearranged and ERG-deregulated	3-7 Favorable	ERG and IKZF1 deletions
MEF2D-rearranged ALL	3-4 Poor	
ZNF384-rearranged ALL	6-7 Intermediate	Partner gene EP300, CREBBP, TAF15, SYNRG, EWSR1, TCF3, ARID1B

Subset	Prevalence (%) Prognosis	Related aberrations
CDX2: UBTF	2.7-4 Poor	High expression of CDX2 and gain (1q); UBTF::ATX-N7L3; CDX2-cis-deregulation
T-lymphoblastic leukemia/lymphoma		
TAL & LMO rearrangements/del(1)(p32), t(1;14)(p32;q11), t(1;7)(p32;q34), t(7;9)(q34;q32), t(11;14)(p15;q1), t(11;14)(p13;q1), t(7;11)(q35;p13)	30-40 Favorable	SIL-TAL1 rearrangement, TCR rearrangements with TAL1, TAL2, LMO1, and LMO2
HOXA aberrations/inv(7)(p15q34), t(7;7)(p15;q34), t(10;11)(p13;q14), t(v;11q23), del(9)(q34)	20-25 Depends on additional lesions	TCR-HOXA rearrangement, MLLT10 and MLL rearrangements with various partners, SET-NUP214 rearrangement
TLX1-10q24 rearrangements/t(7;10)(q34;q24), t(10;14)(q24;q11)	20-30 No impact	TCR-TLX11 rearrangement
ETP ALL	10-15 Unfavorable	Deregulation of myeloid transcription factors, of members of RAS pathway and of epigenetic regulators
TLX3-5q35 rearrangement/t(5;14)(q35;q32)	10 No impact	TLX3-BCL11B rearrangement
t(8;14)(q24;q11)	1 Unfavorable	MYC involvement
ABL1 rearrangements	~3 Potentially improved by TKI	NUP214, EML1; ETV6
LYL/MEF2C rearrangement and immature cluster/t(7;19)(q34;p13), del(5)(q14)	3-17 Unfavorable	TCR with LYL1 MEF2C rearrangements
NKX2-1/NKX2-2 rearrangements/ inv(14)(q11.2q13), t(7;14)(q34;q13), inv(14)(q13q32.33), t(14;20)(q11;p11)	6 No impact	TCR/IGH-NKX2- or NKX2-2 rearrangements

Eventually, ALL cases will be classified according to the latest world health organization (WHO) classification scheme for ALL with as much accuracy as possible based on our institutional capabilities (**Table 5**).

Table 5. WHO classification of acute lymphoblastic leukemia/lymphoma

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, Not otherwise specified
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2) [BCR-ABL1]
• B-lymphoblastic leukemia/lymphoma with t(v;11q23.3) *KMT2A* rearranged
• B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1) *[ETV6-RUNX1]*
• B-lymphoblastic leukemia/lymphoma with hyperdiploidy
• B-lymphoblastic leukemia/lymphoma with hypodiploidy
• B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *[IGH-IL3]*
• B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3) *[TCF3-PBX1]*
• B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like * • ABL class (involving ABL1, ABL2, CSF1R, PDGFRA, PDGFRB) • JAK rearrangements (primarily involving JAK2) • EPOR rearrangements • CRLF2 rearrangements (CRLF2-R)
• B-lymphoblastic leukemia/lymphoma with iAMP21 *
T-lymphoblastic leukemia/lymphoma
• Early T-cell precursor leukemia *
* Provisional entity

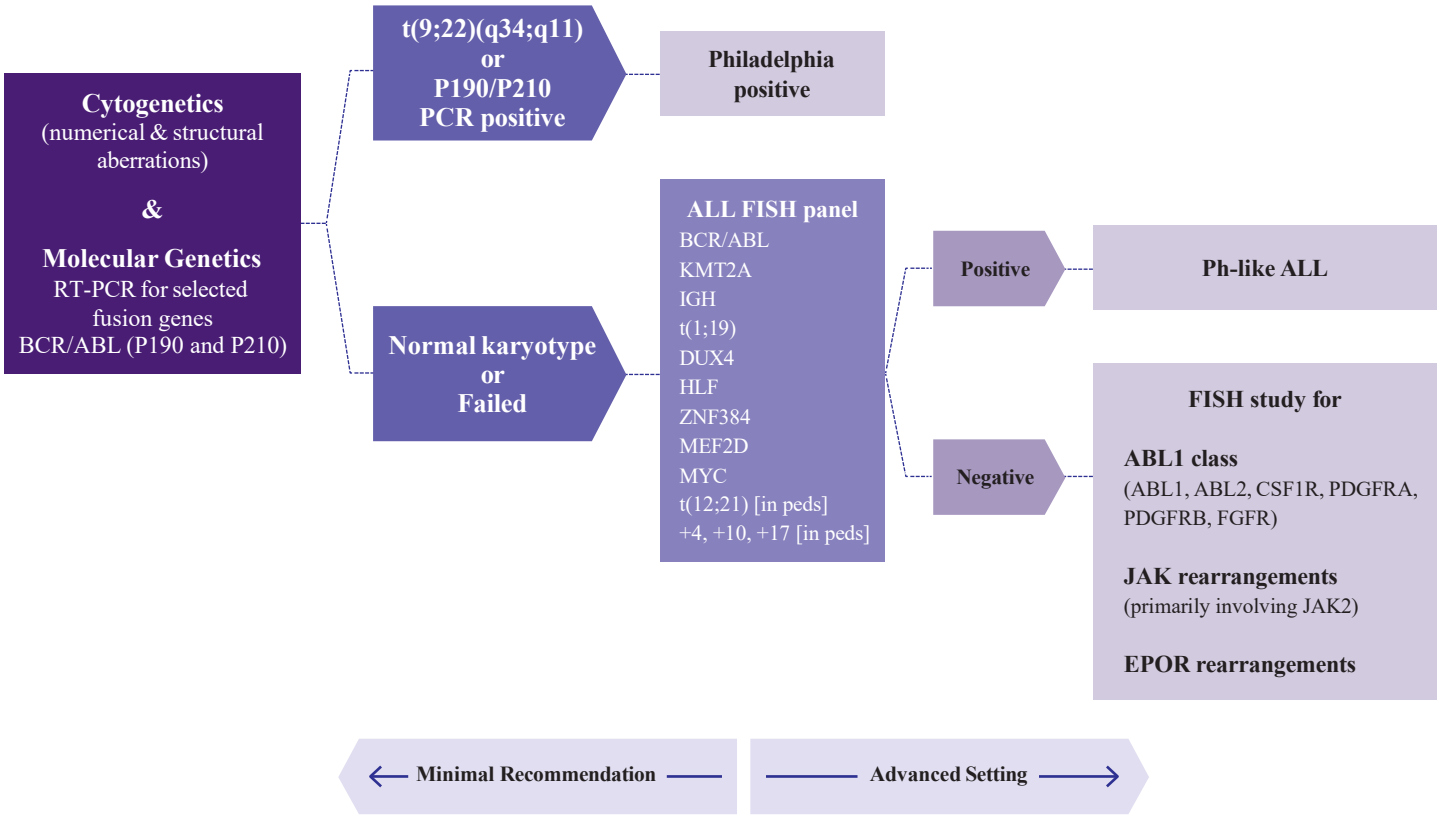


Figure 4. depicts our general approach to classify ALL cases based on genetic analysis. To this end, we incorporate modalities including karyotyping, fluorescent in situ hybridization (FISH), and reverse transcriptase polymerase chain reaction (PCR).

Risk Assessment 3

It is crucial to risk stratify patients diagnosed with ALL on an individual basis, taking into account demographic, pathological, and clinical data. The incorporation of MRD response has significantly improved prognostic accuracy. Patients without poor prognostic factors (PF) and/or those with a favorable post-induction MRD trajectory account for 50% to 60% of all cases and are classified as standard risk (SR). This group has a 5-year overall survival (OS) rate exceeding 50% to 60%, and up to 70% to 80% in selected good-risk subsets. Conversely, patients with categorized as high risk (HR), with a 5-year OS of 40% to 50%. This distinction is vital for formulating an effective risk-oriented treatment strategy. The following diagram shows our practical approach to this point (**Figure 5**).

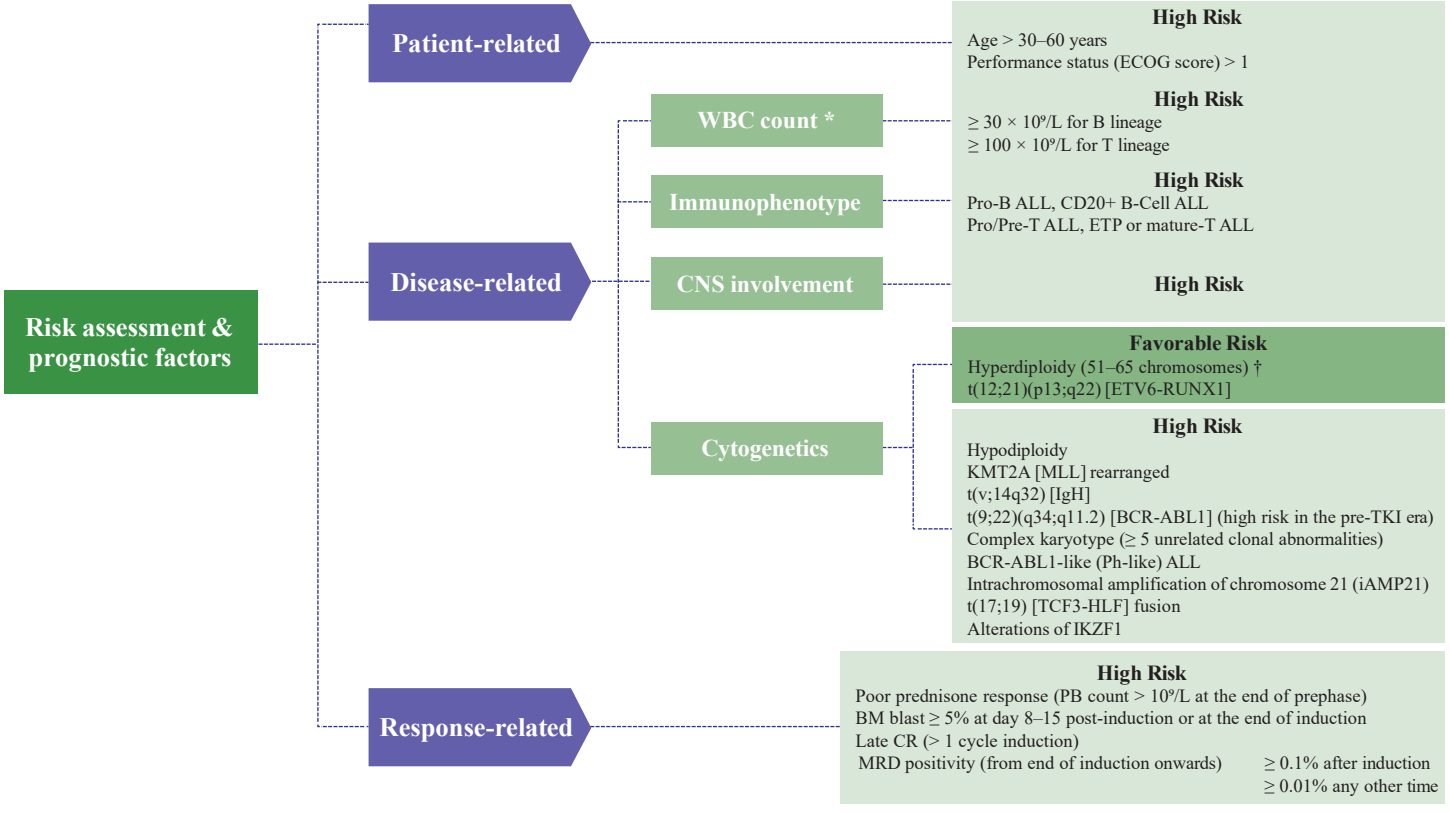


Figure 5. Risk assessment in Acute Lymphoblastic Leukemia (ALL).

* Studies in adult patients have demonstrated that WBC counts may lose independent prognostic significance when cytogenetic factors and MRD assessments are considered. Data showing the effect of WBC counts on prognosis in adult patients with ALL are less firmly established than in the pediatric population. Therefore, adult patients with ALL may not necessarily be classified as high risk based on high WBC count alone.

†Trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome. ‡Blast count in peripheral blood after pre-phase $\geq 1 \times 10^9$ /L.

CNS: Central nervous system, CR: Complete remission, ECOG: Eastern cooperative oncology group, ETP-ALL: Early T-cell precursor acute lymphoblastic leukemia, MRD: Measurable residual disease; WBC: White blood cell.

Treatment 4

The treatment for acute lymphoblastic leukemia affecting precursor B-cell and T-cell lineages typically consists of three standard phases: remission induction, intensification (consolidation), and prolonged maintenance therapy. CNS-directed therapy is also an integral part of the treatment approach; initiated early and continues for varying durations, depending on the patient's risk of relapse and the intensity of the primary systemic regimen.

4-1. Newly diagnosed acute lymphoblastic leukemia (ALL)

At our center, treatment is based on age stratification, classifying patients into three distinct groups:

- Adolescents and young adults (AYA)
- Adults
- Elderly patients

Additionally, due to the pivotal importance of the Philadelphia chromosome (t(9;22)) in ALL, the therapeutic approach for each group is further categorized based on Philadelphia chromosome status.

Induction

The primary goal of intensive induction therapy is to achieve CR as early as safely feasible, and as deeply as possible.

During the prephase, corticosteroids are typically administered for 5 to 7 days. The first induction phase lasts approximately 4 weeks and carries the highest risk of complications, necessitating intensive support. This includes the use of granulocyte colony-stimulating factor (G-CSF), transfusions, and optimal prophylaxis and management of infections.

Consolidation

Consolidation therapy is administered to patients in CR. Currently, no single regimen is recommended as the standard of care for Philadelphia chromosome-negative (Ph-) ALL.

However, pediatric-based regimens are favored due to their proven effectiveness.

Maintenance therapy

Maintenance therapy is strongly recommended for all patients, as insufficient maintenance can significantly worsen overall survival (OS). Long-term drug exposure is likely necessary to eradicate MRD. A total treatment duration of 2 to 2.5 years, including maintenance therapy, is recommended. Additionally, intervals of approximately 3 months are suggested for MRD testing during the maintenance phase.

Frontline targeted therapy of Ph-negative B-Cell ALL

Evidence is rapidly accumulating that immunotherapy can enhance antileukemic efficacy. Approximately 40% of adult patients with B-cell ALL express the CD20 antigen in more than 10% to 20% of lymphoblasts. Therefore, anti-CD20 therapy is recommended for the management of CD20-positive ALL, with a minimum of eight doses suggested for optimal effectiveness.

The main chemotherapy regimens used at our center are presented in Appendix A.

Table 6. Response criteria for blood, bone marrow and extramedullary disease

Hematologic response criteria	
CR (complete remission)	• No circulating lymphoblasts or extramedullary disease • No lymphadenopathy, splenomegaly, skin /gum infiltration, testicular mass, CNS involvement • Trilineage hematopoiesis and BM < 5% blasts • ANC > 1 × 109/L • Platelets >100 × 109 /L • If available: MRD <1%
CRi (CR with incomplete blood count recovery)	• Meets all criteria for CR except platelet count or ANC • If available: MRD <1%
Refractory disease (Failure)	• None of the above • If available: MRD ≥1%
Progressive disease	• Increase of at least 25% in the absolute number of circulating or bone marrow blasts OR • development of extramedullary disease
Relapsed disease	• Reappearance of blasts in the blood or bone marrow (> 5%) OR • any extramedullary site after a CR
Response criteria for CNS disease	

CNS remission	• Achievement of CNS1 status in a patient with CNS2 or CNS3 status at diagnosis
CNS relapse	• New development of CNS3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/ eye involvement, or hypothalamic syndrome without another explanation
Response criteria for lymphomatous extramedullary disease *	
CR	• Complete resolution of lymphomatous enlargement by CT. • For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
Partial response	• >50% decrease in the SPD of the mediastinal enlargement. • For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.
Progressive disease	• >25% increase in the SPD of the mediastinal enlargement. • For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.

** CT of neck/chest/abdomen/pelvis with IV contrast and PET/ CT should be performed to assess response for extramedullary disease.*
ANC, Absolute neutrophil count; BM, Bone marrow; CNS, Central nervous system; CR, Complete remission; CT, Computed tomography; PET, Positron emission tomography; SPD, Sum of the product of the greatest perpendicular diameters.

Response assessment is a crucial aspect of the therapeutic regimen. This evaluation is primarily conducted through MRD assessment using next generation flow cytometry (NGF) and appropriate molecular studies. Internationally approved response criteria are employed to assess treatment response at each stage of therapy (**Tables 6 & 7**).

Importance of MRD in Treatment Decisions

The management of ALL has increasingly incorporated MRD assessment to guide treatment modifications.

Prognostic Significance: MRD status is a critical prognostic factor in ALL, influencing treatment decisions and outcomes. Patients with detectable MRD after initial therapy are at a higher risk of relapse.

Timing and Level of MRD: The timing of MRD assessment is essential. Early MRD response, particularly at around 2 to 3 months post-diagnosis, can indicate the need for therapy de-escalation, while later assessments are useful for identifying candidates for treatment escalation.

Threshold Levels: A commonly used threshold for MRD is 0.01% (10^-4), as this aligns with the sensitivity of MRD assays. Higher levels of MRD correlate with shorter times to relapse, making it crucial to monitor these levels closely.

Treatment Modifications Based on MRD

De-escalation of Therapy: Patients showing no detectable MRD at early time points may be candidates for reduced treatment intensity, potentially sparing them from the toxicity of aggressive therapies.

Escalation of Therapy: Conversely, patients with persistent MRD may require intensified treatment strategies, including the use of novel agents such as blinatumomab or CAR T-cell therapy, which have shown efficacy in eradicating MRD.

Salvage Therapy: In cases of relapsed or refractory ALL, achieving MRD negativity during salvage therapy is associated with improved outcomes. Patients who achieve undetectable MRD prior to allogeneic hematopoietic stem cell transplantation (HSCT) have better survival rates.

Future Directions

Standardization of MRD Assessment: There is a need for standardized methodologies for MRD detection to ensure consistent treatment decisions across different protocols. This includes the use of sensitive assays such as next-generation sequencing (NGS) and quantitative polymerase chain reaction (PCR).

Clinical Trials: Ongoing clinical trials are evaluating the role of MRD in treatment strategies, particularly in the context of immunotherapies and targeted therapies. These studies aim to refine MRD-based approaches and improve patient outcomes.

Table 7. Response parameters according to measurable residual disease (MRD)

Consensus recommendations on the timing of MRD assessments	MRD assessment is only considered in patients with hematologic CR or CRi at respective time points. In adults with ALL undergoing frontline treatment, MRD from the bone marrow should be assessed at least: • At the end of induction • After early consolidation (approximately after 3 months of therapy) and then every 6 weeks from peripheral blood or every 12 weeks from bone marrow for at least 3 years (5 years for patients with Ph-positive ALL who did not undergo HSCT in first remission).

Molecular CR	Complete molecular response / MRD negativity	• Patient in CR (complete hematological remission) • MRD not detectable by multiparameter flowcytometry
Molecular/ MRD Response (less than Molecular CR)	Patient in hematological CR, not in molecular CR	• Low-level non-quantifiable MRD • (< 10−4)
Molecular failure/MRD positivity	Patient in hematological CR, not in molecular CR/ molecular response	• Quantifiable MRD (≥ 10−4)
Molecular/ MRD relapse	Patient in hematological CR	• Loss of molecular CR/ molecular response status (≥ 10−4)

ALL, Acute lymphoblastic leukemia; CR, Complete remission; HSCT, Hematopoietic stem cell transplantation; MRD, Measurable residual disease.

Figure 6. Ph-negative ALL treatment algorithm in AYA Group

* The ALL panel considers AYA to be within the age group of 15–39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively studied across all ages.

† Pediatric inspired regimens including Berlin-Frankfurt-Münster regimen and CALGB 10403 regimen (Supplement A).

ALL, Acute lymphoblastic leukemia; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation; CR, Complete remission; MRD: Measurable residual disease; Ph, Philadelphia chromosome; WBC, White blood cell.

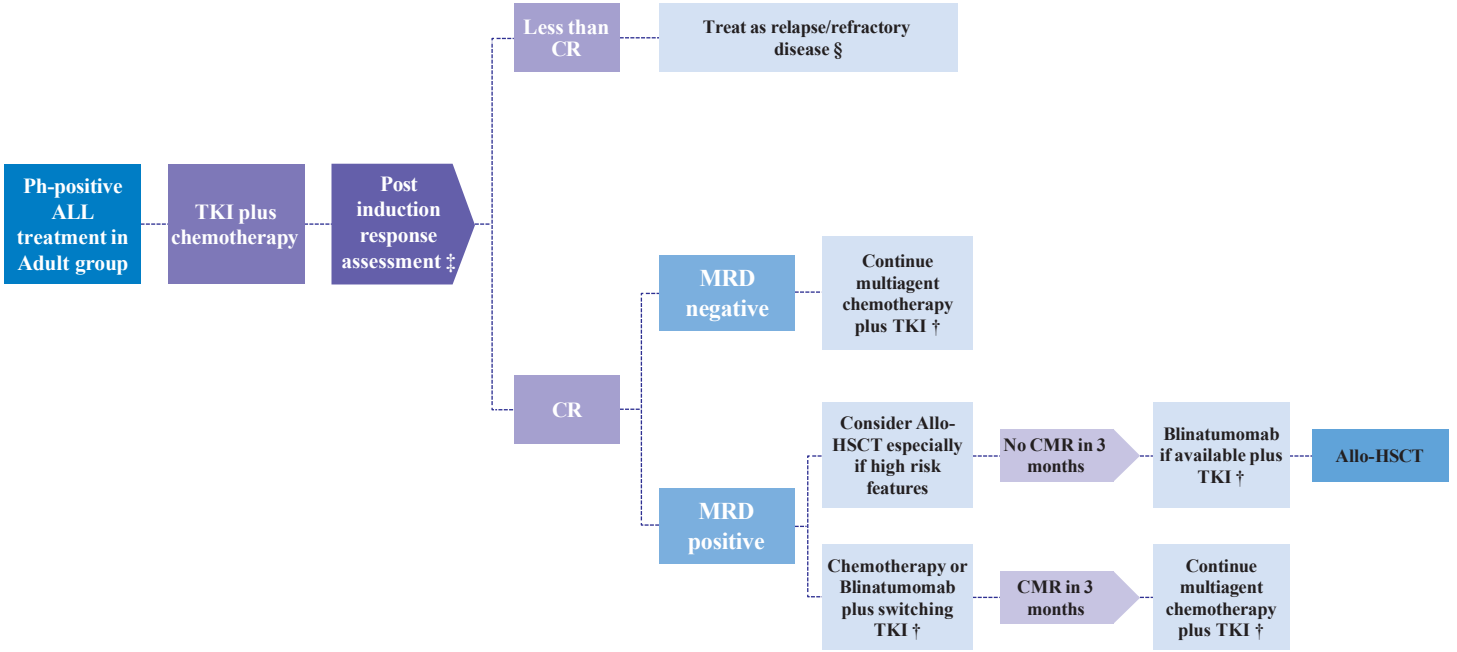


Figure 7. Ph positive ALL treatment algorithm in AYA Group.

* The ALL panel considers AYA to be within the age group of 15–39 years. However, this age is not a firm reference point because some of the recommended regimens have not been comprehensively studied across all ages.

† Dasatinib and Imatinib are the preferred TKIs for induction therapy. TKI therapy is initiated in frontline therapy together with the first chemotherapy cycle and then administered continuously. In patients with persistent MRD or progressive disease, the recommendation is to switch to another TKI (consider using an alternative and broader acting TKI) while screening for TKI resistance mutations and then to choose TKI according to the resistance profile. The recommended duration of TKI treatment is at least until completion of maintenance chemotherapy. The optimal duration is unknown.

ALL, Acute lymphoblastic leukemia; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation; CMR, Complete molecular response; CR, Complete remission; MRD: Measurable residual disease; Ph, Philadelphia chromosome; TKI: Tyrosine kinase inhibitor; WBC, White blood cell.

Figure 8. Ph negative ALL treatment algorithm in adult patients.

* Performance status (ECOG score).

ALL, Acute lymphoblastic leukemia; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation; CR, Complete remission; MRD, Measurable residual disease; Ph, Philadelphia chromosome; WBC, White blood cell.

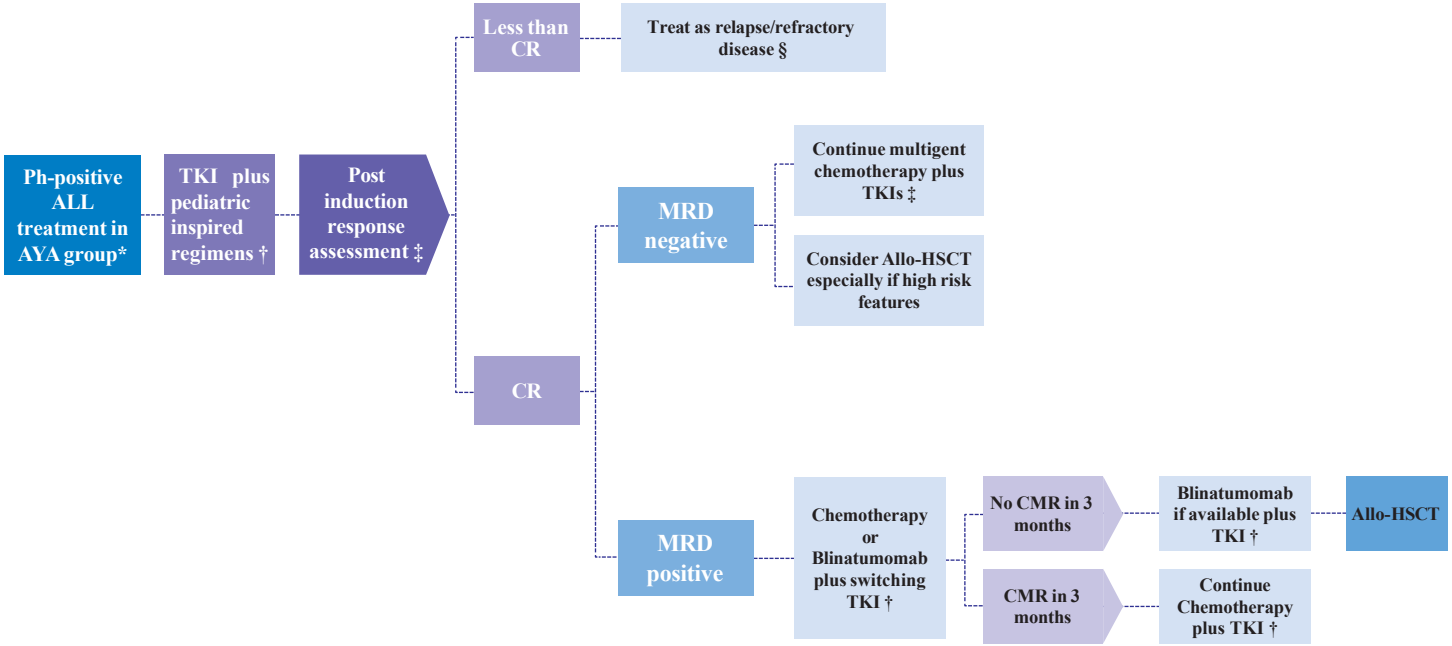


Figure 9. Ph positive ALL treatment algorithm in adult patients.

* Performance status (ECOG score).

† Dasatinib and Imatinib are the preferred TKIs for induction therapy. TKI therapy is initiated in frontline therapy together with the first chemotherapy cycle and administered continuously. In patients with persistent MRD or progressive disease, the recommendation is to switch to another TKI (consider using an alternative and broader acting TKI) while screening for TKI resistance mutations and then to choose TKI according to the resistance profile. The recommended duration of TKI is at least until completion of maintenance chemotherapy. The optimal duration is unknown.

ALL, Acute lymphoblastic leukemia; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation; CMR, Complete molecular response; CR, Complete remission; MRD, Measurable residual disease;

Ph, Philadelphia chromosome; TKI, Tyrosine kinase inhibitor; WBC: White blood cell.

Figure 10. Ph negative ALL treatment algorithm in elderly adult group.

* Performance status (ECOG score).

ALL, Acute lymphoblastic leukemia; CR: Complete remission; MRD, Measurable residual dsiease; Ph, Philadelphia chromosome; WBC: White blood cell.

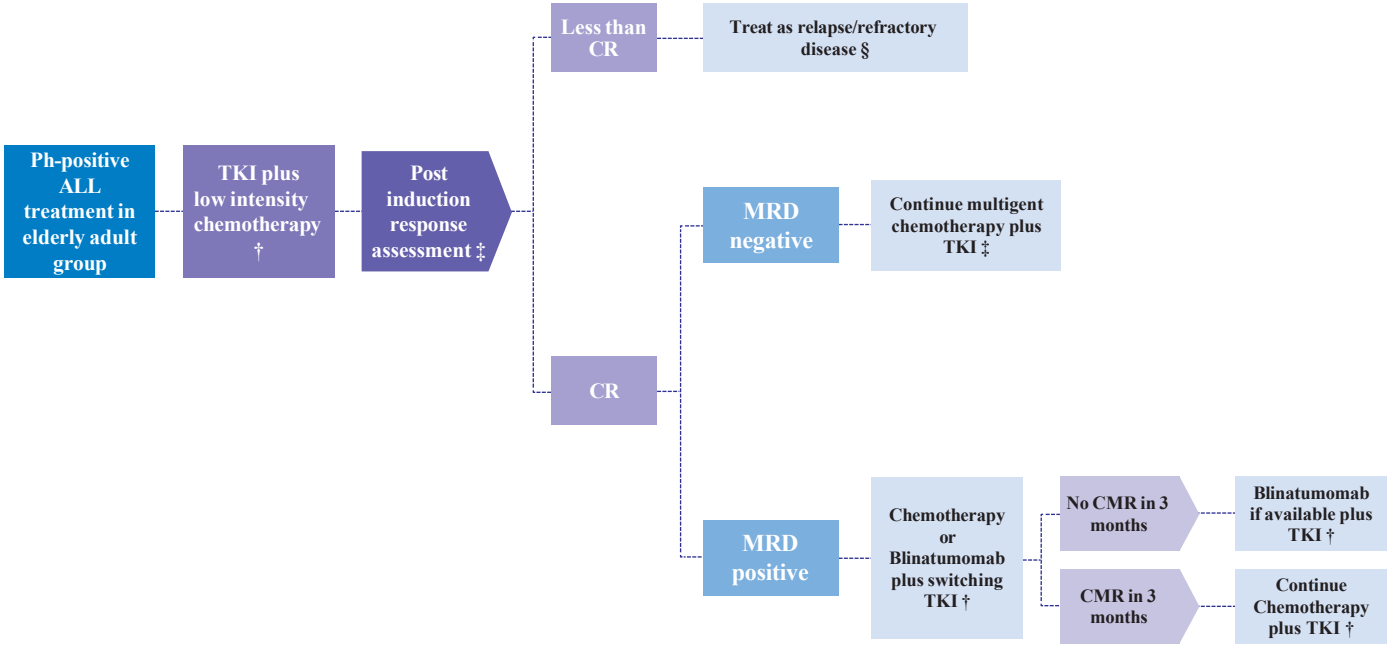


Figure 11. Ph positive ALL treatment algorithm in Elderly Adult Group.

† Dasatinib and Imatinib are the preferred TKIs for induction therapy. TKI therapy is initiated in frontline therapy together with the first chemotherapy cycle and administered continuously. In patients with persistent MRD or progressive disease, the recommendation is to switch to another TKI (consider using an alternative and broader acting TKI) while screening for TKI resistance mutations and then to choose TKI according to the resistance profile. The recommended duration of TKI is at least until completion of maintenance chemotherapy. The optimal duration is unknown.

ALL, Acute lymphoblastic leukemia; CMR, Complete molecular response; CR, Complete remission; MRD, Measurable residual disease; Ph, Philadelphia chromosome; TKI, Tyrosine kinase inhibitor; WBC, White blood cell.

4-2. Extramedullary disease

CNS

Patients with CNS involvement (mostly of the leptomeninges) at diagnosis are treated with the standard systemic chemotherapy regimen (either high dose of methotrexate and/or cytarabine) and additional regularly repeated intra-thecal (IT) methotrexate (usually with steroids and cytarabine) until lymphoblast clearance in the CSF. It may also warrant treatment with cranial irradiation of 18 Gy in 1.8 to 2.0 Gy/fractions. The recommended dose of irradiation, where given, is highly dependent on the intensity of systemic chemotherapy; thus, it is critical to adhere to a given treatment protocol in its entirety.

Testicles

Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of the induction therapy should be considered for irradiation to the testes in the scrotal sac, which is typically done concurrently with the first cycle of consolidation chemotherapy. The testicular total dose should be 24 Gy in 2.0 Gy/fractions.

4-3. Relapse/Refractory disease

Despite significant improvements in remission rates, with CR achieved in approximately 90% of cases, around 5-10% of adult patients with ALL are initially refractory to induction therapies. Additionally, 30% to 60% of those who achieve complete remission will ultimately experience a relapse. Although BM is the most frequent site of relapse, extramedullary relapses can occur, and incidence may even increase with more widespread use of immunotherapies.The prognosis for patients with relapsed or refractory ALL is influenced by several factors, including the duration of the initial remission, the response to previous salvage therapy, the disease burden at the time of relapse, and the patient's age. The only curative option available is to achieve a second complete remission through salvage therapy, followed by allogeneic hematopoietic stem cell transplantation (HSCT). However, less than half of these patients achieve a second complete remission, and only a limited subset qualifies for this procedure. **Table 8** outlines the definition of relapse by site in patients with ALL.

Table 8. Definition of relapse by site

Isolated marrow	• Lymphocytes ≥ 25% of nucleated marrow cells
Isolated CNS	• Cells > 5/mm^3 CSF and unambiguous lymphoblasts • identified in cytospin preparation • Intracerebral mass on CT/MRI without lymphoblasts • in CSF, PB, or marrow (biopsy is mandatory)

Isolated testis	• Painless swelling (unilateral/bilateral) of testicle(s) • with enlargement more than 2 deviation scores larger • by Prader orchidometer (biopsy is mandatory)
Isolated infiltrates at other sites	• Biopsy proven infiltration
Multiple sites	• Simultaneous involvement of ≥ 2 compartments or • localizations • Bone marrow is involved if it contains > 5% • lymphoblasts

CNS, Central nervous system; CSF, Cerebrospinal fluid; CT, Computed tomography; MRI, Magnetic resonance imaging; PB, Peripheral blood.

The following evaluations are recommended in case of relapse suspicion:

- Enumeration of CD19, CD20 and CD22 expression on blast cells (as it may have therapeutic relevance)
- Cytogenetic evaluation
- HLA profiling of the patient and siblings should be carried out urgently, and unrelated donor search should be initiated if a sibling match is not available.
- In the case of Ph+ ALL, BCR-ABL1 tyrosine kinase domain mutations should be evaluated.
- Patients with relapsed Ph+ ALL should be offered the new generations of TKIs, according to the results of mutational analysis of their BCR-ABL1 transcripts.

Conventional approaches

Although some individuals can be rescued with additional chemotherapy alone, in general, only allogeneic hematopoietic stem cell transplantation offers a reasonable chance for cure and long-term survival. Thus, treatment for relapse is often considered as "a bridge to transplant". Outcomes are better for patients who are MRD-negative before transplantation.

The use of conventional combination chemotherapy regimens, along with single agent chemotherapy with clofarabine or liposomal vincristine are reserved for patients treated in centers with limited access to latest therapeutic options like bispecific antibodies (e.g., blinatumomab) or antibody drug conjugates (e.g., Inotuzumab Ozogamicin) (**Tables 9-13**).

- In refractory ALL, fludarabine and anthracycline containing regimens (e.g., FLAG, CLAG, FLAG-M, CLAG-M, EMA) is usually given.
- In relapsed ALL, induction regimens similar to a standard four-drug combination chemotherapy is recommended except for two key differences: administration of dose-intensified dexamethasone and randomized assignment of anthracycline to either idarubicin or mitoxantrone.

Table 9. Recommended conventional salvage regimens for relapsed / refractory ALL

Alkylator Combination Regimen	
Etoposide 100 mg/m^2 over 1.5 hours Mitoxantrone 8 mg/m^2 over 1 hour Ifosfamide 1.5 mg/m^2 over 30 minutes	$D_1 - D_5$ $D_1 - D_3$ $D_1 - D_5$
Clofarabine/Cyclophosphamide/Etoposide Regimen	
Induction therapy (1-2 cycles) (Clofarabine 40 mg/m^2 over 2 hours (Etoposide 100 mg/m^2 over 2 hours (Cyclophosphamide 440 mg/m^2 over 1 hour (Prednisone 0.5 mg/kg Consolidation Therapy (1-3 cycles) (Same regimen for 4 days (Max 4 cycles (induction + consolidation)	 $D_1 - D_5$ $D_1 - D_5$ $D_1 - D_5$ $D_1 - D_5$
FLAG-IDA	
Fludarabine 30 mg/m^2 over 30 minutes Cytarabine 2,000 mg/m^2 over 4 hours Idarubicin 10 mg/m^2 G-CSF 5 mcg/kg subcutaneous continued until neutrophils > 1.5 $\times 10^9$ /L.	$D_1 - D_5$ $D_1 - D_5$ $D_1 - D_3$ D_6
MOpAD Regimen	
Methotrexate 200 mg/m^2 (reduce by 50% for GFR < 90 mL/min) Vincristine 1.4 mg/m^2 (reduce to 1 mg for pre-existing neuropathy) (reduce to 1 mg if bilirubin 2-3 mg/dL) (hold if bilirubin >3 mg/dL) (maximum dose 2 mg) Pegylated-L-Asparaginase 2,500 IU/m^2 (no capping of dose) (reduce by 50% if direct bilirubin 2-3 mg/dL) (hold for bilirubin ≥ 3 mg/dL) (hold if serous pancreatitis, thrombosis not controlled with anticoagulation, or disseminated intravascular coagulation) Dexamethasone 40 mg	D_1 , D_{15} D_1 , D_8 , D_{15} D_2 , D_{16} $D_1 - D_4$ $D_{15} - D_{18}$

ALL, Acute lymphoblastic leukemia; GFR, Glomerular filtration rate.

Specific salvage for B-ALL

- Blinatumomab (If available)

Table 10. Blinatumomab dosing schedule

Pre-phase Therapy (Before treatment with Cycle 1 induction)
Day 0 | Dexamethasone 10 mg/m^2 orally or IV (max 24 mg)

Cycle 1 Induction therapy (6 weeks)
Days 1-7 | Blinatumomab 9 mcg continuous infusion over 24 hours
Days 8-28 | Blinatumomab 28 mcg continuous infusion over 24 hours
2 weeks rest

Cycle 2 Induction therapy (6 weeks)
Days 1-28 | Blinatumomab 28 mcg continuous infusion over 24 hours
2 weeks rest

Consolidation therapy (3 × 6 weeks cycles)
Days 1-28 | Blinatumomab 28 mcg continuous infusion over 24 hours
2 weeks rest

Maintenance therapy (4 × 12 weeks cycles)
Days 1-28: Blinatumomab 28 mcg continuous infusion over 24 hours
8 weeks rest

Note: For patients < 45 kg, BSA-based dosing should be used.
Note: Blinatumomab may be given up to a total of 9 cycles (2 cycles of induction followed by 3 cycles of consolidation followed by 4 cycles of continued therapy)

- Inotuzumab Ozogamicin (If available)

Table 11. Inotuzumab Ozogamicin dosing schedule

Cycle 1 Induction therapy (4 weeks)
Day 1| Inotuzumab Ozogamicin 0.8 mg/m^2
Days 8,15 | Inotuzumab Ozogamicin 0.5 mg/m^2
1 week rest

Subsequent cycles every 4 weeks for up to 6 cycles

Once CR or CRi achieved, dose of Inotuzumab Ozogamicin should be reduced to 0.5 mg/m^2

- CD19-targeted CAR-T therapy (If available)

Tisagenlecleucel (Kymriah™)

Specific salvage for T-ALL

- Nelarabine (If available)

Table 12. Nelarabine dosing schedule

Schedule 1 (age > 16 years)
Days 1, 3, 5 | Nelarabine 1,500 mg/m^2 over 2 hours
Repeat cycle every 3 weeks
Schedule 2 (age ≤ 21 years)
Day 1-5 | Nelarabine 650 mg/m^2 over 60 minutes
Repeat cycle every 3 weeks

- Nelarabine, Etoposide, Cyclophosphamide

Table 13. Nelarabine, Etoposide, Cyclophosphamide regimen

Days 1-5 | Etoposide 100 mg/m^2
Cyclophosphamide 440 mg/m^2
Days 7-11 | Nelarabine 650 mg/m^2
Intrathecal therapy
Methotrexate or combination drugs typically preceding a nelarabine dose by 6 hours or following it by 2 day

CNS Relapse

- Although extramedullary relapse is frequently an isolated clinical finding, many occurrences are associated with recurrent disease detectable in the marrow.
- CNS relapses are associated with a higher level of MRD in the marrow than testicular relapses. Submicroscopic marrow involvement at a level of 10–4 or higher at the time of overt extramedullary relapse confers a poor outcome.
- Patients with extramedullary relapse and undetectable disease in marrow require intensive systemic treatment to prevent subsequent hematologic relapse.
- For most patients, chemoradiation therapy (CRT) is a fundamental component of successful treatment for CNS relapse.
- Treatment regimens generally include IT chemotherapy combined with systemic reinduction chemotherapy. Consolidation therapy constitutes intensive systemic chemotherapy due to the presumption of subclinical marrow involvement and CRT if not administered during initial induction treatment. Prolonged maintenance regimens should also be prescribed, which includes additional IT therapy.

Testicular Relapse

- One-third of patients with early testicular relapse and two-thirds of patients with late testicular recurrence became long-term survivors after salvage chemotherapy and testicular irradiation.
- Because isolated testicular relapse frequently heralds systemic recurrence, treatment must include intensification of systemic therapy in addition to local control with either irradiation or orchiectomy, with most current regimens utilizing a dose of 2,400 cGy.

The optimal treatment and prognosis for patients with relapse at unusual extramedullary sites are unclear. However, the same principles that apply to the clinical management of CNS or testicular relapse probably apply to this subgroup.

Supportive Therapy 5

5-1. Crisis management

Optimal management of patients with ALL requires careful attention to supportive care, including immediate treatment or prevention of metabolic and infectious complications and rational use of blood products. Other important supportive care measures, such as use of indwelling catheters, amelioration of nausea and vomiting, pain control, and continuous psychosocial support for the patient and family, are essential.

Hyperleukocytosis

- Hyperleukocytosis is usually defined as peripheral blood leukocyte count exceeding 100 ×109/L. Although it can affect any organ system, symptoms usually arise from involvement of the cerebral, pulmonary, and renal microvasculature. Symptomatic hyperleukocytosis is rare in ALL and typically occurs with much higher WBC counts than in patients with AML.
- The term "leukostasis" refers to 'symptomatic hyperleukocytosis' which is a medical emergency that needs prompt recognition and initiation of therapy to prevent renal and respiratory failure or intracranial hemorrhage.
- The management of hyperleukocytosis and leukostasis involves supportive measures and reducing the number of circulating leukemic blast cells by induction chemotherapy, hydroxyurea, low-dose chemotherapy, and leukapheresis.
- Hydroxyurea may be used as a bridging strategy in patients with a not yet diagnosed hematological malignancy or with contraindications to induction chemotherapy.
- A single leukapheresis procedure can reduce the WBC count by 20-50%. Most authors have reported reaching a peripheral blood count of less than 100 × 10^9 /L as the goal of leukapheresis and some advocate that the patient's symptoms will guide the adequacy of leukapheresis. In most patients, a single procedure may control leukostasis symptoms, and rare patients may require additional procedures.
- It is important to keep in mind that patients with hyperleukocytosis and leukostasis are also at increased risk of DIC and TLS.

- Platelet transfusions and standard measures to restore normal coagulation such as transfusion of fresh frozen plasma or fibrinogen should be initiated immediately in these patients**.** Platelet transfusion does not increase the risk of leukostasis significantly, in contrast to red blood cell transfusion which has a higher impact on blood viscosity than platelets. For stable patients with hemoglobin values higher than 7-8 g/dL, red blood cell transfusion should be avoided.

TLS (Tumor Lysis Syndrome)

Tumor lysis syndrome can be classified as laboratory or clinical (**Table 14**).

- Laboratory TLS is defined as biochemical changes without clinical manifestation. Patients can have severe metabolic derangements without symptoms. This condition requires treatment.
- Clinical TLS is defined as biochemical changes which are accompanied by clinical features (e.g., seizures, cardiac dysrhythmia, or death) and need urgent management.

Definition. Presentation of two or more of the following metabolic abnormalities during the same 24-hour period within 3 days before to 7 days after initiation of therapy:

- Hyperkalemia (K)
- Hyperuricemia (UA)
- Hyperphosphatemia (P)
- Hypocalcemia (Ca)

Table 14. TLS risk classification

High risk	Advance stage Burkitt leukemia /lymphoma
	Lymphoblastic lymphoma with LDH ≥ 2× ULN
	Early stage Burkitt leukemia /lymphoma with LDH ≥ 2× ULN
	ALL with WBC ≥ 100 $\times 10^9$ /L or LDH ≥ 2× ULN
	AML with WBC ≥ 100 $\times 10^9$ /L
	DLBCL with baseline LDH ≥ 2× ULN and bulky disease
Intermediate risk	Early stage Burkitt leukemia /lymphoma with LDH < 2× ULN
	ALL with WBC < 100 $\times 10^9$ /L with LDH < 2× ULN
	AML with WBC 25-100 $\times 10^9$ /L
	AML with WBC < 25 $\times 10^9$ /L with LDH ≥ 2× ULN
	DLBCL with baseline LDH ≥ 2× ULN and non-bulky disease
	CLL with WBC ≥ 50 $\times 10^9$ /L

Low risk	Indolent lymphomas
	AML with WBC < 25 ×10^9 /L with LDH < 2× ULN
	CLL
	CML
	Multiple myeloma

ALL, Acute lymphoblastic leukemia; AML, Acute myeloid leukemia; CLL, Chronic lymphocytic leukemia; CML, Chronic myeloid leukemia; DLBCL, Diffuse large B cell lymphoma; LDH, Lactate dehydrogenase; ULN, Upper limit normal; WBC, White blood cell.

Prevention of TLS

Low risk patients should receive hydration and allopurinol. High risk patients should receive hydration and rasburicase in an inpatient setting. To avoid xanthine accumulation and lack of substrate for rasburicase, concomitant allopurinol should not be administered.

- Allopurinol recommended dosage is 10 mg/kg/day (300 ± 100 mg/m2/day) PO/IV for 3-8 days.
- IV hyperhydration of 3,000 – 5,000 mL/m²/d (5% DW + 0.45% NaCl) is initiated. Initially, no extra KCl may be added. Slight hypokalemia needs no therapy.
- IV alkalinization of urine for at least 24 – 48 h is recommended with NaHCO3 40 – 80 mmol/L (100 – 200 mmol/m²/d)
- Monitoring:
- Keep urine output at 100 – 250 ml/m2 /h
- For inadequate output: furosemide IV 1 – 10 mg/kg/d (prevent fluid overload)
- Control of NaHCO3 supply: urine pH 7.0 – 7.5 is optimal
- Maintain urine specific gravity <1,010 mOsm/L
- Lab tests: CBC, Ca, P, UA & creatinine q 12 - 24 h, in critical cases (more frequent at the beginning of intervention)

Treatment of TLS

- Vigorous hydration
- Management of hyperuricemia
- Frequent monitoring of electrolytes and aggressive correction
- Specific therapy with rasburicase. Recombinant urate oxidase is indicated in case of hyperuricemia (UA ≥ 7 mg/L or UA ≥ 420 µmol/L), initially decreased renal function, large tumor burden /high proliferative rate, or WBC ≥ 100 ×10^9 /L.
- One dose (3 to 6 mg) of rasburicase is usually enough.
- Re-dosing should be individualized and is indicated for patients with any of the following risk factors: urgent need for initiation therapy in a bulky tumor, situations where adequate hydration may be difficult or impossible, acute renal failure.
- Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of

rasburicase. Note that rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.

- Hemodialysis: Hemodialysis should be considered for every patient with excessively elevated serum levels of UA, phosphate, and/or potassium not responsive to pharmacologic interventions and for those patients in whom, acute renal failure develops despite interventions to prevent volume overload, electrolyte abnormalities, or uremia.

5-2. Drug toxicity

Despite going through vigorous protocols for preparation and administration of chemotherapy drugs, there is still a chance for drug toxicity or complications. The inherent more toxic profile of these drugs makes these circumstances more demanding and necessary to alertly be prepared and promptly address these complications.

Methotrexate toxicity

- Poor elimination of MTX. A definite minority of patients turn out to be intrinsically poor eliminators of methotrexate (MTX). Unfortunately, the only measure available to reliably define this population is the first exposure to high dose of methotrexate. The personnel should be extremely vigilant, and close clinical and lab monitoring of the patient on high dose (HD) MTX is crucial. Nevertheless, all patients - not merely the intrinsically poor eliminators - should be considered at risk for delayed MTX elimination. Similarly, any high dose of the drug - not merely the first one - could be poorly metabolized. The major route of MTX elimination is through the kidneys, which primarily makes this organ vulnerable to HD-MTX toxicity unless efficient prophylactic measures (e.g., hyperhydration/alkalinization) are undertaken. Hence, renal function should be carefully monitored on a regular basis before and during HD-MTX therapy (**Table 15**). A minor fraction of MTX is cleared through the bile. Although less efficient compared to the renal route, biliary excretion of the drug becomes more important as renal function deteriorates.

Table 15. Dose adjustment of high dose MTX by GFR

	GFR (mL/min/1.73 m^2)			
	> 60	30-60	10-30	< 10
Dose of MTX	100%	50%	0	0

GFR, Glomerular filtration rate; MTX, Methotrexate.

- MTX-induced renal failure should be managed conservatively, as it usually resolves within 2 – 3 weeks after withdrawing the drug. In case of uremia or elec-

trolyte abnormalities, hemodialysis is indicated, though MTX itself is not readily dialyzable. Alternate pathways of MTX elimination or detoxification should be also considered:

- Cholestyramine (Cuemid, Questran) is a hydrophilic resin, acting as an annex. It is capable of binding bile acids with the admixed MTX in the gut via exchange for chloride anions, thus interrupting the enterohepatic cycle so that MTX will be excreted in the feces. The drug dosage is usually 2 g given q3–6 h PO (preferably via NGT). Depending on the dosage, it may cause hyperchloremic acidosis and/or constipation, which are both manageable.
- Active charcoal might also be effective via "passive" adsorption of MTX.
- Acute encephalopathy. An acute neurotoxicity syndrome with stroke-like features like blurred vision, aphasia, agitation, lethargy, convulsions, obtunded sensorium, coma, and hemiparesis has also been described during MTX therapy. Other symptoms may include headache, anorexia, nausea, emesis, arterial hypertension, dizziness, and confusion. MTX encephalopathy has been observed with both parenteral as well as oral administration of the drug and at variable dose levels. It is usually associated with MTX-induced nephrotoxicity or otherwise impaired renal function leading to poor MTX elimination.
- It has been shown that therapy with aminophylline is effective and safe in managing this adverse event, with recovery being prompt and complete or near complete in the majority of patients. It has been used at the dose of 2.5 mg/kg bolus infusion over 45–60 minutes, or 0.5 mg/kg/h continuous infusion for 12 h. Rapid-release oral theophylline preparations could also be beneficial to yield a plasma concentration of 10–30 μmol/L. Since this event is reversible with aminophylline treatment, further therapy with MTX is usually feasible and uneventful.

L-asparaginase toxicity

- Hypersensitivity reaction. There is a significant incidence of hypersensitivity reactions with asparaginase products in some regimens. For grade 1 and 2 reactions (rash, flushing, urticaria, and drug fever ≥38°C) without symptoms like bronchospasm, hypotension, edema, or need for parenteral intervention, drug infusion may be continued with consideration for anti-allergic premedication such as hydrocortisone, famotidine or ranitidine, diphenhydramine, and acetaminophen. Measures that can be followed to prevent or attenuate the severity of infusion or hypersensitivity reactions include prolonging the infusion to ≥2 hours, concurrent infusion of normal saline, and use of appropriate premedication provided above.

Of particular concern is grade 2 or higher systemic allergic reactions, urticaria, or anaphylaxis; for these episodes can be (but are not necessarily) associated with neutralizing antibodies. In case of a hypersensitivity reaction to the native E. coli asparaginase (ASP) formulation, drug infusion should be stopped and never repeated. The following two options exist:

- A pegylated E. coli asparaginase - Pegaspargase (Oncaspar® Medac/Enzon)

should be used at 2,500 U/m2 (max 3,750 U), bolus infusion over 1 hour. Treatment could be repeated with 2 weeks interval depending on the time point of this adverse event. One dose of Pag-ASP substitutes four doses of the unmodified E. coli ASP.

- Erwinia chrysanthemi ASP (Erwinase® Speywood). This preparation can be used if available, with a dose of 10,000 U/m2/d every other day as intramuscular injection. Each six doses of Erwinase® substitute four doses of native E. coli ASP. Unless the manufacturer of the drug precisely delineated the issue of safety, the IV route should be avoided.

A test dose of 10-50 U or 0.2 U/kg body weight should be administered intravenously over 15 minutes at the beginning of the first dose of any ASP preparation (so far as it is approved for IV use). If no reaction occurs during the test drip and within 30 minutes thereafter, the rest of the prescribed dose may be delivered. However, while a positive test dose is predictive, an uneventful one does not exclude the subsequent development of an allergic reaction. Therefore, the patient must be observed closely during each ASP infusion.

- Thrombotic and bleeding complications. ASP is implicated in both thrombotic and bleeding complications. In particular, the combination of ASP and steroids may be associated with an increased risk of thrombosis. Permanent central venous catheters are in general, another risk factor for thrombotic events, although the thrombogenic potential may vary with different formulations. Careful history regarding a thrombophilic as well as hemorrhagic diathesis should be taken prior to therapy with ASP.

Cerebral thrombosis, ischemia, or stroke

- Discontinue asparaginase and consider antithrombotic therapy. In case of grade 3 or less severe reaction, if signs or symptoms fully resolved, consider resuming asparaginase at lower rates and/or with longer intervals between doses. For grade 4, permanently discontinue asparaginase.

Non-CNS Thromboembolism

- In case of grade 2 or greater thromboembolic event, hold asparaginase until symptoms resolved and treat with appropriate antithrombotic therapy. Upon resolution of symptoms and antithrombotic therapy stabilized or completed, consider resuming asparaginase.

Non-CNS Hemorrhage

- For grade 2 or more severe hemorrhage, hold asparaginase until the severity attenuates to grade 1, then resume. Consider coagulation factor replacement. Do not hold drug delivery for asymptomatic abnormal laboratory findings.

Intracranial Hemorrhage

- Discontinue asparaginase. Consider coagulation factor replacement. For grade 3 or less, if signs or symptoms fully resolved, consider resuming asparaginase at lower rates and/or with longer intervals between doses. For grade 4, permanently discontinue asparaginase. Magnetic resonance angiography (MRA)/ venography (MRV) should be considered to rule out suspicious bleeding associated with sinus venous thrombosis.
- Hepatotoxicity. Asparaginase is hepatotoxic. Vincristine (VCR) is also metabolized in the liver. Hence, it is prudent to administer ASP at least 12 h after VCR. This sequence allows sufficient time for VCR to be cleared out, making severe VCR-associated neuropathy unlikely. The following adjustments should be considered in case of hepatic impairments.
  - Direct bilirubin ≤3.0 mg/dL, continue asparaginase.
  - Direct bilirubin 3.1–5.0 mg/dL, hold asparaginase until bilirubin <2.0 mg/dL, then resume.
  - Direct bilirubin >5.0 mg/dL, either discontinue asparaginase or hold asparaginase until bilirubin <2.0 mg/dL, then resume with consideration for dose reduction and close monitoring.
  - Grade 3 transaminitis (AST or ALT elevation), hold until grade 1, then resume.
  - Grade 4 transaminitis, hold until grade 1. If resolution to grade 1 occurred in less than a week, then resume. Otherwise, either discontinue or resume with caution and close monitoring.
- **Hyperglycemia.** Hyperglycemia may be encountered during therapy with L-asparaginase, making blood/urine sugar monitoring necessary. For grade 3 or higher, hold asparaginase and steroids until blood glucose level is regulated with insulin, then resume.
- **Hypertriglyceridemia.** Treat hypertriglyceridemia as indicated. In case of grade 4 reaction, hold asparaginase until normalized triglyceride level, then resume.
- **Pancreatitis.** Permanently discontinue asparaginase in the presence of grade 3 or 4 pancreatitis. In the case of grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until these findings resolved and then resume.

Drug extravasation

General measures for management of drug extravasation:

- The best management is prevention.
- Aspirate 3–5 ml of blood via the original cannula, discarding the content.
- Try to aspirate and discard the content of blisters with the aid of a thin needle.
- Then remove the original cannula.
- In case of vinca alkaloid extravasation, infiltrate the lesion with hyaluronidase (Hylase®, Wyeth). Inject in two fractions, one through the original cannula before removing it, and one via additional thin needle(s). You will need 1-6 ampoules of the drug (150-900 U).

- Elevate the involved arm using a sling until swelling resolves.
- Immediately undertake the specific measures as described in table 8.
- Cover the lesion with a sterile dry dressing.
- Check locoregional vital parameters frequently and on a regular basis.
- If gangrene develops despite local measures, with absent erythema being often an early sign thereof, a plastic surgeon should be consulted. Early wide excision of the necrotic lesion and the surrounding inflamed-looking tissues, proper dressing, and delayed grafting should be considered, particularly in case of anthracycline extravasation. The extent of anthracycline extravasation is best delineated by exposure of the lesion to UV light.
- Monitor the patient for several months, as necrosis may not develop until several weeks.
- Document the evolution of this adverse event and the outcome of the undertaken measures thoroughly.

A few specific measures and interventions have been shown to be useful in the management of extravasation of vesicant or aggressive cytotoxic agents (**Table 16**).

Table 16. Specific measures for management of extravasation

Drug	Measures	Comments
Daunorubicin Doxorubicin	• Cooling	• Ice pack for 15 min. • Repeat q4-6 h for days
	• DMSO 99%	• 4 drops /10 cm^2 involved skin area to air dry with no bandage • Alternatively, DMSO ointment (Dolobene®)
Vincristine Vinblastine	• No cooling	• Rather warm mildly for 1-2 hours (dry heat)
	• Hyaluronidase (Hylase®)	• 150-900 U diluted in normal saline to be injected ID/SC intralesional
Etoposide	• No cooling	• Rather warm mildly for 1-2 hours (dry heat)
	• Hyaluronidase (Hylase®)	• 150-900 U diluted in normal saline to be injected ID/SC intralesional
	• Hydrocortisone cream	• Thin film over involved skin area bid • Alternatively, DMSO ointment (Dolobene®)
DMOS, Dimethyl sulfoxide; ID, Intradermal; SC, Subcutaneous		

5-3. Infection prophylaxis

Bacterial

- Fluoroquinolone prophylaxis during neutropenia (for patients intolerant to fluoroquinolone, consider oral third generation cephalosporins)

Fungal

- Fluconazole prophylaxis during neutropenia until resolution of neutropenia; 400 mg PO/day

Pneumocystis jirovecii

- TMP/SMX; throughout anti-leukemic therapy; single-strength (400/80 mg) tablet daily

Viral

- HSV prophylaxis during active therapy; Acyclovir 400-800 mg PO/BID

Vaccination

- Live vaccines should not be administered during chemotherapy. Vaccination should be deferred in patients who are unlikely to respond (patients who received induction and/or consolidation chemotherapy, or rituximab within 6 months. All household members should be up to date with vaccines (See below).

5-4. Transfusion support

The thresholds for blood transfusion in leukemic patients undergoing chemotherapy are comparable to those for individuals with cytopenias resulting from other hematologic disorders. By considering the chemotherapy regimen and the resulting cytopenia, clinicians can better anticipate their patients' blood component needs.

As a standard practice for leukemic patients undergoing chemotherapy and after hematopoietic stem cell transplantation (HSCT), red blood cells (RBCs), platelet concentrates (PCs—whether derived from whole blood or apheresis), and fresh frozen plasma (FFP) should be leukocyte-reduced (containing <1 × 10^6 leukocytes per unit) and irradiated. Leukocyte reduction helps minimize febrile non-hemolytic transfusion reactions (FNHTR), reduces the likelihood of alloimmunization to leukocyte antigens, and lowers the risk of cytomegalovirus (CMV) transmission.

Considering the immune changes associated with chemotherapy, it is essential to review special considerations regarding the safety of blood products. As a result, specific modifications to blood components are necessary for this population. The modified blood components include:

- CMV-negative red blood cells (RBCs)

- Leukocyte-reduced RBCs and platelet concentrates (PCs):
  Pre-storage leukocyte reduction
  Post-storage leukocyte reduction (using an issued filter)
- Irradiated blood products
- Photochemical treated (PCT) components

CMV negative RBCs

A comparison of CMV seronegative blood with leukoreduced blood showed comparable outcomes in terms of transfusion-transmitted CMV infection.

Leukocyte reduced RBCs and PCs

It is estimated that each unit of blood component contains varying amounts of white blood cells (WBCs), as shown in Table 1. According to standards in the United States, leukoreduced components should have residual leukocyte levels as follows:

- <5 × 10^6 WBCs/unit for RBCs and apheresis platelet concentrates (PCs).
- <8.3 × 10^5 WBCs/unit for whole blood-derived platelets (random PCs).

According to European standards, the threshold level for residual leukocytes is set at <1 × 10^6 per unit.

Leukoreduction is increasingly recognized as a method that is equivalent to providing CMV safety. In addition to safeguarding against CMV transmission, leukoreduction also helps minimize HLA sensitization. Moreover, pre-storage leukoreduction reduces the incidence of FNHTR by lowering the levels of cytokines produced by the fewer WBCs present in the leukoreduced product.

Irradiation

Transfusion-associated graft-versus-host disease (TA-GvHD) is a rare complication that occurs when viable donor T lymphocytes in cellular blood products initiate an immune response against the recipient. Patients with leukemia undergoing chemotherapy and those who have received hematopoietic stem cell transplantation (HSCT) are at an increased risk for TA-GvHD and should receive irradiated cellular blood products to mitigate this risk.

The Association for the Advancement of Blood & Biotherapies (AABB) recommends the following irradiation guidelines:

- A dose of 2500 cGy (25 Gy) should be delivered to the internal midplane of a freestanding irradiation instrument canister.
- A dose of 1500 cGy (15 Gy) is required at any other point within the canister.

To ensure quality control, special labels, such as radiochromic film labels that change color upon irradiation, are attached to units to confirm that an adequate dosage has been administered.

Photochemical treatment (PCT)

Recent advancements have resulted in the development of pathogen reduction technology using photochemical treatment (PCT). In the United States, the only FDA-approved method involves the addition of a psoralen compound during the manufacturing process, followed by exposure to ultraviolet (UV) light. This process inactivates microorganisms by causing damage to their nucleic acids.

The use of psoralens and long-wavelength UV irradiation has been specifically developed to mitigate the risks of bacterial and viral contamination in platelet transfusions. Psoralens bind reversibly to nucleic acids through intercalation and, upon UV illumination, form covalent mono-adducts, and crosslinks with both RNA and DNA.

Other methodologies, such as those using riboflavin and UV light or UV light alone, are available in various regions. Unlike non-pathogen-reduced platelet concentrates (PCs), which require several days of testing before being released from the donor center, pathogen-reduced platelets (PRPs) can be transferred immediately to hospital transfusion services. This not only reduces the risk of CMV transmission but also makes them equivalent to irradiated products in mitigating the risk of transfusion-associated graft-versus-host disease (TA-GVHD). Since PRPs do not require additional modifications or testing to meet US FDA irradiation or bacterial contamination testing standards, they present an attractive option for blood banks.

RBCs Transfusion

The latest AABB guidelines for RBC transfusion provide specific recommendations for hematology and oncology patients, setting a transfusion threshold of 7 g/dL based on conditional, low-certainty evidence. For patients with pre-existing cardiovascular disease, a more restrictive RBC transfusion threshold of 8 g/dL is recommended.

In adult recipients, one unit of red blood cells (RBC) typically raises the hemoglobin concentration by approximately 1 g/dL (equivalent to a 3-4% increase in hematocrit). For children, the appropriate dose should be calculated using the following formula:

Volume (mL RBC): Target Hb after transfusion gr / dL) - pre transfusion Hb gr / dL) × 4× (weight/ kg)

PCs Transfusion

Nearly all leukemic patients will require platelet concentrate (PC) transfusions during and after chemotherapy, with a greater dependency observed in acute myeloid leukemia compared to acute lymphoblastic leukemia. According to current evidence and guidelines endorsed by the AABB, the American Society of Clinical Oncology (ASCO), and the Children's Oncology Group (COG), prophylactic PC transfusions should be administered to non-bleeding, non-febrile patients when platelet counts fall to ≤10,000/μL. In patients with acute leukemia who do not receive prophylactic platelet transfusions, there is a significantly higher incidence of World Health Organization (WHO) Grade 4 hemorrhage. Prophylactic platelet transfusions may be considered at higher counts based on clinical

discretion. For patients with additional bleeding risk factors, such as fever, infection, or post- HSCT, the threshold for these transfusions is generally raised. In such cases, even though the supporting data may be limited, the British Society of Haematology (BSH) guidelines suggest considering an increase in the threshold for prophylactic platelet transfusions to between 10,000 and 20,000/μL for patients exhibiting these bleeding risk factors.

Additionally, in situations involving specific transplant or chemotherapy-related toxicities that could elevate the risk of bleeding—such as acute graft-versus-host disease (GvHD), mucositis, hemorrhagic cystitis, or diffuse alveolar hemorrhage—a threshold of 20,000/μL or even higher may be warranted based on careful clinical assessment.

The recommended platelet count threshold for administering PC transfusions before procedures vary among different societal guidelines and institutional practices, with limited evidence from randomized trials to inform these recommendations. For procedures like central venous catheter (CVC) placement, the AABB, ASCO, and BSH suggest prophylactic platelet transfusion for patients with platelet counts below 20,000/μL. Similarly, there is no conclusive evidence supporting a specific platelet threshold before more invasive procedures such as lumbar puncture (LP) or epidural anesthesia. The AABB recommends prophylactic transfusion for patients undergoing LP with a platelet count under 50,000/μL, while the BSH advises a threshold of less than 40,000/μL.

Random donor platelet concentrates (RD-PC) are typically used to replace thrombocytes. Apheresis single donor platelet concentrates (SD-PC) should be utilized for patients who are refractory to RD-PCs and for primary candidates undergoing hematopoietic stem cell transplantation (HSCT). One SD-PC is approximately equivalent to six RD-PCs and contains between 3.5 × 10^11 and 4 × 10^11 platelets. The recommended starting dose for thrombocytopenic patients is one unit of RD-PC per 10 kg of body weight or 5 mL of SD-PC per kg. For example, in a patient weighing 70 kg, the transfusion of one unit of RD-PC is expected to raise the platelet count by about 5,000/μL, while one unit of SD-PC may increase it by approximately 35,000 to 40,000/μL within an hour. However, in cases of splenomegaly or conditions associated with increased platelet consumption, such as sepsis or disseminated intravascular coagulation (DIC), larger doses are often necessary.

Platelet refractoriness

Platelet refractoriness, characterized by inadequate platelet increments following transfusion, poses a significant clinical challenge often encountered during the transplant period. This condition is defined by a corrected count increment (CCI) of less than 5,000/μL one hour after transfusion of fresh ABO-identical PCs on at least two consecutive occasions.

CCI is a laboratory evaluation of the effectiveness of PCs transfusion, and is calculated by the following formula:

[(Post-transfusion platelet count </μL>) - (Pre- transfusion platelet count </μL>)] × (body surface area < m^2 >) / (number of platelets transfused < ×10^11/μL>).

Granulocyte Transfusion

Granulocyte transfusions may be considered for patients with refractory bacterial or fungal infections who are experiencing severe neutropenia (absolute neutrophil count [ANC] <500/μL) and are expected to recover marrow function. However, the largest randomized controlled trial to date has not shown a clear benefit from this treatment.

Hematopoietic Stem Cell Transplantation 6

Hematopoietic stem cell transplantation (HSCT) during first remission remains controversial. However, interpretation of current evidence is difficult because of the lack of true randomization. Even so, results from both adult and pediatric studies suggest allogeneic transplantation benefits some high-risk patients.

Because of their unfavorable prognosis, patients with the Philadelphia chromosome–positive ALL and those with a poor initial response to induction therapy have been recommended to undergo allogeneic stem cell transplantation during the first remission. Ph-like ALL and early T-precursor phenotype also confer poor risk and should be considered for transplantation.

The following is our institutional practical approach towards HSCT for ALL.

6-1. Indications

- First complete remission (CR1)
  - Ph-Negative
    - High risk patients (any of the following)
      Adverse cytogenetics
      WBC (≥ 30 × 10^9/L for B lineage and ≥100 × 10^9/L for T lineage)
      Age > 40 years
      Immunophenotype (Pro-B cell ALL or ETP-T cell ALL)
      Extramedullary involvement or CNS involvement at diagnosis
    - MRD positive (≥10-4 after consolidation)
    - MRD positive after induction (≥10-3) may be considered (Optional)
    - No CR after induction (day 28-32)
    - Reappearance of MRD
  - Ph-Positive:
    - No complete molecular response (CMR) in 3 months
    - Reappearance of MRD

- Second complete remission (CR2) and subsequent remissions

Time of transplant. Optimal timing of HSCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplantation. Apparently, proceeding to HSCT with MRD is not optimal.

6-2. Post-transplant prophylaxis/pre-emptive treatment

Generally, for patients with relapsed ALL after allogeneic transplantation, a second transplant or donor T-lymphocyte infusion occasionally results in sustained remission. The following is our institutional approach for post-HSCT ALL relapse.

- Ph positive
  - TKI should be started as soon as possible after engraftment in the absence of uncontrolled GVHD or infections and continued until MRD negativity is confirmed by three consecutive tests or sustained for at least 3 months.
  - Switching to a second-generation TKI is recommended if BCR-ABL transcript levels remain detectable after 6 to 8 weeks of posttransplant Imatinib.
  - For patients undergoing transplantation during CR1, TKI treatment should be given for 12 months with continuous MRD negativity. For patients undergoing HSCT during CR2 or a later remission, treatment should be given indefinitely unless this is precluded by poor tolerability or safety concerns. Individual adjustments may be needed in cases of severe toxicity.
  - Patients with a history of CNS involvement should be treated with Dasatinib.
  - Patients with early molecular recurrence (i.e., within the 3 months after HSCT) or BCR-ABL transcripts at a level higher than 10-4 any time after HSCT, appear to derive little benefit from imatinib and should be started on a second-generation TKI instead (e.g., Nilotinib 200 mg every 12 hours or Dasatinib 50-100 mg/d).
  - Post transplant TKI optimal dosage
    - Imatinib: 600 mg /day
    - Nilotinib: 200 mg bid
    - Dasatinib: 100 mg /day
- Ph negative/ pretransplant positive MRD
  - A prophylactic donor lymphocyte infusion (DLI) is indicated in patients with a high-risk of relapse, but at a stage when there is no evidence of the underlying disease. Usually, prophylactic DLI is given starting from day +90 or +100 after HSCT, provided that the patient is off immunosuppression and free of GVHD for about 1 month.
  - DLI could be repeated according to subsequent MRD and GVHD status.
  - Prophylactic DLI could be considered as a single-shot intervention.

6-3. Post-transplant Relapse

Definitions

- Hematologic relapse is defined as the reappearance of leukemia cells in peripheral blood or blast cells accounting for at least 5% of nucleated cells in the bone marrow, or extramedullary infiltration for patients who have achieved complete remission after HSCT.
- Molecular relapse is defined as the reoccurrence of MRD as assessed by multiparameter flow cytometry (MFC) and/or PCR.
- Cytogenetic relapse is defined as the reappearance of the initial cytogenetic abnormalities or the conversion from complete donor chimerism to mixed donor chimerism.

Treatment of bone marrow relapse

- Withdrawal of immune suppression is considered for patients who experience relapse without onset of GVHD
- Ph-positive: TKI ± DLI
- Ph-negative: Chemotherapy + DLI
- Second transplant

Treatment of extramedullary relapse

- Systematic chemotherapy and/or radiotherapy plus DLI is recommended for most cases.

Treatment of molecular/cytogenetic relapse

- Withdrawal of immune suppression is considered for patients who experience relapse without onset of GVHD
- Targeted therapy: CAR T cell therapy, Blinatumomab, Inotuzumab Ozogamicin (if available)
- Donor Lymphocyte Infusion (DLI). A DLI can be repeated with 1-log escalated dose 6–8 weeks after the first DLI when MRD is still present and no GVHD is observed.

Follow up 6

Surveillance in survivors who do not receive cellular therapy

Complete blood count and routine blood chemistry during maintenance therapy

- 1st year: every 2 months
- 2nd and 3rd year: every 3 months
- 4th and 5th year: every 6 months

For evaluation of MRD, which is now the most important prognostic parameter, bone marrow aspiration is required at 3-monthly intervals for at least 5 years.

Immunizations

- Vaccination in survivors who did not receive cellular therapy (except those receiving anti B-cell antibodies) (Table 17)
- In survivors who received anti B-cell antibody therapy, the above vaccines can be given, but should be delayed for at least 6 months after chemotherapy and the last dose of antibody.
- Vaccination in survivors who have received cellular therapy (e.g., HSCT, CAR T-cell therapy) should comply with RIOHCT vaccination guideline.
- In survivors who received anti B-cell antibody therapy, the above vaccines can be given, but should be delayed for at least 6 months after chemotherapy and the last dose of antibody.
- Vaccination in survivors who have received cellular therapy (e.g., HSCT, CAR T-cell therapy) should comply with RIOHCT vaccination guideline.

Table 17. Vaccination schedule in survivors

Vaccine	Population	Recommended dose / Timing
Influenza vaccine	• All survivors	Annually
Pneumococcal vaccine	• Adult survivors ≥ 65 years • Adult survivors who are immuno-compromised	

Vaccine	Population	Recommended dose / Timing
Tetanus, diphtheria, pertussis vaccine (Td/Tdap)	• Adult survivors < 65 years who have not received Tdap previously • Adult survivors < 65 years for whom vaccine status is unknown • Other survivors	• Substitute 1 dose of Tdap for Td booster • Boost with Td or Tdap booster every 10 years • Td or Tdap booster every 10 years
COVID-19 vaccine	• All survivors	

Cardiovascular disease risk assessment/ anthracycline-induced cardiac toxicity (Table 18)

Consider two-dimensional echocardiogram with doppler flow study within 1 year after completion of anthracycline therapy for survivors with

- High cumulative anthracycline dose defined as a cumulative doxorubicin dose of 250 mg/m^2 or higher or equivalent.
- Low cumulative anthracycline dose plus 1 or more heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age > 65 years
  - High cumulative anthracycline dose
  - Low-normal left ventricle EF (50%–54%) at baseline
  - History of other cardiovascular comorbidities (i.e., atrial fibrillation, known coronary artery disease, baseline evidence of structural heart disease)
  - Smoking
  - Obesity
  - Physical inactivity

Table 18. Anthracycline toxicity equivalence ratio used in children's oncology group (COG) for assessment of cardiotoxicity

Doxorubicin*	Daunorubicin	Idarubicin	Epirubicin	Mitoxantrone
1	1	5	0.67	4
* Reference value				

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