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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Acute Lymphoblastic Leukemia

Version 2.2025 — December 16, 2024

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NCCN Guidelines Version 2.2025
Pediatric Acute Lymphoblastic Leukemia

NCCN Guidelines Index
Table of Contents
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NCCN Guidelines Panel Disclosures

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pediatric Acute Lymphoblastic Leukemia

NCCN Guidelines Index
Table of Contents
Discussion

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 2.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2025 include:

PEDALL-10
- T-ALL first relapse disease
  - Treatment modified: Clinical trial (preferred) or *Systemic therapy* ~~Chemotherapy~~

PEDALL-11
- Multiple relapse or Refractory disease
  - Treatment, 2nd bullet modified: *Systemic therapy* ~~Chemotherapy~~

PEDALL-G (7 of 13)
- Regimens for Relapsed/Refractory ALL, BCR::ABL1-negative ALL
  - Other Recommended Regimens: Revumenib added as an option for KMT2Ar R/R BCR::ABL1-negative ALL
- Footnote u added: Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. (Also PEDALL-G 9)

PEDALL-G (9 of 13)
- Regimens for Relapsed/Refractory ALL, T-ALL
  - Other Recommended Regimens: Revumenib added as an option for KMT2Ar R/R T-ALL

PEDALL-G (12 of 13)
- Reference added: Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). J Clin Oncol 2024:JCO2400826.

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

Global changes:
- References updated throughout the guideline.
- All instances of Ph modified to BCR::ABL1

PEDALL-1
- Classification
  - First bullet modified: Together, these studies allow determination of the World Health Organization (WHO) *and International Consensus Criteria (ICC)* ALL subtypes and genetic risk groups (*ALL Subtypes* [PEDALL-A] *and* Genetic Risk Groups for B-ALL *[PEDALL-B]*)

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

PEDALL-1A

- Footnote b modified: B-ALL/LL subtypes include those not otherwise specified (NOS), with high hyperdiploidy, hypodiploidy, and intrachromosomal amplification of chromosome 21 (iAMP21), with commonly recurring genetic abnormalities: t(9;22)(q34.1;q11.2)[BCR::ABL1]; BCR::ABL1–like ~~(Ph-like)~~ B-ALL; t(v;11q23.3)[KMT2A rearrangement]; t(12;21)(p13.2;q22.1)[ETV6::RUNX1]; ETV6::RUNX1-like features, t(1;19)(q23;p13.3)[TCF3::PBX1]; t(5;14)(q31.1;q32.3)[IGH::IL3]; t(17;19)(q22;p13.3)[TCF3::HLF]; and t(17;18)(q22;q21.2)[TCF4::HLF] and with other defined genetic abnormalities that include rearrangements of DUX4, MEF2D, ZNF384, and NUTM1; IG::MYC fusion; and PAX5alt, ~~and with~~ PAX5 p.P80R, *IKZF1 p.N159Y, and CDX2/UBTF. Of note, in cases of poor response to ALL therapy for ALL with IG::MYC rearrangement, therapy for mature B-cell lymphoma may be considered.*
- Footnote e modified: Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO ~~2016~~ *2022 and ICC 2022* criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis. *ALL-directed therapy can be initiated for MPAL. Khoury JD, et al. Leukemia 2022;36:1703-1719; Arber DA, et al. Blood 2022;140:1200-1228; Alexander TB, et al. Nature 2018;562:373-379.*
- Footnote f modified: For Burkitt leukemia/lymphoma; see the *NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas* ~~NCCN Guidelines for B-Cell Lymphomas~~.
- Footnote i modified: The following immunophenotypic findings are particularly notable: CD10 negativity correlates with KMT2A rearrangement (KMT2Ar); ETP T-ALL (*ETP T-ALL* typically *lacks* ~~lacking~~ expression of CD5, CD8, and CD1a and *has* expression of one or more myeloid/stem cell markers); CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20; and CRLF2 overexpression as a surrogate for genomic alterations of the CRLF2 gene including ~~CRLF2::~~P2RY8*::CRLF2* and IGH::CRLF2 (Harvey RC, et al. Blood 2012;120:2529). Flow cytometric DNA ploidy analysis could be considered for rapid identification of hyperdiploid and hypodiploid B-ALL.
- Footnote k modified: The BCR::ABL1–like ~~(Ph-like)~~ phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, or PDGFRB and mutations involving CRLF2, FLT3, IL7R, SH2B3, JAK1, JAK3, and JAK2 (in combination with CRLF2 gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. Low-density array (LDA) (Harvey RC, et al. Blood 2013;122:21), NGS-based assays, *FISH*, and multiplex RT-PCR are used to detect a signature or cryptic rearrangements and mutations characteristic of BCR::ABL1–like ALL. The safety and efficacy of targeted agents in this population is an area of active research.

PEDALL-2

- Workup
  - 5th bullet modified: Pregnancy testing~~, fertility counseling, and preservation~~ as indicated
  - 6th bullet added: Fertility counseling is recommended for all patients, with fertility preservation as clinically appropriate [see NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology]
  - 7th bullet added: Psychosocial assessment is encouraged (for AYA, see NCCN Guidelines for AYA Oncology)
  - 8th bullet added: For AYA, counseling on cessation of smoking, drugs/illicit substances, vaping, and alcohol is encouraged (see NCCN Guidelines for Smoking Cessation)
  - Last bullet
    - ◊ 2nd sub bullet modified: For non-Down syndrome-related ALL the majority of patients do not have an identifiable leukemia predisposition syndrome. One important exception is *low* hypodiploid *(32–39 chromosomes)* ALL where *pathologic* germline TP53 *variants* ~~mutations~~ are common and testing should be considered.
    - ◊ 3rd sub bullet modified: Other *pathologic* germline *variants* ~~mutations~~ associated with ALL risk have been reported. A complete family history can help identify risk for a cancer predisposition syndrome, although de-novo *variants* ~~mutations~~ have been reported.
    - ◊ 4th sub bullet added: There are increasing data to suggest that ALL can present as a second malignancy.

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

PEDALL-2A

- Footnote m added: Fertility preservation is an option for certain patients. Options include sperm cryopreservation, oocyte cryopreservation, harvesting of ovarian or testicular tissue for cryopreservation, or embryo cryopreservation. Referral to a fertility preservation/reproductive health program should be considered for certain patients. Mulder RL, et al. Lancet Oncol 2021;22:e45-e56; Mulder RL, et al. Lancet Oncol 2021;22:e57-e67.
- Footnote p modified: *Genes for pathologic germline variants are* ~~Germline mutations in genes~~ often somatically mutated in ALL, particularly PAX5, ETV6, and IKZF1, and have been shown to confer predisposition to developing B-ALL. Pui CH, et al. Nat Rev Clin Oncol 2019;16:227-240.
- Footnote q added: Hunger SP, et al. J Clin Oncol 1992;10:156-163; Hijiya N, et al. Cancer 2009;115:23-35.

PEDALL-3

- Algorithm modified to include complete remission and less than complete remission.
- Footnote t modified: Standard risk criteria *include* ~~are consistent with NCI:~~ white blood cell (WBC) count <50,000/mm^3 and ≥1 y to <10 y, *but there are other clinical features that may impact initial risk stratification.* For further details, see the Risk Stratification Definitions (PEDALL-F).
- Footnote u modified: High-risk criteria *include* ~~are consistent with NCI:~~ WBC count ≥50,000/mm^3 and <1 y or ≥10 y, *but there are other clinical features that may impact initial risk stratification*. For further details, see the Risk Stratification Definitions (PEDALL-F).

PEDALL-A

- New section added: ALL Subtypes

PEDALL-B

- Genetic Risk Groups For B-ALL
  - Intermediate risk features modified: MEF2Dr, ZNF384r, PAX5alt, PAX5 P80R, ETV6::RUNX1-like, *t(1;19): TCF3::PBX1*
- Footnote c modified: Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone: near-haploid (24–31 chromosomes); low-hypodiploid (32–39 chromosomes); or high-hypodiploid (40–43 chromosomes). Low hypodiploid ALL is also often associated with TP53 loss-of-function *somatic* mutations *in which half are observed to be germline pathogenic variants associated with* ~~and~~ Li-Fraumeni syndrome. *Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013;45:242-252.*
- Footnote f modified: IKZF1 deletions with deletions in CDKN2A, CDKN2B *(homozygous)*, PAX5, or PAR1 region in the absence of ERG deletion, which are called IKZF1plus, as well as those with concomitant 22q11.22 deletions are especially associated with worse outcomes. However, DUX4 rearrangements with IKZF1 alterations do not confer poor prognosis. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360:470-480; Stanulla M, Dagdan E, Zaliova M, et al. IKZF1plus defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. J Clin Oncol 2018;36:1240-1249; Mangum DS, Meyer JA, Mason CC, et al. Association of combined focal 22q11.22 deletion and IKZF1 alterations with outcomes in childhood acute lymphoblastic leukemia. JAMA Oncol 2021;7:1521-1528.

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

PEDALL-C (1 of 14)

- Infection Control
  - 3rd bullet, 3rd sub bullet modified: Consider antifungal prophylaxis during induction, especially in patients receiving anthracyclines. Azoles have potential interactions with vincristine and should be used with caution. Consider micafungin or other echinocandin antifungal drugs during induction and potentially during other high-intensity phases. Prophylaxis with liposomal amphotericin *can be considered* ~~is also allowed~~.
  - 5th bullet
    - ◊ 1st sub bullet modified: During induction, all patients with fever (as defined by Infectious Diseases Society of America [IDSA] or institutional standards) should be evaluated by a medical provider and treated immediately with broad-spectrum antibiotics, regardless of absolute neutrophil count (ANC). *Following completion of induction, antibiotics may not be indicated for fever based on clinical status.*
    - ◊ 5th sub bullet modified: *For patients with signs of* ~~Antibiotics should be administered as soon as possible and within one hour of presentation with~~ fever, neutropenia, or sepsis, *antibiotics should be administered as soon as possible*. Recommend stress dose steroids for patients with sepsis.

PEDALL-C (2 of 14)

- 10th sub bullet
  - 1st sub sub bullet modified: In a hemodynamically stable patient, monotherapy with *a broad-spectrum antibiotic* ~~an anti-pseudomonal agent~~ *with activity against gram-positive and gram-negative bacteria (including Pseudomonas)* is recommended.
  - 7th sub sub bullet modified: If blood cultures at 24–48 hours identify Gram-positive bacteria, *consider obtaining* ~~obtain~~ one set of repeat blood cultures and *starting* ~~start~~ vancomycin (or linezolid in a patient with a history of vancomycin-resistant enterococci [VRE]) pending results of repeat cultures and final identification and susceptibilities of the Gram-positive bacteria. If cultures at 48 hours do not reveal a Gram-positive infection and vancomycin was started, it can be discontinued at 48 hours.
- 11th sub bullet: Filgrastim (granulocyte colony-stimulating factor [G-CSF]), pegfilgrastim, *and* sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF])~~, and granulocyte transfusions~~ are not generally recommended but may be used at the discretion of the health care provider in situations of *prolonged neutropenia or* serious/life-threatening infections *with* ~~in the context of~~ neutropenia. *Similarly, granulocyte transfusions are not generally recommended but may be used at the discretion of the health care provider in situations of serious/life-threatening infection in the context of neutropenia.*

PEDALL-C (3 of 14)

- 1st bullet, 1st sub bullet modified: Additional diagnostic investigation, such as *imaging* ~~radiographic evaluation~~ of lungs, *abdomen*, and sinuses *if symptomatic*, should be considered and empirical antifungal therapy should be started for patients with neutropenia and prolonged (≥4–7 days) fever despite empirical antibiotics and who are expected to remain neutropenic, or who have new symptoms (eg, cough, facial pain, swelling).
- 2nd bullet modified: *Consider vaccination with inactivated vaccines and live vaccines (*~~Patients should be vaccinated for~~ varicella, measles, mumps, and rubella*)* 3 months after chemotherapy following the CDC schedule for immunocompetent individuals. For patients receiving regimens that include anti–B-cell antibodies, vaccinations should be delayed at least 6 months.

PEDALL-C (4 of 14)

- Methotrexate (MTX) Toxicity Management
  - 4th bullet added: Doses of leucovorin >25 mg should be given IV due to saturable absorption when given orally.

PEDALL-C (5 of 14)

- Mucositis
  - Prevention, 3rd bullet: Bland rinses such as 0.9% saline solution, sodium bicarbonate, or *artificial saliva products* ~~Biotene mouthwash~~ (non-alcoholic and unsweetened) should be used twice daily and after meals.

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

PEDALL-C (6 of 14)
- Steroid Management
  - 2nd bullet, 2nd sub bullet, 1st sub sub bullet removed: Consider hydrocortisone (10 mg/m^2/day) with dexamethasone.
- PRES
  - 1st sub sub bullet modified: Anti-hypertensive therapy as needed to maintain blood pressure in age-appropriate range. ~~Avoid calcium channel blockers if possible due to increased risk of hemorrhage. Typically occurs in setting of hypertension in first months of treatment.~~

PEDALL-C (8 of 14)
- Thiopurines Management
  - 1st bullet, 4th sub bullet modified: For patients with significant gastrointestinal (GI) symptoms (ie, nausea, vomiting) and/or grade 4 alanine transaminase (ALT), aspartate transaminase (AST) and/or direct bilirubin >2 mg/dL, *and/or hypoglycemia*, consider obtaining mercaptopurine metabolites. *For* ~~In~~ patients with elevated methylated metabolites and ANC indicating that the dose of 6-MP should be increased, *or for those with GI toxicity or hypoglycemia that are dose limiting*, consider the addition of allopurinol 50 mg/m^2 with a 50%–75% decreased dose of 6-MP. Careful ANC monitoring should be considered with this approach, as the interaction of 6-MP and allopurinol carries a significant risk of myelosuppression.

PEDALL-C (9 of 14)
- Behavior and Psychosocial Support
  - 2nd bullet modified: Neurocognitive monitoring during therapy *and after completion of therapy* should be considered for all patients, given established risk for neurocognitive late effects associated with *CNS-directed* ~~IT chemo~~therapy.

PEDALL-C (10 of 14)
- Asparaginase Toxicity Management changed to Asparaginase Therapy
  - 8th Bullet moved here from Hypersensitivity, Allergy, and Anaphylaxis section: Therapeutic drug monitoring (TDM) for asparaginase therapy using the serum asparaginase activity (SAA) is available as a CLIA-certified test with a turnaround time of <1 week, allowing for real-time decision-making and therapeutic adjustments. Generally accepted SAA assay targets include a minimum trough of ≥0.1 IU/mL. However, data indicate that when SAA levels fall below 0.4 IU/mL, asparagine is no longer completely depleted and begins to rebound, suggesting an optimal trough of ≥0.4 IU/mL. Modifications in asparaginase dose or schedule depend on the clinical context.

PEDALL-C (11 of 14)
- Hepatotoxicity (elevation in bilirubin, AST, ALT)
  - 2nd bullet added: Calaspargase, when combined with chemotherapy, has been associated with severe, life-threatening, and potentially fatal instances of SOS. Calaspargase should not be administered to patients with severe hepatic impairment.

PEDALL-C (12 of 14)
- New page added on Toxicity Management for Inotuzumab ozogamicin, Blinatumomab and Tisagenlecleucel

PEDALL-E
- Page heading modified: Special Considerations for *Patients with Down Syndrome and Infants* ~~Vulnerable Populations~~
- Down Syndrome Considerations
  - 3rd bullet added: Patients ≥10 years of age receiving blinatumomab should receive seizure prophylaxis for the duration of the blinatumomab cycle.
- Infant Considerations
  - 1st bullet modified: Respiratory syncytial virus (RSV) prophylaxis *with a single dose of nirsevimab IM or monthly* palivizumab IM ~~monthly~~ should be considered before the onset of ~~and continued through~~ the RSV season.

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

PEDALL-F (1 of 3)
- Footnote d modified: At Day 10 of Induction IA, based on results of FISH, karyotype, and ~~Rapid Heme Panel (~~targeted fusion sequencing panel~~)~~, "Initial Risk Group" is assigned.

PEDALL-F (2 of 3)
- Post-Induction Therapy Risk Group Stratification
  - COG Initial High Risk (B-ALL only):
    - ◊ Average Risk added: N/A
  - High Risk, 6th bullet modified: CNS-3 *or testicular disease*

PEDALL-G (2 of 13)
- Footnote i added: The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118). (Also for PEDALL-G 6A of 13)
- Footnote j added: It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.

PEDALL-G (8 of 13)
- Regimens for Relapsed/Refractory ALL
  - Other Recommended Regimens: Ponatanib added as a category 2B TKI option to consider

PEDALL-G (10 of 13)
- CD19-targeting CAR T-Cell Therapy
  - Tisagenlecleucel, 7th bullet modified: The role of consolidative allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel (persistence of B-cell aplasia) *and negative NGS MRD have* ~~has~~ been associated with durable clinical responses without subsequent HCT.

PEDALL-H
- This section was extensively updated.

PEDALL-I
- Response Criteria for Blood and Bone Marrow:
  - 1st bullet, 2nd sub bullet modified: Marrow with trilineage hematopoiesis (TLH) and <5% *blasts* (M1) or <1% *blasts* by flow or molecular testing

PEDALL-J (1 of 2)
- 7th bullet, 1st sub bullet, 3rd sub sub bullet added: Prior to HCT.

PEDALL-K (1 of 5)
- Indications for HCT (B-cell) in First Remission:
  - 3rd bullet, 2nd sub bullet modified: HCT is not *routinely* indicated for *BCR::ABL1*~~Ph~~+ ALL in CR1 (while on TKI plus systemic chemotherapy) *provided that the patient has achieved MRD negativity (<0.01%) post-consolidation and is being treated on an intensive pediatric regimen plus TKI. Consider HCT (for BCR::ABL1+ ALL) if relapse (any time point), or MRD ≥0.01% (by week 9–12).*
- Footnote removed: Ph+ ALL in CR1 does not require HCT provided that the patient is MRD negative (<0.01%) post-consolidation and being treated on an intensive pediatric regimen plus TKI. Consider HCT (for Ph+ ALL) if relapse (any time point), or MRD ≥0.01% (by week 9–12).

Continued

Updates in Version 1.2025 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 6.2024 include:

PEDALL-K (2 of 5)

- Footnote c modified: For *late bone marrow or* isolated extramedullary relapses, if patient achieves *MRD-negative* CR2 with reinduction/*therapy for relapsed disease* ~~salvage therapy~~, no HCT is indicated.
- Footnote d modified: The recommendations may differ based on the treatment regimen. *Consideration of HCT can also be made in the setting of MRD of 0.01%–0.09% given an increased risk of relapse. Hogan LE, et al. J Clin Oncol 2023;41:4118-4129; Parker C, et al. Lancet 2010;376:2009-2017.*

PEDALL-K (3 of 5)

- Principles of Hematopoietic Cell Transplant
  - Impact of Pre-HCT MRD Status
    - 1st bullet modified: An increased risk of relapse has been noted in children with ≥0.1% MRD pre-HCT for ALL, suggesting the need to attain an MRD level <0.1% prior to HCT. *An increased risk of relapse has also been noted in children with an MRD of 0.01%–0.09%.*

DIAGNOSIS

Pediatric[a] acute lymphoblastic leukemia (ALL)[b,c,d,e,f,g] →

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts[h] upon hematopathology review of bone marrow aspirate and biopsy materials (peripheral blood can be substituted for bone marrow if there are sufficient numbers of circulating lymphoblasts [at least 1,000 per microliter as a general guideline] and the clinical situation precludes bone marrow aspirate and biopsy), which includes:

- **Morphologic assessment of Wright-Giemsa–stained bone marrow aspirate smears, and hematoxylin and eosin (H&E)–stained core biopsy and clot sections**
- **Comprehensive flow cytometric immunophenotyping[i]**
- **Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal residual disease (MRD) analysis[j] (PEDALL-J)**

GENETIC CHARACTERIZATION

Optimal risk stratification and treatment planning require testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:

- **Karyotyping of G-banded metaphase chromosomes**
- **Interphase fluorescence in situ hybridization (FISH) testing, including probes capable of detecting the major recurrent genetic abnormalities[b]**
- **Reverse transcriptase-polymerase chain reaction (RT-PCR) testing for *BCR::ABL1* in B-cell acute lymphoblastic leukemia (B-ALL) (quantitative or qualitative) including determination of transcript size (ie, p190 vs. p210)**
  - **If *BCR::ABL1* negative: encourage testing for gene fusions and mutations associated with *BCR::ABL1*–like (Ph-like) ALL[k]**
- **Assessment of various potentially actionable or prognostic mutations and gene fusions via next-generation sequencing (NGS) or alternative methods (Genetic Risk Groups for B-ALL [PEDALL-B])**

Additional optional tests include:

- **Additional assessment (eg, microarray comparative genomic hybridization [CGH] and/or NGS) in cases of aneuploidy or inadequate karyotype**
- **Whole transcriptome sequencing to identify B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LL) subtypes defined by gene expression profile (ie, *ETV6::RUNX1*-like, *PAX5alt*, *MYCr*)**

CLASSIFICATION

- **Together, these studies allow determination of the World Health Organization (WHO) and International Consensus Criteria (ICC) ALL subtypes and genetic risk groups (ALL Subtypes [PEDALL-A] and Genetic Risk Groups for B-ALL [PEDALL-B])**
- **Patients should undergo evaluation and treatment at specialized centers**

→ **Workup (PEDALL-2)**

Footnotes on PEDALL-1A

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[a] The Pediatric ALL Panel considers "pediatric" to include any patient aged ≤18 years, and certain adolescent and young adult (AYA) patients >18 years of age. Practice patterns vary with regard to AYA patients from center to center in terms of whether patients with ALL are treated primarily by pediatric or adult oncologists. This guideline is intended to apply to AYA patients treated in a pediatric oncology setting, and this may include patients up to age 30 years. The NCCN Guidelines for Acute Lymphoblastic Leukemia are intended to apply to AYA patients treated in an adult oncology setting.

[b] B-ALL/LL subtypes include those not otherwise specified (NOS), with high hyperdiploidy, hypodiploidy, and intrachromosomal amplification of chromosome 21 (iAMP21), with commonly recurring genetic abnormalities: t(9;22)(q34.1;q11.2)[*BCR::ABL1*]; *BCR::ABL1*–like B-ALL; t(v;11q23.3)[*KMT2A* rearrangement]; t(12;21)(p13.2;q22.1)[*ETV6::RUNX1*]; *ETV6::RUNX1*-like features, t(1;19)(q23;p13.3)[*TCF3::PBX1*]; t(5;14)(q31.1;q32.3)[*IGH::IL3*]; t(17;19)(q22;p13.3)[*TCF3::HLF*]; and t(17;18)(q22;q21.2)[*TCF4::HLF*] and with other defined genetic abnormalities that include rearrangements of *DUX4*, *MEF2D*, *ZNF384*, and *NUTM1*; *IG::MYC* fusion; and *PAX5alt*, *PAX5* p.P80R, *IKZF1* p.N159Y, and *CDX2/UBTF*. Of note, in cases of poor response to ALL therapy for ALL with *IG::MYC* rearrangement, therapy for mature B-cell lymphoma may be considered.

[c] T-cell ALL/lymphoma (T-ALL/LL) subtypes include T-ALL/LL, NOS and early T-cell precursor (ETP) lymphoblastic leukemia/lymphoma.

[d] FISH probes that may be useful include: centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; dual-color probe set to detect cryptic t(12;21), which will also allow detection of iAMP21 (when ≥5 copies of the *RUNX1* gene are detected); probes to detect *BCR::ABL1* and *KMT2A* rearrangements; probes to detect *ABL1*, *ABL2*, and *PDGFRB* rearrangements; probes for *CDKN2A* at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) *IGH::CRLF2* rearrangements; and probes to detect *JAK2* rearrangements.

[e] Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2022 and ICC 2022 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis. ALL-directed therapy can be initiated for MPAL. Khoury JD, et al. Leukemia 2022;36:1703-1719; Arber DA, et al. Blood 2022;140:1200-1228; Alexander TB, et al. Nature 2018;562:373-379.

[f] For Burkitt leukemia/lymphoma; see the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas.

[g] While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) would likely also benefit from ALL-like regimens. Such patients should be treated at a center that has experience with LL.

[h] In many treatment protocols, a value of >25% marrow blasts is used to define leukemia. Unlike with myeloid leukemias, there is no agreed-upon lower limit for the proportion of blasts required to establish a diagnosis of ALL. In general, the diagnosis should be avoided when there are <20% blasts. Presentations of ALL with low blast counts are uncommon; there is no compelling evidence that not treating a patient when there are <20% marrow lymphoblasts has an adverse effect on outcome. Alaggio R, et al. Leukemia 2022;36:1720-1748.

[i] The following immunophenotypic findings are particularly notable: CD10 negativity correlates with *KMT2A* rearrangement (*KMT2A*r); ETP T-ALL (ETP T-ALL typically lacks expression of CD5, CD8, and CD1a and has expression of one or more myeloid/stem cell markers); CD20 positivity: definition not clear, most studies have used >20% of blasts expressing CD20; and *CRLF2* overexpression as a surrogate for genomic alterations of the *CRLF2* gene including *P2RY8::CRLF2* and *IGH::CRLF2* (Harvey RC, et al. Blood 2012;120:2529). Flow cytometric DNA ploidy analysis could be considered for rapid identification of hyperdiploid and hypodiploid B-ALL.

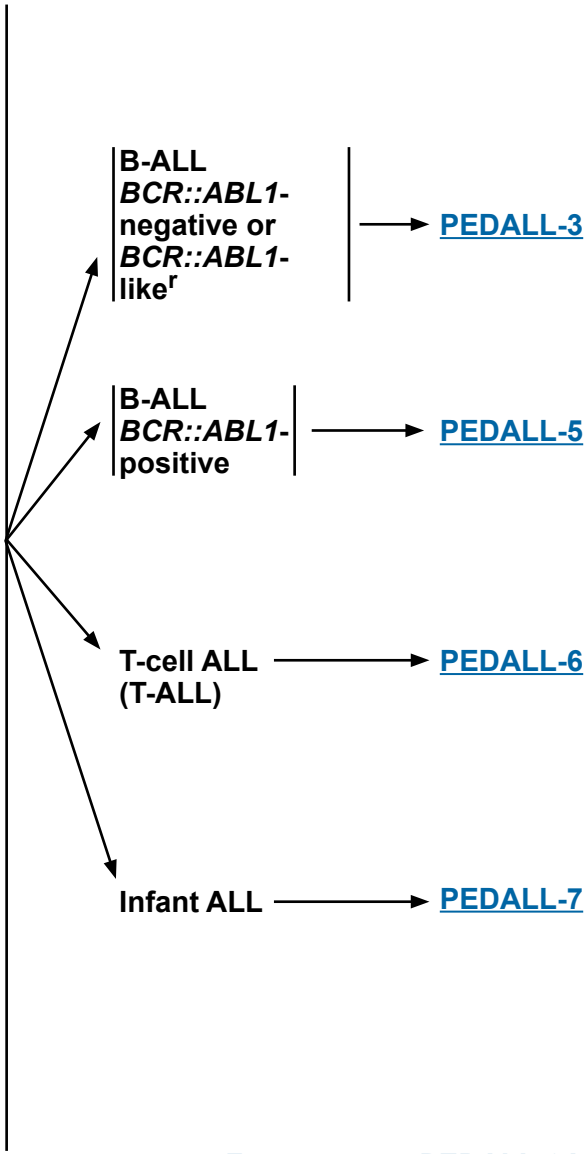
[j] By either flow cytometric analysis or by identification of clonal immunoglobulin or T-cell receptor (*TCR*) gene rearrangements.

[k] The *BCR::ABL1*–like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2,* or *PDGFRB* and mutations involving *CRLF2, FLT3, IL7R, SH2B3, JAK1, JAK3,* and *JAK2* (in combination with *CRLF2* gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. Low-density array (LDA) (Harvey RC, et al. Blood 2013;122:21), NGS-based assays, FISH, and multiplex RT-PCR are used to detect a signature or cryptic rearrangements and mutations characteristic of *BCR::ABL1*–like ALL. The safety and efficacy of targeted agents in this population is an area of active research.

Note: All recommendations are category 2A unless otherwise indicated.

WORKUP[l]

- History and physical (H&P)
- Complete blood count (CBC), differential, chemistry profile, liver function tests (LFTs)
- Tumor lysis syndrome (TLS) panel: lactate dehydrogenase (LDH), uric acid, potassium, calcium, phosphorus (see Tumor Lysis Syndrome in Principles of Supportive Care [PEDALL-C])
- Disseminated intravascular coagulation (DIC) panel: D-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Pregnancy testing as indicated
- Fertility counseling is recommended for all patients, with fertility preservation[m] as clinically appropriate [see NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology]
- Psychosocial assessment is encouraged (for AYA, see NCCN Guidelines for AYA Oncology)
- For AYA, counseling on cessation of smoking, drugs/illicit substances, vaping, and alcohol is encouraged (see NCCN Guidelines for Smoking Cessation)
- CT/MRI of head with contrast, if neurologic symptoms
- Chest x-ray to rule out mediastinal mass
- Whole body PET/CT if lymphoblastic lymphoma (LL) suspected
- Lumbar puncture (LP)[n,o] with intrathecal (IT) chemotherapy
  - Evaluation and Treatment of Extramedullary Involvement (PEDALL-D)
- Testicular exam, including scrotal ultrasound as indicated
- Infection evaluation:
  - Screen for opportunistic infections, as appropriate
- Assessment of left ventricular function (echocardiogram or cardiac nuclear medicine scan) in all patients who will receive anthracyclines as part of treatment plan
- Central venous access device of choice
- Consider pharmacogenomic testing for *TPMT, NUTD15* (Pharmacogenomics [PEDALL-H])
- Consider predisposition syndromes
  - Down syndrome is an important ALL predisposition syndrome.
  - For non-Down syndrome-related ALL the majority of patients do not have an identifiable leukemia predisposition syndrome. One important exception is low hypodiploid (32–39 chromosomes) ALL where pathologic germline *TP53* variants are common and testing should be considered.
  - Other pathologic germline variants associated with ALL risk have been reported.[p] A complete family history can help identify risk for a cancer predisposition syndrome, although de novo variants have been reported.
  - There are increasing data to suggest that ALL can present as a second malignancy.[q]
  - For patients with possible cancer predisposition syndromes, principles of cancer risk assessment and counseling should be taken into consideration (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic).



Footnotes on PEDALL-2A

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[l] The following list represents minimal recommendations; other testing may be warranted according to clinical symptoms and clinician discretion.
[m] Fertility preservation is an option for certain patients. Options include sperm cryopreservation, oocyte cryopreservation, harvesting of ovarian or testicular tissue for cryopreservation, or embryo cryopreservation. Referral to a fertility preservation/reproductive health program should be considered for certain patients. Mulder RL, et al. Lancet Oncol 2021;22:e45-e56; Mulder RL, et al. Lancet Oncol 2021;22:e57-e67.
[n] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or central nervous system (CNS) bleeding. See Evaluation and Treatment of Extramedullary Involvement (PEDALL-D).
[o] Timing of LP should be consistent with the chosen treatment regimen. Pediatric-inspired regimens typically include LP and prophylactic IT chemotherapy at the time of diagnostic workup. The Panel recommends that LP be done concurrently with initial IT therapy.
[p] Genes for pathologic germline variants are often somatically mutated in ALL, particularly *PAX5, ETV6,* and *IKZF1,* and have been shown to confer predisposition to developing B-ALL. Pui CH, et al. Nat Rev Clin Oncol 2019;16:227-240.
[q] Hunger SP, et al. J Clin Oncol 1992;10:156-163; Hijiya N, et al. Cancer 2009;115:23-35.
[r] *BCR::ABL1*-like ALL is classified using LDA, FISH, RT-PCR, and NGS (Roberts KG, et al. N Engl J Med 2014;37:1005-1015).

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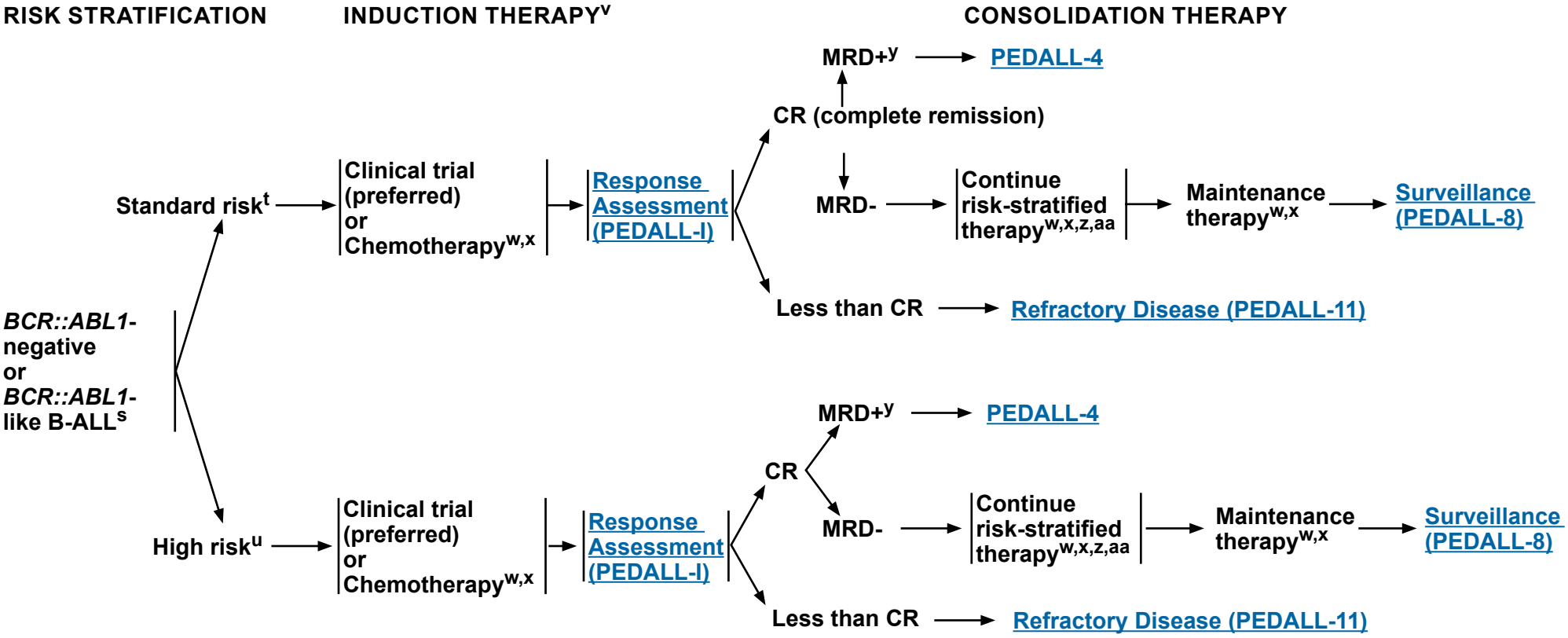

[s] For patients with Down syndrome, see Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E).

[t] Standard risk criteria include white blood cell (WBC) count <50,000/mm^3 and ≥1 y to <10 y, but there are other clinical features that may impact initial risk stratification. For further details, see the Risk Stratification Definitions (PEDALL-F).

[u] High-risk criteria include WBC count ≥50,000/mm^3 and <1 y or ≥10 y, but there are other clinical features that may impact initial risk stratification. For further details, see the Risk Stratification Definitions (PEDALL-F).

[v] Principles of Supportive Care (PEDALL-C).

[w] Principles of Systemic Therapy (PEDALL-G).

[x] For patients with *BCR::ABL1*-like ALL, tyrosine kinase inhibitors (TKIs) may be considered. For more information, see Principles of Systemic Therapy (PEDALL-G).

[y] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).

[z] Risk Stratification Definitions for Post-Induction Therapy (PEDALL-F, 2 of 3).

[aa] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome (CRS) and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.

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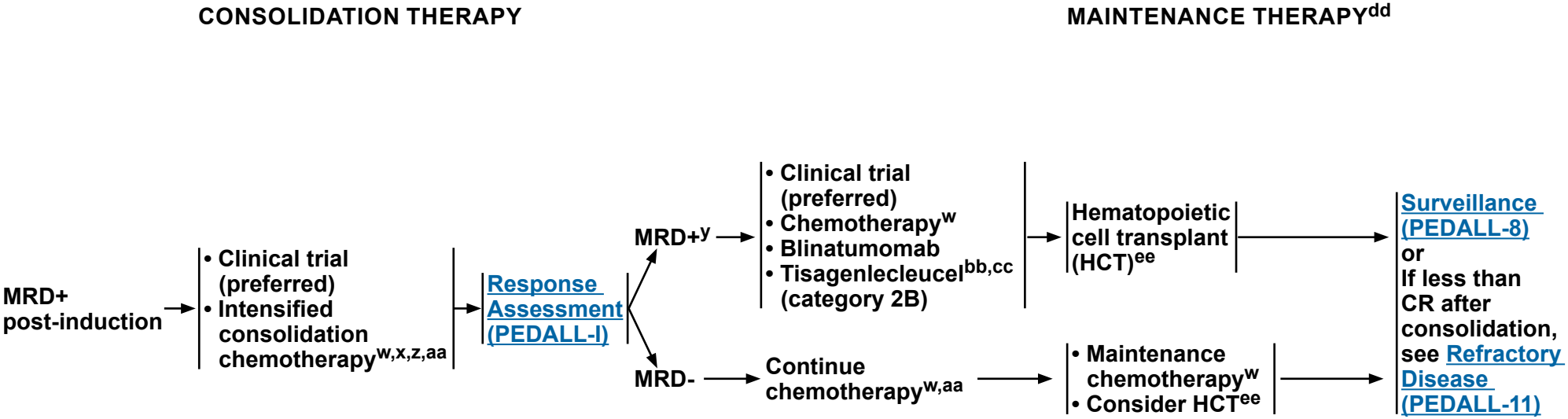

[w] Principles of Systemic Therapy (PEDALL-G).
[x] For patients with *BCR::ABL1*-like ALL, TKIs may be considered. For more information, see Principles of Systemic Therapy (PEDALL-G).
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[z] Risk Stratification Definitions for Post-Induction Therapy (PEDALL-F, 2 of 3).
[aa] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[bb] The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. See Tisagenlecleucel section in the Principles of Systemic Therapy (PEDALL-G [10 of 13]).
[cc] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia have been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year relapse-free survival was 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT (Laetsch TW, et al. J Clin Oncol 2023;41:1664-1669). See Principles of Hematopoietic Cell Transplant (PEDALL-K).
[dd] To confirm adherence to oral chemotherapy during maintenance therapy, clinicians can take a detailed history, perform pill counts, and/or measure metabolites.
[ee] Principles of Hematopoietic Cell Transplant (PEDALL-K).

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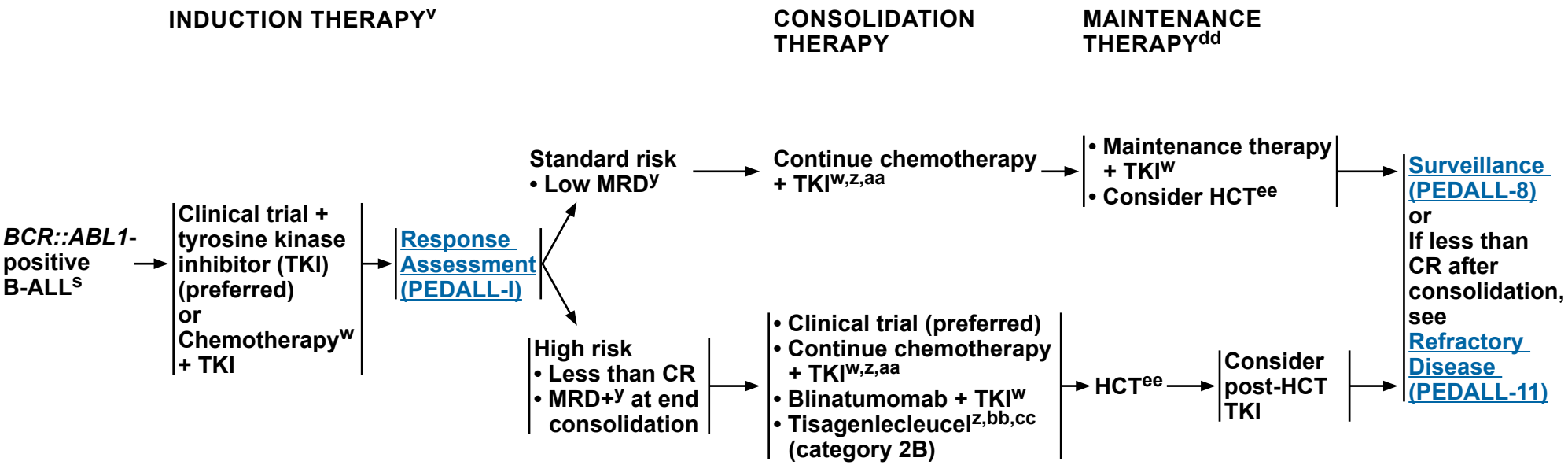

[s] For patients with Down syndrome, see Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E).
[v] Principles of Supportive Care (PEDALL-C).
[w] Principles of Systemic Therapy (PEDALL-G).
[y] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
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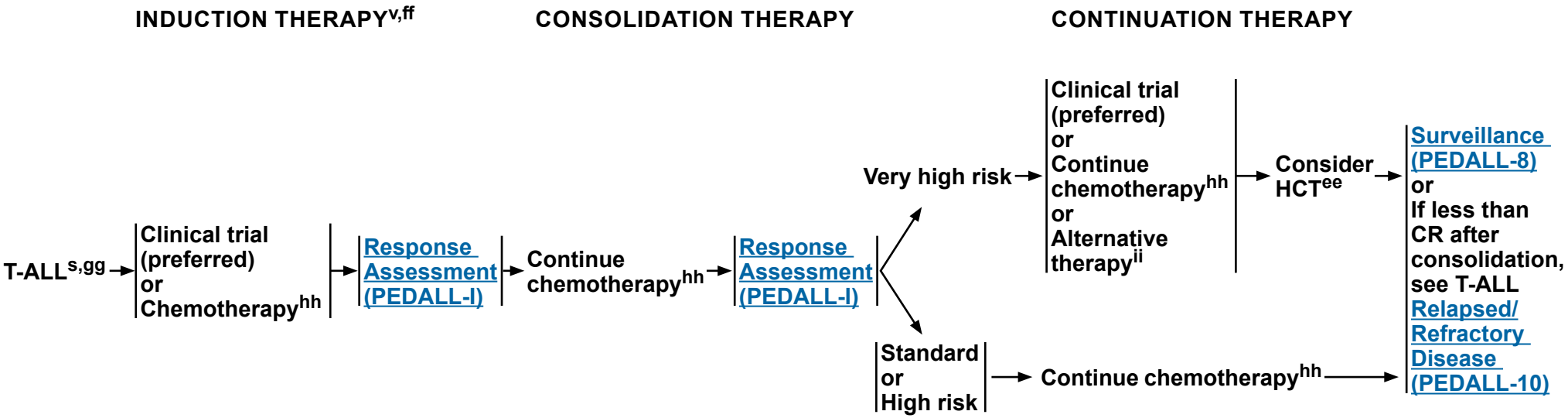

T-ALL Post-Induction Risk Group Definitions:

Risk Group	Features[y]
Very High	End consolidation MRD >0.1%
High	Absence of standard- and very-high-risk features
Standard	Day 29 MRD <0.01% and CNS-1 and absence of testicular disease and no steroid pretreatment[jj]

[s] For patients with Down syndrome, see Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E).
[v] Principles of Supportive Care (PEDALL-C).
[y] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
[ee] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[ff] MRD and morphologic marrow response should be assessed after induction, and if not MRD negative, repeat assessment after consolidation therapy. Assess MRD at additional time points based on chemotherapy regimen and response as indicated. See Minimal Residual Disease (PEDALL-J).
[gg] The Panel believes it is reasonable to use bortezomib with Berlin-Frankfurt-Münster (BFM) backbone chemotherapy in patients with pediatric T-cell LL (T-LL), because it was shown to improve event-free survival (EFS)/overall survival (OS) in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[hh] See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-G, 2 of 13).
[ii] See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-G, 9 of 13).
[jj] The specific definition of steroid pretreatment differs by protocol. Refer to regimen-specific definition of steroid pretreatment.

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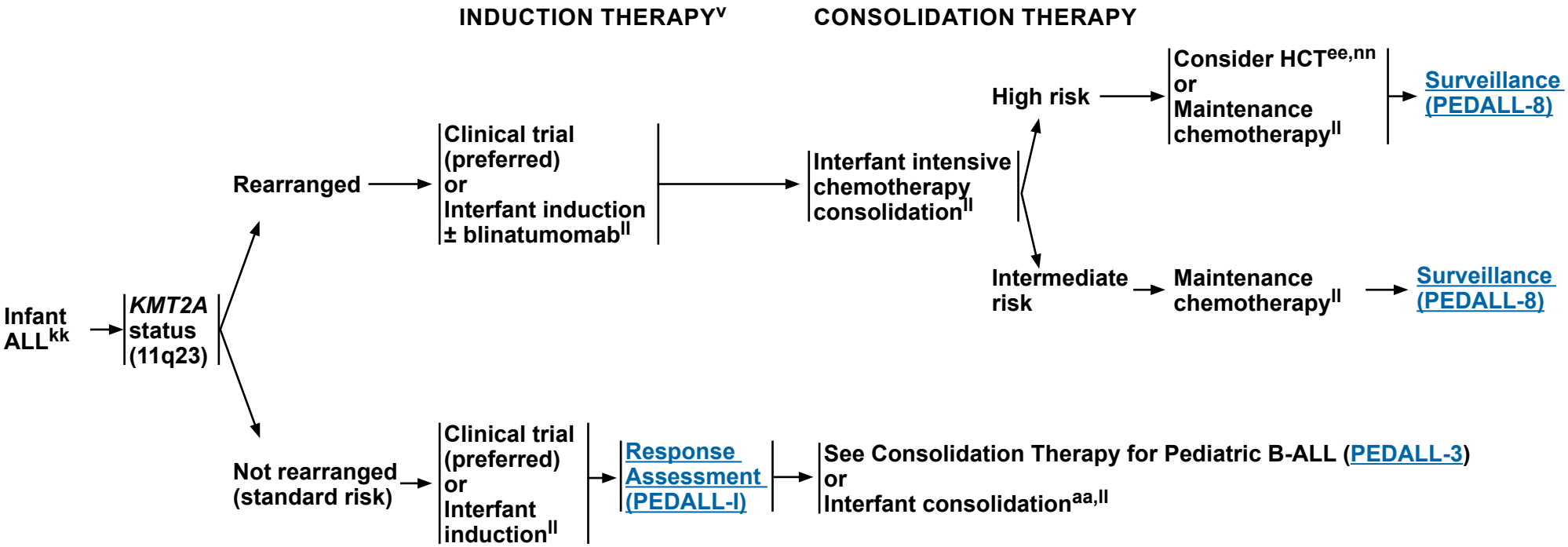

Infant Risk Group Definitions[mm]:

Risk Group	Features[y]
High	*KMT2A*-rearranged; *and* Age <3 mo with any WBC count or age <6 mo with WBC count ≥300,000; *or* Remains MRD+ after intensive consolidation therapy (any age/WBC count)
Intermediate	*KMT2A*-rearranged and not high risk
Standard	*KMT2A* not rearranged

[v] Principles of Supportive Care (PEDALL-C).

[y] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).

[aa] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.

[ee] Principles of Hematopoietic Cell Transplant (PEDALL-K).

[kk] Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E).

[ll] Principles of Systemic Therapy for Infant ALL (PEDALL-G, 2 of 13).

[mm] Reproduced with permission: Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood 2019;133:205-214.

[nn] If donor available, prefer non-total body irradiation (TBI)-based prep regimen and age ≥6 mo at time of HCT.

Note: All recommendations are category 2A unless otherwise indicated.

SURVEILLANCE[oo]

- **Year 1 (every 1–4 months):**
  - **Physical exam, including testicular exam (where applicable)**
  - **CBC with differential**
  - **LFTs until normal**
- **Year 2 (every 2–6 months):**
  - **Physical exam including testicular exam (where applicable)**
  - **CBC with differential**
- **Year 3+ (every 6–12 months or as indicated):**
  - **Physical exam including testicular exam (where applicable)**
  - **CBC with differential**

Procedures and Molecular Testing

- **Bone marrow aspirate and cerebrospinal fluid (CSF) for suspected relapse**
  - **If bone marrow aspirate is done: Flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular testing, and MRD testing**
- **Consider periodic *BCR::ABL1* transcript-specific quantification (*BCR::ABL1*+ ALL)**
- **See Response Assessment (PEDALL-I) for definitions of relapse**

Monitoring for Late Effects

- **Echocardiogram (frequency based on cumulative anthracycline dose or sooner, as clinically indicated)**
- **Neuropsychological testing as clinically indicated given increased risk of neurotoxicity in ALL survivors**
- **Monitor for healthy weight and encourage healthy lifestyle choices given increased risk of obesity in patients with history of childhood ALL**
- **Refer to the ALL Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers from the Children's Oncology Group (COG): http://www.survivorshipguidelines.org**
- **For psychosocial and behavioral considerations, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology**

→ **Relapse**
See First Relapse Disease for
B-ALL (PEDALL-9)
or T-ALL (PEDALL-10)

[oo] Surveillance recommendations apply after completion of chemotherapy, including maintenance.

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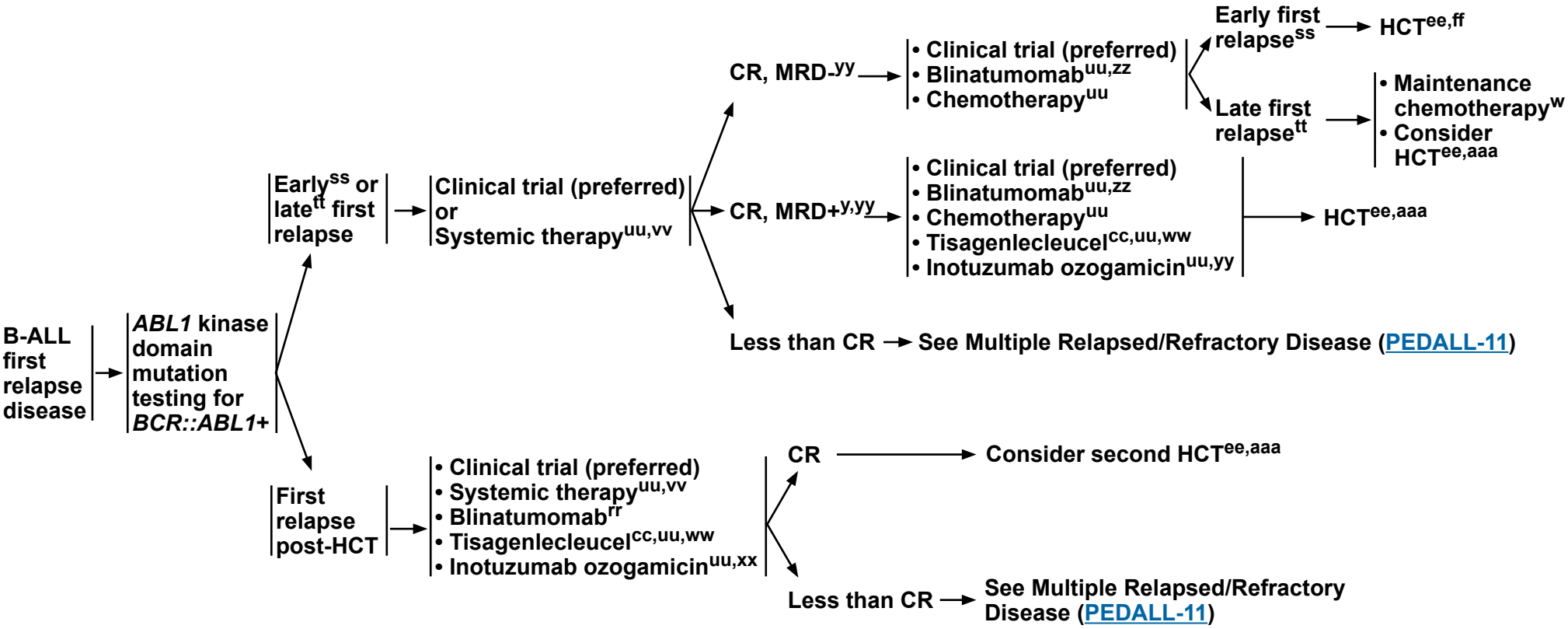

Footnotes on PEDALL-9A

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FOOTNOTES

[v] Principles of Supportive Care (PEDALL-C).
[w] Principles of Systemic Therapy (PEDALL-G).
[y] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
[cc] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia have been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year relapse-free survival was 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT (Laetsch TW, et al. J Clin Oncol 2023;41:1664-1669). See Principles of Hematopoietic Cell Transplant (PEDALL-K).
[ee] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[ff] MRD and morphologic marrow response should be assessed after induction, and if not MRD negative, repeat assessment after consolidation therapy. Assess MRD at additional time points based on chemotherapy regimen and response as indicated. See Minimal Residual Disease (PEDALL-J).
[pp] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.
[qq] NCCN Guidelines for Palliative Care.
[rr] For *BCR::ABL1*+ ALL add TKI to the treatment; see Regimens for Relapsed/Refractory *BCR::ABL1*-positive ALL (PEDALL-G, 8 of 13).
[ss] Early relapse is defined as <36 mo from initial diagnosis for isolated or combined bone marrow relapse OR <18 mo from initial diagnosis for isolated extramedullary relapse.
[tt] Late relapse is defined as ≥36 mo from initial diagnosis for isolated or combined bone marrow relapse OR ≥18 mo from initial diagnosis for isolated extramedullary relapse.
[uu] Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-G, 7 of 13).
[vv] If patients experience relapse >3 months from initial diagnosis, consider treatment with the same induction regimen. For *BCR::ABL1*-negative, *BCR::ABL1*-like and *BCR::ABL1*-positive B-ALL, see PEDALL-G (1 of 13); for T-ALL, see PEDALL-G (2 of 13).
[ww] See Tisagenlecleucel in the Principles of Systemic Therapy (PEDALL-G, 10 of 13).
[xx] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic sinusoidal obstructive syndrome (SOS) and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761040s003lbl.pdf. Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.
[yy] Minimal Residual Disease (PEDALL-J).
[zz] This recommendation for blinatumomab pertains only to patients with bone marrow relapse with or without extramedullary involvement (Locatelli F, et al. JAMA 2021;325:843-854; Brown PA, et al. JAMA 2021;325:833-842; Hogan LE, et al. J Clin Oncol 2023; 41:4118-4129).
[aaa] For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HCT should be considered.

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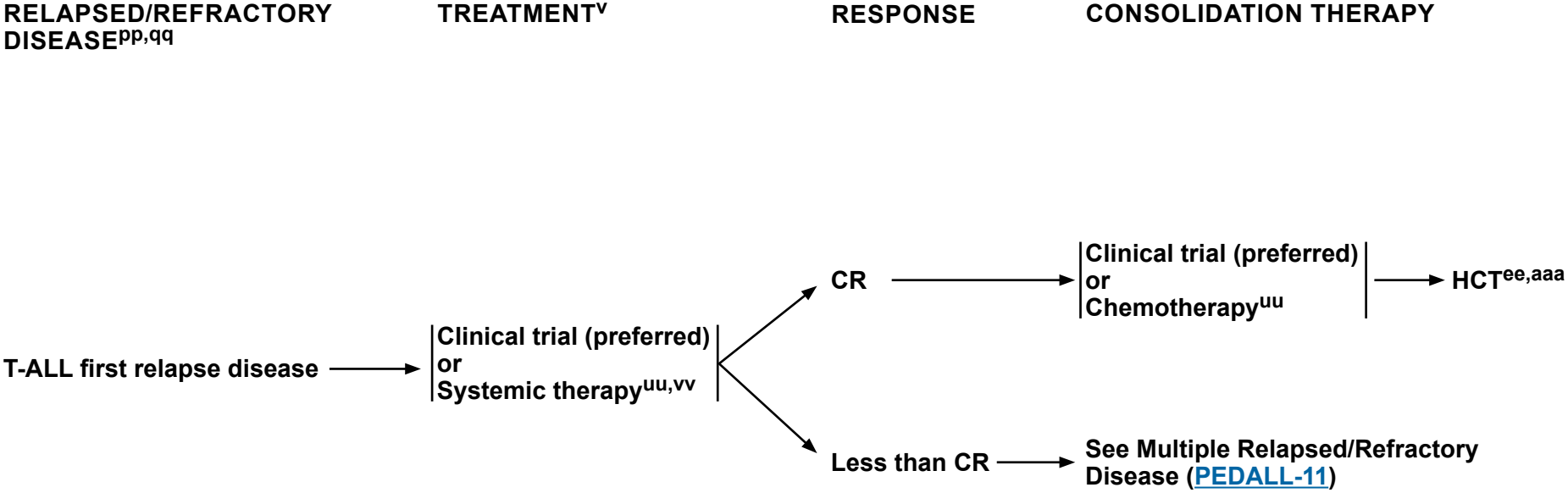

[v] Principles of Supportive Care (PEDALL-C).
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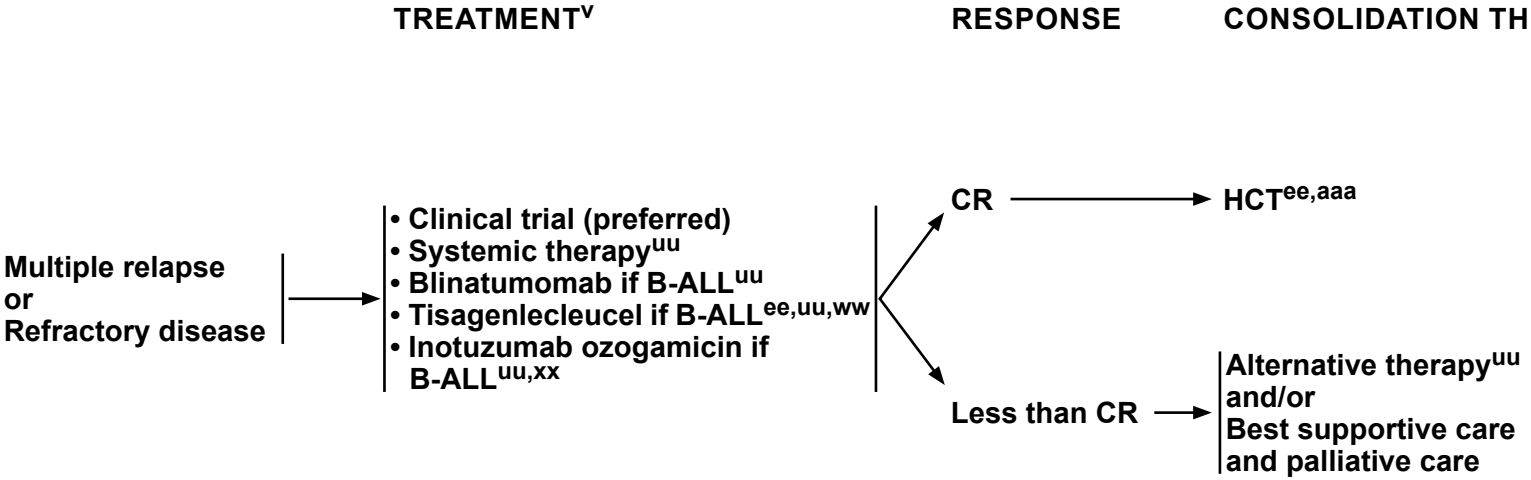
[uu] Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-G, 7 of 13).
[vv] If patients experience relapse >3 months from initial diagnosis, consider treatment with the same induction regimen. For *BCR::ABL1*-negative, *BCR::ABL1*-like, and *BCR::ABL1*-positive B-ALL, see PEDALL-G (1 of 13); for T-ALL, see PEDALL-G (2 of 13).
[aaa] For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HCT should be considered.

Note: All recommendations are category 2A unless otherwise indicated.

MULTIPLE RELAPSE/REFRACTORY DISEASE[pp,qq]



[v] Principles of Supportive Care (PEDALL-C).

[cc] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia have been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year relapse-free survival was 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT (Laetsch TW, et al. J Clin Oncol 2023;41:1664-1669). See Principles of Hematopoietic Cell Transplant (PEDALL-K).

[ee] Principles of Hematopoietic Cell Transplant (PEDALL-K).

[pp] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

[qq] NCCN Guidelines for Palliative Care.

[uu] Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-G, 7 of 13).

[ww] See Tisagenlecleucel in the Principles of Systemic Therapy (PEDALL-G, 10 of 13).

[xx] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic SOS and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761040s003lbl.pdf. Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.

[aaa] For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HCT should be considered.

Note: All recommendations are category 2A unless otherwise indicated.

ALL SUBTYPES

B-ALL/LL

WHO HAEM4R[1]	WHO HAEM5[2]	ICC 2022[3]
NOS	NOS	NOS
With hyperdiploidy	With hyperdiploidy	Hyperdiploid
With hypodiploidy	With hypodiploidy	Low hypodiploid
		Near haploid
With iAMP21	With iAMP21	With iAMP21
With t(9;22)(q34;q11.2); *BCR-ABL1*	With *BCR::ABL1* fusion	With t(9;22)(q34;q11.2)/*BCR::ABL1* • with lymphoid-only involvement • with multilineage involvement
BCR-ABL1–like*	With *BCR::ABL1-like* features	*BCR::ABL1*-like • *ABL1* class rearranged • JAK-STAT activated • NOS
With t(12;21)(p13.2;q22.1); *ETV6-RUNX1*	With *ETV6::RUNX1*	With t(12;21)(p13.2;q22.1)/*ETV6::RUNX1*
	With *ETV6::RUNX1*-like features	*ETV6::RUNX1*-like*
With t(1;19)(q23;p13.3); *TCF3-PBX1*	With *TCF3::PBX1* fusion	With t(1;19)(q23;p13.3)/*TCF3::PBX1*
With t(v;11q23.3); *KMT2A* rearranged	With *KMT2A* rearrangement	With t(v;11q23.3)/*KMT2A* rearranged
With t(5;14)(q31.1;q32.1); *IGH/IL3*	With *IGH::IL3* fusion	With t(5;14)(q31.1;q32.1)/*IL3::IGH*
	With *TCF3::HLF* fusion	With *HLF* rearrangement

*= provisional entity
NOS = not otherwise specified

[1] Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.
[2] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-1748.
[3] Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

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ALL SUBTYPES

B-ALL/LL WITH OTHER DEFINED GENETIC ALTERATIONS

WHO HAEM4R[1]	WHO HAEM5[2]	ICC 2022[3]
	With *DUX4* rearrangement	With *DUX4* rearrangement
	With *MEF2D* rearrangement	With *MEF2D* rearrangement
	With *MYC* rearrangement	With *MYC* rearrangement
	With *NUTM1* rearrangement	With *NUTM1* rearrangement
	With *PAX5* p.P80R	With mutated *PAX5* P80R
	With *PAX5*alt	With *PAX5* alteration*
	With *ZNF384* rearrangement*	*ZNF384 (362)* rearrangement
		With *UBTF::ATXN7L3/PAN3*, *CDX2* (“CDX2/UBTF”)
		With mutated *IKZF1* N159Y
		With mutated *ZEB2* (p.H1038R)/ *IGH::CEBPE**
		ZNF384 rearranged-like*
		KMT2A rearranged-like*

*= provisional entity

[1] Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.
[2] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-1748.
[3] Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

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ALL SUBTYPES

T-ALL/LL

WHO HAEM4R[1]	WHO HAEM5[2]	ICC 2022[3]
T-lymphoblastic leukemia/ lymphoma	T-lymphoblastic leukemia/ lymphoma, NOS	T-lymphoblastic leukemia/lymphoma, NOS
Early T-cell precursor lymphoblastic leukemia	Early T-precursor lymphoblastic leukemia/ lymphoma	Early T-precursor lymphoblastic leukemia/ lymphoma, NOS
		Early T-cell precursor ALL with *BCL11B* rearrangement
NK-lymphoblastic leukemia/ lymphoma		
		TAL1-2 rearrangement*
		TLX3 rearrangement*
		HOXA dysregulated*
		TLX1 rearrangement*
		LMO1-2 rearrangement*
		NKX2 rearrangement*
		SPI1 rearrangement*
		BHLH, other*

*= provisional entity
NOS = not otherwise specified

[1] Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.
[2] Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-1748.
[3] Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

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GENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	GENETICS[a,b]	
Favorable-risk features	• High hyperdiploidy (51–67 chromosomes) ▸ Double trisomy (DT) of chromosomes 4 and 10 or triple trisomy of chromosomes 4, 10, and 17 are among trisomies that have the most favorable outcome	• Cryptic t(12;21)(p13;q22): *ETV6::RUNX1* fusion • *DUX4r* • *NUTM1r*
Intermediate-risk features	• *MEF2Dr*, *ZNF384r*, *PAX5alt*, *PAX5* P80R, *ETV6::RUNX1*-like, t(1;19): *TCF3::PBX1*	
Unfavorable-risk features	• Hypodiploidy (<44 chromosomes)[c,d] • *KMT2Ar* (t[4;11] or others) • t(9;22)(q34;q11.2): *BCR::ABL1* • *BCR::ABL1*–like ALL ▸ JAK-STAT (*CRLF2r*,[e] *EPORr, JAK1/2/3r, TYK2r,* mutations of *SH2B3, IL7R, JAK1/2/3*) ▸ ABL class (rearrangements of *ABL1, ABL2, PDGFRA, PDGFRB, FGFR1*) ▸ Other (*NTRKr, FLT3r, LYNr, PTK2Br*)	• t(17;19): *TCF3::HLF* and t(17;18): *TCF4::HLF* • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1*[f]

[a] There is emerging evidence that several molecular markers not listed here may have an impact on prognosis. The Panel will review these data and update the table as they become available.

[b] Emerging evidence suggests new subtypes: *ETV6*::*RUNX1*-like, and the other defined genetic abnormalities: rearrangements of *DUX4*, *MEF2D, ZNF384*, and *NUTM1*; *IG::MYC* fusion; *PAX5alt;* and *PAX5* p.P80R. Further confirmatory studies are necessary to assess the risk associated with these alterations.

[c] Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone: near-haploid (24–31 chromosomes); low-hypodiploid (32–39 chromosomes); or high-hypodiploid (40–43 chromosomes). Low hypodiploid ALL is also often associated with *TP53* loss-of-function somatic mutations in which half are observed to be germline pathogenic variants associated with Li-Fraumeni syndrome. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013;45:242-252.

[d] There are other results that are not <44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hyperdiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. Single nucleotide polymorphism (SNP) array or whole genome sequencing to look for loss of heterozygosity (LOH) can distinguish true hyperdiploidy from masked hypodiploidy. Carroll AJ, Shago M, Mikhail FM, et al. Masked hypodiploidy: Hypodiploid acute lymphoblastic leukemia (ALL) mimicking hyperdiploid ALL in children: A report from the Children's Oncology Group. Cancer Genet 2019;238:62-68.

[e] Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood 2010;115:5312-5321.

[f] *IKZF1* deletions with deletions in *CDKN2A, CDKN2B* (homozygous), *PAX5,* or *PAR1* region in the absence of *ERG* deletion, which are called *IKZF1*plus, as well as those with concomitant 22q11.22 deletions are especially associated with worse outcomes. However, *DUX4* rearrangements with *IKZF1* alterations do not confer poor prognosis. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360:470-480; Stanulla M, Dagdan E, Zaliova M, et al. IKZF1plus defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. J Clin Oncol 2018;36:1240-1249; Mangum DS, Meyer JA, Mason CC, et al. Association of combined focal 22q11.22 deletion and IKZF1 alterations with outcomes in childhood acute lymphoblastic leukemia. JAMA Oncol 2021;7:1521-1528.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

Infection Control

- Prior to the start of induction chemotherapy for patients with newly diagnosed disease, viral serologies (ie, herpes simplex virus [HSV] IgG, cytomegalovirus [CMV] IgG, Epstein-Barr virus [EBV] panel) and quantitative immunoglobulins (ie, IgA, IgM, IgG) may be considered.
- During chemotherapy, consider IgG monitoring and when IgG levels are <400 mg/dL, consider replacement in populations at high risk (infants and trisomy 21, see Special Considerations for Patients with Down Syndrome and Infants [PEDALL-E]), patients with suspected immune deficiency, patients with a history of recurrent opportunistic infections, and patients receiving immunotherapies that can result in prolonged B-cell aplasia, including tisagenlecleucel.
- Prophylaxis guidelines
  - All patients with ALL are at high risk for *Pneumocystis jirovecii* (*Pneumocystis carinii*) and should take prophylaxis throughout anti-leukemic therapy.
    - ◊ Preferred therapy is trimethoprim/sulfamethoxazole (TMP/SMX) with dosage of 5 mg/kg/day TMP 2–3 days per week, with a maximum total dose of 320 mg/day (or as per institutional standard). Doses may be given once a day or divided twice daily.
    - ◊ TMP/SMX may be held for a short period of time if blood counts are low, but should be reinstated once counts have recovered and appropriate adjustments in chemotherapy dosing have been made. Try to avoid permanently discontinuing or holding TMP/SMX for prolonged myelosuppression. TMP/SMX may be held when high-dose methotrexate (MTX) is administered and restarted when MTX clearance is achieved per protocol or institutional guidelines.
    - ◊ If TMP/SMX intolerant, can consider atovaquone, dapsone, or pentamidine (aerosolized or intravenously [IV]).
  - Consider fluoroquinolone (ie, levofloxacin, moxifloxacin) prophylaxis in patients receiving anthracyclines during induction therapy for newly diagnosed ALL or therapy for relapsed ALL who are anticipated to have neutropenia.[1,2] For patients unable to tolerate fluoroquinolones due to allergy or other toxicity, alternative antibiotics per institutional standard can be considered or consider monitoring without antibiotics.[3,4]
  - Consider antifungal prophylaxis during induction, especially in patients receiving anthracyclines. Azoles have potential interactions with vincristine and should be used with caution.[4-7] Consider micafungin or other echinocandin antifungal drugs during induction and potentially during other high-intensity phases. Prophylaxis with liposomal amphotericin can be considered.
- Considerations with prolonged use of corticosteroids
  - Adrenal insufficiency is associated with steroid use, particularly in induction, and potential need for stress dose steroids with fevers.
  - Signs/symptoms of infection and sepsis, including fever, may be masked while on chronic corticosteroid therapy. There should be a low threshold for admission, monitoring, and preemptive antibiotics for patients with ALL in phases with long-term corticosteroid treatment.
- Fever and neutropenia
  - During induction, all patients with fever (as defined by Infectious Diseases Society of America [IDSA][8] or institutional standards) should be evaluated by a medical provider and treated immediately with broad-spectrum antibiotics, regardless of absolute neutrophil count (ANC). Following completion of induction, antibiotics may not be indicated for fever based on clinical status.
  - Perform a comprehensive assessment of patient for severity of illness (including signs and symptoms of shock) and localizing signs and symptoms of infection.
  - Evaluate central venous line site for presence of infection.
  - Every effort should be made to collect bacterial culture specimens before administration of antibiotics; however, empiric antibiotic therapy should NOT be delayed for the purposes of specimen collection only.
  - For patients with signs of fever, neutropenia, or sepsis, antibiotics should be administered as soon as possible. Recommend stress dose steroids for patients with sepsis.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE

- Fever and neutropenia (continued)
  - Both aerobic and anaerobic blood cultures of appropriate volume (based on age and weight) should be collected based on institutional guidelines.
  - Consider obtaining a urine culture in all febrile patients and infants, or in any patient with genitourinary symptoms or with a urinary catheter in place before empirical antibiotics are dispensed.
  - Consider obtaining nasopharyngeal or sputum specimens for viral testing and bacterial cultures in patients with respiratory tract infections.
  - Consider obtaining chest imaging (chest radiograph or CT scan) in patients with lower respiratory tract signs and symptoms (eg, hypoxia).
  - Consider obtaining abdominal ultrasound or CT scan in patients with significant abdominal pain.
  - If meningitis or meningoencephalitis is suspected:
    - ◊ Perform an LP for opening pressure, cell count, glucose, protein, and other cultures (eg, bacterial aerobic, bacterial anaerobic, fungal, acid-fast bacilli [AFB]) or viral PCR tests (eg, enterovirus, HSV) as clinically indicated.
    - ◊ Initiate or modify antimicrobial therapies accordingly, ensuring use of agents that penetrate into the CSF.
  - In patients with diarrhea who have received antibiotics in the previous 2 weeks, consider sending stool for *Clostridium difficile.*
  - In patients with skin lesions, culture or biopsy lesions suspected of being infected and send for cytologic testing, Gram and fungal staining, and bacterial and fungal cultures. Aspiration may be useful for Gram staining and bacterial aerobic culture.
  - Vesicular lesions should be tested (eg, HSV, varicella zoster virus [VZV] PCR). Institute proper isolation precautions and begin empiric therapy with acyclovir pending results.
  - Empiric antimicrobial therapy selection
    - ◊ In a hemodynamically stable patient, monotherapy with a broad-spectrum antibiotic with activity against gram-positive and gram-negative bacteria (including *Pseudomonas*) is recommended.
    - ◊ In a hemodynamically unstable patient (eg, hypotension, respiratory failure, ill-appearing) initiation of additional antibiotics (eg, vancomycin, aminoglycoside) is prudent pending results of cultures and patient's clinical progression.
    - ◊ Additions or modifications to initial empiric therapy should be guided by the patient's clinical syndrome, past history of infections and antimicrobial susceptibilities, and colonization status.
    - ◊ Addition of a second antibiotic active against Gram-negative bacteria is prudent for patients with a history of prior infections or colonization with these Gram-negative organisms or in patients who are hemodynamically unstable pending the results of cultures.
    - ◊ Appropriate coverage for viridans group streptococci may be considered in empiric antibiotics for fever occurring in patients after high-dose cytarabine.
    - ◊ Modifications to the initial empirical antibiotic regimen should be guided by the patient's clinical and microbiological data.
    - ◊ If blood cultures at 24–48 hours identify Gram-positive bacteria, consider obtaining one set of repeat blood cultures and starting vancomycin (or linezolid in a patient with a history of vancomycin-resistant enterococci [VRE]) pending results of repeat cultures and final identification and susceptibilities of the Gram-positive bacteria. If cultures at 48 hours do not reveal a Gram-positive infection and vancomycin was started, it can be discontinued at 48 hours.
  - Filgrastim (granulocyte colony-stimulating factor [G-CSF]), pegfilgrastim, and sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) are not generally recommended but may be used at the discretion of the health care provider in situations of prolonged neutropenia or serious/life-threatening infections with neutropenia. Similarly, granulocyte transfusions are not generally recommended but may be used at the discretion of the health care provider in situations of serious/life-threatening infection in the context of neutropenia.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE

- Fever and neutropenia (continued)
  - Additional diagnostic investigation, such as imaging of lungs, abdomen, and sinuses if symptomatic, should be considered and empirical antifungal therapy should be started for patients with neutropenia and prolonged (≥4–7 days) fever despite empirical antibiotics and who are expected to remain neutropenic, or who have new symptoms (eg, cough, facial pain, swelling).
    - ◊ If yeast (*Candida* species) is suspected, initiation of an echinocandin (ie, micafungin, caspofungin) or liposomal amphotericin is appropriate.
    - ◊ If mold coverage is warranted, then voriconazole, liposomal amphotericin, posaconazole, or an echinocandin (ie, micafungin, caspofungin) may be used, based on clinical and diagnostic results.
- Consider vaccination with inactivated vaccines and live vaccines (varicella, measles, mumps, and rubella) 3 months after chemotherapy following the CDC schedule for immunocompetent individuals. For patients receiving regimens that include anti–B-cell antibodies, vaccinations should be delayed at least 6 months.[9]
  - It may be appropriate to refer to Infectious Disease or Immunology for guidance regarding specific vaccinations for each individual patient.
- For guidance on COVID-19 vaccination, see the CDC for Use of COVID-19 Vaccines in the US
- For guidance on management of concurrent COVID-19 in patients with cancer, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections
- For specific information regarding COVID-19 vaccinations and management of pediatric ALL in patients who become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), see:
  - https://www.hematology.org/covid-19/covid-19-and-pediatric-all

Tumor Lysis Syndrome (TLS)

- Laboratory TLS (presence of 2 or more metabolic abnormalities in the same 24-hour period)
  - High uric acid (> upper limit of normal [ULN] for children)
  - High phosphorus (>6.5 mg/dL in children)
  - High potassium (>6.0 mmol/L)
  - Low calcium (corrected calcium <7.0 mg/dL)
- TLS can be asymptomatic or can cause seizures, cardiac arrhythmias, acute renal failure, neuromuscular abnormalities, hypotension, and/or death.
- TLS risk factors
  - High WBC count (eg, >100 x 10^9/L)
  - Elevated LDH (>2 x ULN)
  - Bulky disease
  - Evidence of TLS prior to initiation of therapy
  - Oliguria
  - Preexisting renal impairment
  - Dehydration
- Prophylaxis/management of TLS
  - Low-intensity initial therapy (corticosteroid monotherapy for 3–7 days) may be used for patients at high risk for TLS to reduce risk of renal complications.
  - Begin hyperhydration with 1.5–2x maintenance IV fluids without potassium. Urine alkalinization is no longer recommended. If urine output remains low after achieving an optimal state of hydration, a loop diuretic agent (eg, furosemide) may be used to promote diuresis, with a target urine output of at least 2 mL/kg/h.
  - Monitor tumor lysis labs (ie, potassium, calcium, phosphorus, uric acid, creatinine) regularly from time of admission until tumor burden is substantially decreased. Patients with hyperleukocytosis and/or symptoms of TLS at presentation especially require frequent monitoring.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE

- **Hyperuricemia**
  - Allopurinol should be started prior to initiation of chemotherapy for patients with low WBC (eg, <100 x 10^9/L) and LDH <2 x ULN, and low tumor burden. Discontinuation of allopurinol and prompt initiation of rasburicase is recommended if there is a concern for TLS, because it has been shown to be safe and effective in preventing new-onset renal failure and was associated with an improved glomerular filtration rate.
  - For ongoing control of TLS, consider restarting allopurinol after rasburicase therapy is completed.
  - Rasburicase is indicated prophylactically for patients with high WBC count (eg, >100 x 10^9/L), LDH >2 x ULN, high tumor burden, or those presenting with renal dysfunction, elevated uric acid (eg, >8 mg/dL), or inability to tolerate hydration. The first dose of rasburicase should be given prior to starting chemotherapy even if uric acid is <8 mg/dL in such cases.
  - Rasburicase is contraindicated in patients with G6PD deficiency due to an increased risk of methemoglobinemia or hemolysis. However, in patients with TLS at risk for end-organ injury with unknown G6PD status, the benefit of rasburicase may outweigh the risk.
  - Rasburicase is given as a single dose of 0.1–0.2 mg/kg. The maximum dose is 6 mg and should be repeated only if necessary based on laboratory values.
  - If rasburicase is used, blood samples for the measurement of the uric acid level must be placed on ice to prevent ex vivo breakdown of uric acid by rasburicase and thus a spuriously low level.
- **Hyperkalemia:** Manage per standard hyperkalemia algorithms, such as in Pediatric Advanced Life Support (PALS). Ensure that all exogenous sources of potassium, such as in IV fluids, have been removed. Frequent measurement of potassium levels (every 4–6 hours), continuous cardiac monitoring, and the administration of oral sodium polystyrene sulfonate are recommended. Glucose plus insulin or beta agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of dysrhythmia while awaiting hemodialysis and/or hemofiltration, which most effectively remove potassium.
- **Hyperphosphatemia:** Manage with phosphorous-restricted diet; consider phosphate binder such as sevelamer. Do not use calcium carbonate in patients at risk for TLS as this may prompt formation of calcium phosphate crystals and worsen renal and other organ function, especially if the calcium phosphate product is >60 mg^2/dL^2.
- **Hypocalcemia:** Correct hyperphosphatemia; calcium supplementation should not be used unless patient is symptomatic with tetany, muscle spasm, Trousseau/Chvostek signs, etc.
- Consider hemodialysis/continuous renal replacement therapies (CRRT) in patients with worsening renal function whose electrolyte abnormalities do not correct with medical management.

Methotrexate (MTX) Toxicity Management

- Caution use of medications that compete for excretion (eg, penicillins, proton pump inhibitors [PPIs]) and nephrotoxic medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], amphotericin) with MTX due to potential effect on clearance.
- In the event a patient receiving high-dose MTX experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended when plasma MTX concentrations are two standard deviations above the mean expected MTX plasma concentration as determined by MTXPK.org, or if the 36-hour plasma MTX level is above 30 µM, 42-hour level is above 10 µM, or 48-hour level is above 5 µM. Optimal administration of glucarpidase is within 48 to 60 hours from the start of MTX infusion. Leucovorin should be dosed based on pre-glucarpidase plasma MTX concentration and should be continued for at least 2 days following glucarpidase administration. However, since leucovorin is a substrate for glucarpidase, it should not be administered within 2 hours prior to or following glucarpidase.[10]
- Measurements of plasma MTX levels after glucarpidase by standard immunoassay methods do not distinguish MTX from its metabolites and may overestimate the true MTX concentration.
- Doses of leucovorin >25 mg should be given IV due to saturable absorption when given orally.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

- **MTX neurotoxicity**
  - Can occur following high-dose or IT MTX, more frequently in patients >10 years.
  - May present with seizures and/or stroke-like symptoms, typically within 21 days of IV or IT MTX.
  - MRI may allow for discrimination between MTX neurotoxicity and posterior reversible encephalopathy syndrome (PRES).
  - Most patients make a full recovery without intervention.
  - Patients who present with seizures may benefit from anti-epileptics for the remainder of their therapy. Anti-epileptics that are non-hepatic enzyme inducers, such as levetiracetam and lacosamide, are preferred in order to avoid potential interactions with chemotherapy. Final choice of anti-epileptic should be made with all patient factors taken into consideration and with the input of a pediatric neurology specialist, when available.
  - Potential interventions include aminophylline and dextromethorphan, but there is limited evidence for any of these.
  - Risk of recurrence with continued MTX treatment is low, though providers may wish to introduce MTX gradually to avoid further neurotoxicity and consider alternate IT therapy such as cytarabine for central nervous system (CNS) treatment, closely following acute MTX neurotoxicity.
- **Leucovorin may be given after IT chemotherapy containing MTX for patients with Down syndrome or those who have experienced excessive toxicity with prior IT MTX. Suggested dosing (if given): Give leucovorin at 24 and 30 hours after LP at 5 mg/m^2/dose orally or IV two times a day for 2 doses only.**

Mucositis

- Assess current dental care measures. Evaluate oral cavity and condition of teeth and gums before initiating chemotherapy. Examine for ulcers, erythema, and pain. Dental consult recommended prior to start of chemotherapy.
- Prevention:
  - ◊ Cryotherapy during rapid infusions: Hold ice chips or cold water in patient's mouth prior to, during, and after infusion—at least 5 minutes prior until 30 minutes after completion or as tolerated.
  - ◊ Use chlorhexidine mouthwash for its bactericidal effect.
  - ◊ Bland rinses such as 0.9% saline solution, sodium bicarbonate, or artificial saliva products (non-alcoholic and unsweetened) should be used twice daily and after meals.
- Management:
  - ◊ Topical agents: Rinses should be used at the first sign of redness or breakdown 4 times a day. Increase as needed for comfort. Rinses should be bland such as salt and sodium bicarbonate.
  - ◊ Supportive care measures: Maintain hydration, adequate nutrition with enteral or parenteral sources, control of bleeding, use of prophylaxis medications to prevent viral (HSV) or fungal (*Candida*) infections, pain management with topical anesthetics, and use of oral or IV analgesics.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

Anthracycline-Related Cardiotoxicity

- Most patients with ALL will not be exposed to a cumulative dose of anthracycline and/or radiation therapy, which puts them at high risk for cardiotoxicity; however, some patients may have underlying conditions or prior/anticipated therapies, which place them at higher risk of anthracycline-related cardiotoxicity, particularly in the setting of relapsed/refractory disease.
- Consider dexrazoxane prior to each dose for patients with:
  - Anticipated cumulative anthracycline dose ≥250 mg/m^2 of doxorubicin equivalent.
    - ◊ Anthracycline dose conversion:
      - – Doxorubicin: Multiply total dose x 1
      - – Daunorubicin: Multiply total dose x 0.5
      - – Mitoxantrone: Multiply total dose x 4–10 (mitoxantrone has been considered to be 4 to 5 times more cardiotoxic than doxorubicin, but newer data suggest it might be as much as 10 times more toxic[11])
  - Past or anticipated radiation with potential impact to the heart (radiation to chest, abdomen, spine, or total body irradiation [TBI]).
  - Recommended dose of dexrazoxane is 10 x the doxorubicin dose given over 5–15 minutes immediately before the chemotherapeutic agent.
  - Recent studies have not found any increase in risk of secondary malignancy in patients who receive dexrazoxane.

Steroid Management

- Patients unable to take oral steroids can be treated with IV formulations.
- Acute side effects
  - Steroid-induced hyperglycemia
    - ◊ Omit dextrose from IV fluids.
    - ◊ Control glucose using insulin to decrease infection complications.
  - Steroid-induced psychosis and mood alteration
    - ◊ Consider antipsychotics. If no response, consider 50% dose reduction or switching from dexamethasone to prednisone, if applicable.
  - Gastric prophylaxis should be considered during all treatment phases that include corticosteroid therapy.
    - ◊ Options include oral antacids (eg, calcium carbonate), sucralfate, histamine-2 antagonists (eg, famotidine), or PPIs.
    - ◊ PPIs should be held during high-dose MTX administration until levels are “cleared.”
    - ◊ There are significant interactions between agents that reduce gastric acid (such as PPIs, antacids, and histamine-2 antagonists) and TKIs that may affect the bioavailability of certain *BCR::ABL1* TKIs (eg, dasatinib).
  - Steroid-induced hypertension
    - ◊ Monitor sodium intake.
      - – Antihypertensives may be indicated if systolic blood pressure is consistently >95th percentile for age, height, and sex, or if early signs of PRES are present (ie, headaches, visual changes).
  - PRES
    - ◊ Anti-hypertensive therapy as needed to maintain blood pressure in age-appropriate range.
    - ◊ Clinical diagnosis is made with signs/symptoms as well as MRI findings.
    - ◊ Consider anti-epileptics.
    - ◊ Typically self-resolves with aggressive control of hypertension (see above for management).
    - ◊ Monitor and replenish magnesium.
  - Bone fractures
    - ◊ For bone fractures associated with steroids, hold steroids until fractures are healed (based on radiographic or symptomatic improvement), then resume without dose modification. Bisphosphonates for patients with recurrent fracture and severe osteopenia may be considered.
  - Pancreatitis: Dexamethasone may be held at discretion of treating oncologist.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

Steroid Management (continued)

- Steroid myopathy may present with proximal limb and neck flexor weakness. Respiratory muscles may also become weak in more severe cases.
  - ◊ Consider holding or reducing the dose per treatment protocol.
  - ◊ Consider physical therapy referral.

- Long-term side effects of corticosteroids
  - Osteonecrosis/avascular necrosis (AVN)
    - ◊ There is no evidence for vitamin D and calcium replacement in pediatric patients in regard to prevention and treatment of osteonecrosis/AVN.[12-15]
    - ◊ Corticosteroids should not be withheld in induction or intensification blocks, but if severe AVN occurs during therapy, should consider holding corticosteroids during maintenance therapy. If MRI findings have significantly improved or patient's symptoms have resolved in 6 months, can consider resuming corticosteroids at that time. Prednisone may be preferred instead of dexamethasone.
    - ◊ There are no recommendations for screening for osteonecrosis and AVN in pediatric patients with ALL at this time. However, providers should have a low threshold to obtain MRI (more sensitive) or plain film of affected joint(s) in patients with symptoms consistent with osteonecrosis/AVN.

Vincristine Management

- Consider starting a bowel regimen to avoid constipation if receiving vincristine. If bowel regimen is not initiated with vincristine, closely monitor for need.
  - May hold dose for ileus or typhlitis, then restart at 50% of previous dose once symptoms resolve, then escalate to full dose as tolerated.
- Peripheral neuropathy
  - For foot drop and other motor neuropathies, physical therapy should be offered where available. Do not hold or decrease dose unless symptoms are grade ≥3.
  - For vocal cord paralysis, hold dose, then restart at 50% of previous dose once symptoms resolve, then escalate to full dose as tolerated.
  - For pain control, consider use of gabapentin, pregabalin, or other GABA analog. Some patients may additionally require use of pain medication such as opioids.
    - ◊ Neuropathic pain can last for months to years, even following discontinuation of vincristine. Therefore, and because vincristine is a crucial component of leukemia therapy, all decreased or discontinued dosing for neuropathic pain is at the primary provider's discretion.
    - ◊ For severe neuropathic pain (grade >3), may hold dose, then restart at 50% of previous dose once symptoms resolve, then escalate to full dose as tolerated.
  - Patients experiencing severe and early neuropathies, especially in the presence of pes cavus, may benefit from genetic testing to rule out Charcot-Marie-Tooth disease, type 1A neuropathy, or hereditary neuropathy with liability to pressure palsies.
  - Use of strong CYP3A4 inhibitors, such as azoles (eg, voriconazole, posaconazole), may increase risk of vincristine-associated peripheral neuropathy.
- For jaw pain, do not hold or modify dose, but treat with analgesics as indicated.
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) associated with vincristine may develop. Typical signs include hyponatremia and concentrated urine. Management typically includes fluid restriction and endocrine consultation should be considered.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE

Thiopurines Management - See **Pharmacogenomics (PEDALL-H)**

- Sinusoidal obstruction syndrome (SOS) of the liver, previously called veno-occlusive disease (VOD), is most common with 6-thioguanine (6-TG).
  - Risk factors include thiopurine exposure, thiopurine methyltransferase (TPMT) polymorphisms, and HCT.
  - Small hepatic vessel thrombi classically lead to acute SOS with painful hepatomegaly, ascites, hyperbilirubinemia, thrombocytopenia, multiorgan failure, and a high risk of mortality. Defibrotide may be used in severe cases.
  - The use of thiopurines (most commonly 6-TG) may result in chronic SOS, which presents with disproportionate thrombocytopenia and evidence of chronic portal hypertension.
  - For patients with significant gastrointestinal (GI) symptoms (ie, nausea, vomiting) and/or grade 4 alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or direct bilirubin >2 mg/dL, and/or hypoglycemia, consider obtaining mercaptopurine metabolites. For patients with elevated methylated metabolites and ANC indicating that the dose of 6-MP should be increased, or for those with GI toxicity or hypoglycemia that are dose limiting, consider the addition of allopurinol 50 mg/m^2 with a 50%–75% decreased dose of 6-MP.[16,17,18] Careful ANC monitoring should be considered with this approach, as the interaction of 6-MP and allopurinol carries a significant risk of myelosuppression.

Transfusions

- Products should be irradiated and leukodepleted when possible.

Hyperleukocytosis

- Leukostasis occurs more often in those with a high WBC count (>200 × 10^9/L), those with a T-cell immunophenotype, infants, and those with *KMT2A* or *BCR::ABL* rearrangements. The risk of leukostasis is lower in ALL compared with acute myeloid leukemia (AML).
- Symptomatic hyperleukocytosis may require emergent treatment, particularly for patients with WBC count >400 x 10^9/L (seen in <3% of patients with ALL).
- Leukapheresis has been demonstrated to reduce complications of leukostasis in patients with ALL, but in cases of hyperleukocytosis without symptoms of leukostasis, leukapheresis provides no clinical advantage over aggressive chemotherapy. Leukapheresis may also be associated with adverse outcomes.[19,20]
  - In cases where leukapheresis is indicated for symptomatic leukostasis, leukapheresis should be discontinued once symptoms resolve and WBC count is <400 x 10^9/L.
  - Chemotherapy must be initiated rapidly following leukapheresis to prevent rapid reaccumulation of circulating blasts.
- Transfusion of red blood cells (RBCs) should be avoided in patients with hyperleukocytosis until the WBC count is below 100 × 10^9/L due to hyperviscosity. Platelet transfusions should be used to reduce the risk of CNS hemorrhage.
- Lab errors may result in both chemistry and coagulation studies due to the fragility of blast cells in tubes. Consider point-of-care testing where possible and use good clinical judgment before treating lab abnormalities aggressively or delaying therapy based on abnormal lab values.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE

Antiemetics (NCCN Guidelines for Antiemesis)
- Given as needed prior to chemotherapy and post chemotherapy.
- Routine use of corticosteroids as antiemetics are avoided.

Behavior and Psychosocial Support
- For psychosocial/behavioral considerations, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.
- Neurocognitive monitoring during therapy and after completion of therapy should be considered for all patients, given established risk for neurocognitive late effects associated with CNS-directed therapy.[21,22]
- Neurocognitive monitoring could occur at completion of treatment and/or at school entry or re-entry. Baseline assessment may be considered to provide a context in which to appreciate change.
- Consider referral for a comprehensive neuropsychological assessment if there is evidence of new concerns or change.

Nutritional Support
- Consider appetite stimulants or enteral or parenteral support for >10% weight loss.
- In patients unwilling or unable to increase oral intake, may consider feeding tube placement for caloric supplementation prior to consideration of parenteral support.
- Risk of obesity in survivors, despite reduction in total caloric intake, suggests that alternative interventions, particularly those that prevent loss of muscle mass like physical activity, are needed.

Treatment for Pain
- The Panel encourages consultation with pediatric pain or palliative care specialists.
- Bone pain and vincristine-associated neuropathic pain are commonly associated with ALL.

Consideration for Leukemia Predisposition Syndromes
- Given risk of increased treatment-related toxicity, increased risk of secondary malignancy, and need for surveillance beyond what is typical for patients with a history of leukemia, it is important that a clinician perform a thorough family history in order to screen for patients who may have a leukemia predisposition syndrome. If there is a concern for a leukemia predisposition syndrome, consider referral to a genetic counselor or geneticist to identify appropriate clinical testing.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management

Asparaginase Therapy

- Asparaginase should only be used in specialized centers and patients should be closely monitored in the period during and after infusion for allergic response.
- There are three formulations of asparaginase in clinical use:
  - 1) pegaspargase, 2) calaspargase, and 3) asparaginase Erwinia chrysanthemi (recombinant)-rywn (ERW-rywn).[a]
- Calaspargase is the preferred formulation, if available, for patients aged >1 mo – <21.5 years.
- Pegaspargase/calaspargase are common components of therapy for children, adolescents, and young adults with ALL. The toxicity profile of asparaginase products presents significant challenges in clinical management. The following guidelines are intended to help providers address these challenges.
- For more detailed information, refer to Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leuk Lymphoma 2016;57:748-757. All toxicity grades refer to National Cancer Institute; National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 2010. Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
- For pegaspargase/calaspargase, dose capping at 3,750 units/dose (1 vial) can be considered in cases of baseline obesity.
- For ERW-rywn, the FDA approved an IM dosing schedule of 25 mg/m^2 Monday/Wednesday and 50 mg/m^2 Friday based on positive risk:benefit ratio from a phase 2/3 study in addition to 25 mg/m^2 administered IM every 48 hours.[23]
- Therapeutic drug monitoring (TDM) for asparaginase therapy using the serum asparaginase activity (SAA) is available as a CLIA-certified test with a turnaround time of <1 week, allowing for real-time decision-making and therapeutic adjustments. Generally accepted SAA assay targets include a minimum trough of ≥0.1 IU/mL. However, data indicate that when SAA levels fall below 0.4 IU/mL, asparagine is no longer completely depleted and begins to rebound, suggesting an optimal trough of ≥0.4 IU/mL. Modifications in asparaginase dose or schedule depend on the clinical context.

Hypersensitivity, Allergy, and Anaphylaxis[24-27]

- Asparaginase products can cause systemic clinical hypersensitivity reactions, manifested clinically as urticaria, bronchospasm, angioedema, or anaphylaxis. These reactions may be (but are not always) associated with the production of neutralizing antibodies and lack of asparaginase activity. The severity of the reaction does not correlate with the risk of neutralization. In fact, there are patients who develop neutralizing antibodies without any clinical manifestations, which is known as "silent inactivation." ERW-rywn is indicated for patients with hypersensitivity to *E. coli* asparaginase products.
- Pegaspargase/calaspargase are the standard formulations currently in use. While calaspargase is only available IV, pegaspargase is available IV or IM but is usually given IV. With IV pegaspargase/calaspargase, a distinct type of acute clinical reaction (a nonallergic infusion reaction) can also occur. These nonallergic infusion reactions often occur shortly into the infusion (within minutes or even seconds) and have a great deal of clinical overlap with the hypersensitivity reactions, manifesting with flushing, hypotension, tachycardia, dyspnea, tachypnea, and anxiety. It is usually not possible to clinically distinguish this reaction from allergic hypersensitivity. Pegaspargase/calaspargase-induced acute hyperammonemia may mediate at least some of the symptoms and signs associated with these nonallergic infusion reactions. Slowing the infusion to ≥2 hours (but <4 hours for calaspargase), infusing normal saline concurrently, and using anti-allergy premedications given IV or PO (such as hydrocortisone, diphenhydramine or other antihistamines [eg, cetirizine (category 2B for IV cetirizine)], and acetaminophen) can reduce the risk of these reactions.

[a] ERW-rywn is for patients who had an allergic reaction to *E. coli*-derived asparaginase.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management

- Routine premedication has generally been avoided in the past for fear of "masking" hypersensitivity reactions. However, given the difficulty in distinguishing hypersensitivity and non-allergic infusion reactions and the availability of TDM, universal premedication and TDM can be considered, which can reduce the incidence and severity of adverse events and the need for substitution of pegaspargase/calaspargase with ERW-rywn.

Pancreatitis
- In the case of grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until these findings normalize and then resume. Permanently discontinue asparaginase in the presence of grade 4 pancreatitis and cases of grade 3 pancreatitis with persistent symptoms (>72 h) and/or sequalae (eg, pseudocyst formation). For cases of grade 3 pancreatitis in which symptoms and enzyme elevation significantly improve within 72 hours, consider treating again with asparaginase once all findings normalize.[28,29]

Non-CNS Hemorrhage
- For grade 2 or greater hemorrhage, hold asparaginase until grade 1, then resume. Consider coagulation factor replacement. Do not hold for asymptomatic abnormal laboratory investigations.

Non-CNS Thromboembolism
- For grade 2 or greater thromboembolic event, hold asparaginase until resolved and treat with appropriate antithrombotic therapy. Upon resolution of symptoms and once antithrombotic therapy is stable, resume asparaginase.
- Consider checking ATIII levels if administering heparin or low-molecular-weight heparin.
- Line-associated thromboses are also fairly common in treatment. Anticoagulation therapy can be safely administered during treatment.[30,31]

Intracranial Hemorrhage
- Discontinue asparaginase. Consider coagulation factor replacement. Once symptoms/signs fully resolve, can resume asparaginase.
- Perform magnetic resonance angiography (MRA)/magnetic resonance venography (MRV) to rule out bleeding associated with sinus venous thrombosis.

Cerebral Thrombosis, Ischemia, or Stroke
- Discontinue asparaginase. If symptoms/signs fully resolve, can resume asparaginase. Consider antithrombotic prophylaxis when resuming asparaginase.
- Consider evaluation for inherited thrombophilia.

Hyperglycemia
- Treat hyperglycemia with insulin as indicated.

Hypertriglyceridemia
- Treat hypertriglyceridemia as indicated. There is no evidence to suggest a best practice, and physicians are encouraged to use best clinical judgment for their patient. For recurrent hypertriglyceridemia, lipid-lowering agents may be used at discretion of treating clinician.

Hepatotoxicity (elevation in bilirubin, AST, ALT)
- If elevated bilirubin and/or transaminitis per protocol-specific criteria, consider holding asparaginase until improvement, then resume with very close monitoring.
- Calaspargase, when combined with chemotherapy, has been associated with severe, life-threatening, and potentially fatal instances of SOS. Calaspargase should not be administered to patients with severe hepatic impairment.[32]

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SUPPORTIVE CARE
Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel

Inotuzumab Ozogamicin:

- **Cytoreduction should be considered for those with absolute blast count ≥10,000 cells per microliter. On clinical trial, hydroxyurea or a combination of steroids and vincristine was used.**
- **Myelosuppression is common, and prophylactic antimicrobial strategies in accordance with institutional practice should be used.**
- **Liver enzymes, and particularly bilirubin, should be closely monitored, as SOS (or VOD) may occur, particularly among patients at higher risk (including those who are status post-allogeneic HCT, those whose treatment extends beyond two cycles, and/or those who previously received or will receive double-alkylator conditioning prior to allogeneic HCT). For those patients receiving inotuzumab ozogamicin as a bridge to allogeneic HCT, double-alkylator conditioning is strongly discouraged. Ursodiol may be considered for SOS prophylaxis.**
- **Consider defibrotide for patients who develop SOS related to inotuzumab ozogamicin toxicity.[33,34]**

Blinatumomab:

- **Cytoreduction should be considered for those with absolute blast count ≥15,000 cells per microliter, as high tumor burden may increase the risks of toxicity. On clinical trial, steroids were most commonly used.**
- **Patients should be monitored for cytokine release syndrome (CRS), a systemic inflammatory condition characterized by fever or hypothermia, that may progress to hypotension, hypoxia, and/or end organ damage. Infusion should be held with consideration for steroids and/or vasopressors for those with severe symptoms in accordance with manufacturer guidelines and prescriber information. Consider tocilizumab for patients with severe CRS.**
- **Because concurrent severe infection may mimic CRS, an evaluation for underlying infection and consideration of empiric antimicrobial therapy in accordance with institutional practice should be performed.**
- **Patients should be monitored for neurologic toxicity, which may include confusion, word-finding difficulty, somnolence, ataxia, tremor, seizure, or syncope. Infusion should be held with consideration of steroids for those with severe symptoms in accordance with manufacturer guidelines and prescribing information, and restarted (once symptoms have sufficiently improved) with dosing adjustments as per manufacturer guidelines and prescribing information.**

Tisagenlecleucel:

- **Severe CRS and/or neurologic toxicity may accompany therapy, and should be managed in accordance with the manufacturer Risk Evaluation and Mitigation Strategies (REMS) program, to include tocilizumab (preferred for CRS) and steroids (preferred for tocilizumab-refractory CRS and/or neurologic toxicity).**
- **Prophylaxis with anti-seizure medication may be considered during the first month after chimeric antigen receptor [CAR] T-cell infusion.**
- **Severe neutropenia, T-cell depletion, and B-cell aplasia can occur, for which growth factor, prophylactic antimicrobial therapy, and IV immunoglobulin (Ig) administration should be considered, in accordance with institutional practice (NCCN Guidelines for Management of Immunotherapy-Related Toxicities).**

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE
REFERENCES

[1] Sulis ML, Blonquist TM, Stevenson KE, et al. Effectiveness of antibacterial prophylaxis during induction chemotherapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2018;65:e26952.
[2] Alexander S, Fisher BT, Gaur AH, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: A randomized clinical trial. JAMA 2018;320:995-1004.
[3] Egan G, Robinson PD, Martinez JPD, et al. Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: A systematic review of randomized trials. Cancer Med 2019;8:4536-4546.
[4] Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation. Clin Infect Dis 2020;71:226-236.
[5] van Schie RM, Brüggemann RJ, Hoogerbrugge PM, te Loo DM. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother 2011;66:1853-1856.
[6] Brüggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis 2009;48:1441-1458.
[7] Moriyama B, Henning SA, Leung J, et al. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses 2012;55:290-297.
[8] Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline update. J Clin Oncol 2018;36:1443-1453.
[9] Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318.
[10] Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018;23:52-61.
[11] Feijen EAM, Leisenring WM, Stratton KL, et al. Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. JAMA Oncol 2019;5:864-871.
[12] Mostoufi-Moab S, Halton J. Bone morbidity in childhood leukemia: epidemiology, mechanisms, diagnosis, and treatment. Curr Osteoporos Rep 2014;12:300-312.
[13] Kaste SC, Qi A, Smith K, et al. Calcium and cholecalciferol supplementation provides no added benefit to nutritional counseling to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer 2014;61:885-893.
[14] Leblicq C, Laverdiere C, Decarie, et al. Effectiveness of pamidronate as treatment of symptomatic osteonecrosis occurring in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer 2013;60:741-747.
[15] Vrooman LM, Gotti G, Puligandla M, et al. Vitamin D deficiency in childhood acute lymphoblastic leukemia/lymphoma: Results of DFCI 11-001. Pediatr Blood Cancer 2019. ASPHO abstract 028.
[16] Brackett J, Schafer ES, Leung DH, et al. Use of allopurinol in children with acute lymphoblastic leukemia to reduce skewed thiopurine metabolism. Pediatr Blood Cancer 2014;61:1114-1117.
[17] Miller MB, Brackett J, Schafer ES, Rau RE. Prevention of mercaptopurine-induced hypoglycemia using allopurinol to reduce methylated thiopurine metabolites. Pediatr Blood Cancer 2019;66:e27577.
[18] Cohen G, Cooper S, Sison EA, et al. Allopurinol use during pediatric acute lymphoblastic leukemia maintenance therapy safely corrects skewed 6-mercaptopurine metabolism, improving inadequate myelosuppression and reducing gastrointestinal toxicity. Pediatr Blood Cancer 2020;67:e28360.
[19] Abla O, Angelini P, Di Giuseppe G, et al. Early complications of hyperleukocytosis and leukapheresis in childhood acute leukemias. J Pediatr Hematol Oncol 2016;38:111-117.
[20] Nguyen R, Jeha S, Zhou Y, et al. The role of leukapheresis in the current management of hyperleukocytosis in newly diagnosed childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2016;63:1546-1551.
[21] Jacola LM, Partanen M, Lemiere J, et al. Assessment and monitoring of neurocognitive function in pediatric cancer. J Clin Oncol 2021;39:1696-1704.
[22] Annett RD, Patel SK, Phipps S. Monitoring and assessment of neuropsychological outcomes as a standard of care in pediatric oncology. Pediatr Blood Cancer 2015;62 Suppl 5:S460-513.
[23] Maese LD, Loh ML, Choi MR, et al. Recombinant Erwinia asparaginase (JZP458) in acute lymphoblastic leukemia: results from the phase 2/3 AALL1931 study. Blood 2023;141:704-712.
[24] Asselin B, Riazzaru C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma 2015;56:2273-2280.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE
REFERENCES

[25] Salzer W, Bostrom B, Messinger Y, et al. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. Leuk Lymphoma 2018;59:1797-1806.
[26] Burke MJ, Rheingold SR. Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. Leuk Lymphoma 2017;58:540-551.
[27] Cooper SL, Young DJ, Bowen CJ, et al. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. Pediatr Blood Cancer 2019;66:e27797.
[28] Wolthers BO, Frandsen TL, Baruchel A, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study. Lancet Oncol 2017;18:1238-1248.
[29] Kearney SL, Dahlberg SE, Levy DE, et al. Clinical course and outcome in children with acute lymphoblastic leukemia and asparaginase-associated pancreatitis. Pediatr Blood Cancer 2009;53:162-167.
[30] Sibson KR, Biss TT, Furness CL, et al. BSH Guideline: management of thrombotic and haemostatic issues in paediatric malignancy. Br J Haematol 2018;180:511-525.
[31] Bhatt MD, Parmar N, Fowler JA, et al. Feasibility and safety of delivering full-dose anticoagulation therapy in children treated according to Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium therapy protocols. Pediatr Blood Cancer 2019;66:e27483.
[32] Prescribing information for calaspargase pegol-mknl injection, for intravenous use 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761102s013lbl.pdf. Accessed April 25, 2024.
[33] Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant 2018;53:449-456.
[34] Giglio F, Xue E, Greco R, et al. Defibrotide prophylaxis of sinusoidal obstruction syndrome in adults treated with inotuzumab ozogamicin prior to hematopoietic stem cell transplantation. Front Oncol 2022;12:933317.

Note: All recommendations are category 2A unless otherwise indicated.

EVALUATION AND TREATMENT OF EXTRAMEDULLARY INVOLVEMENT

- The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse or seeding of bone marrow.
- CNS involvement should be evaluated by LP at the appropriate timing:
  - Timing of LP should be consistent with the chosen treatment regimen.
  - Pediatric regimens typically include LP at the time of diagnostic workup.
  - The Panel recommends that LP be done concurrently with initial IT therapy.
- Classification of CNS status:
  - CNS-1: No lymphoblasts in CSF regardless of WBC count.
  - CNS-2: WBC count <5/μL in CSF with presence of lymphoblasts.
  - CNS-3: WBC count ≥5/μL in CSF with presence of lymphoblasts, or clinical symptoms (such as facial nerve palsy, brain/eye involvement, CNS hemorrhage, or hypothalamic syndrome).
  - If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC count is ≥5/μL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.
- All patients with ALL should receive CNS prophylaxis. Although the presence of CNS-3 involvement at the time of diagnosis is uncommon (about 3%–7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.
- CNS-directed therapy may include cranial irradiation, IT chemotherapy (eg, MTX, cytarabine, corticosteroids), and/or systemic chemotherapy (eg, high-dose MTX, cytarabine, pegaspargase/calaspargase). Cranial RT is often avoided in favor of IT chemotherapy and systemic therapy when possible due to concern for late effects.
- The use of cranial radiation for patients with ALL with CNS-3 disease at diagnosis varies based on protocol. Patients should be treated according to their protocol.
  - If cranial radiation is done, recommended dosing is 18 Gy at 1.5–1.8 Gy/fraction.
  - Timing of cranial radiation is less clear for patients with T-ALL. It is recommended that a specific treatment protocol be followed in its entirety.
- TBI is given for select patients with high-risk disease receiving HCT; in patients who require cranial irradiation and TBI, cranial RT should be given as a boost before or after TBI.
  - See Conditioning Regimen in the Principles of Hematopoietic Cell Transplant (PEDALL-K 3 of 5)
- The entire brain and posterior half of the globe should be included in the radiation field. The inferior border should include C2. Note that areas of the brain targeted by the radiation field in the management of ALL are different from areas targeted for brain metastases of solid tumors.
- Adequate systemic therapy should be given in the management of isolated CNS relapse. Cranial irradiation to 18 Gy is recommended, with timing depending on treatment protocol.
- Patients receiving cranial irradiation should be monitored for neurocognitive deficits and academic delays, neuroendocrine deficits, secondary malignancy, cataracts, and other late effects.
  - See COG Long-Term Follow-up Guidelines: http://www.survivorshipguidelines.org
- 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 radiation to the testes in the scrotal sac, with timing depending on the particular treatment protocol. Testicular total dose should be 24 Gy in 2.0 Gy/fraction.

Note: All recommendations are category 2A unless otherwise indicated.

SPECIAL CONSIDERATIONS FOR PATIENTS WITH DOWN SYNDROME AND INFANTS[1,2,3]

Patients with Down syndrome and B-ALL/LL have increased sensitivity to chemotherapy, and significantly increased risk of morbidity and treatment-related mortality due to infectious complications during periods of neutropenia. Infants with ALL also experience significant treatment-related complications and toxicities. The use of protocols that have demonstrated safety in these populations is recommended. During treatment of these populations, the following supportive care measures should be considered.

Common Considerations

- During times of profound myelosuppression (ie, induction, consolidation, delayed intensification) monitoring in the hospital is strongly recommended until afebrile, clinically stable, and showing signs of bone marrow recovery.
- During periods of myelosuppression:
  - Consider antibacterial prophylaxis against Gram-positive and Gram-negative organisms (eg, broad-spectrum antibiotics).
  - Consider antifungal prophylaxis (eg, echinocandin or azole).
    - ◊ Use caution with azole agents given with vincristine as it may increase the risk of neurotoxicity.
  - Recommend infectious disease collaboration if considering antimicrobial and/or antifungal prophylaxis to determine the best agent given altered toxicity and effectiveness for many agents in infants.
- Monitor IgG levels monthly and recommend IVIG replacement for levels <400 mg/dL.
- Aggressively manage neutropenic fever with hospitalization, blood cultures, and immediate institution of broad-spectrum IV antibiotics covering both Gram-positive and Gram-negative organisms. Empiric Gram-positive coverage should include an antibiotic appropriate for the treatment of *viridans streptococci* (eg, vancomycin or clindamycin), and both Gram-positive and Gram-negative coverage should be adjusted appropriately for local patterns of antibiotic resistance.
- During times of neutropenic fever, strongly consider antifungal therapy in the absence of clinical response to antibiotics after 3–5 days.
- In patients with neutropenic fever who are very ill or who experience lack of response to antibiotic/antifungal therapy:
  - Consider stress dose steroids.
  - Consider filgrastim (G-CSF).

Down Syndrome Considerations

- If high toxicity from chemotherapy occurs, consider lower chemotherapy doses and/or increased intensity of leucovorin rescue.
- An intermediate dose of MTX (eg, 500 mg/m^2) can be used instead of high-dose MTX.
- Patients ≥10 years of age receiving blinatumomab should receive seizure prophylaxis for the duration of the blinatumomab cycle.

Infant Considerations

- Respiratory syncytial virus (RSV) prophylaxis with a single dose of nirsevimab IM or monthly palivizumab IM should be considered before the onset of the RSV season.
  - RSV treatment with inhaled ribavirin is recommended.
- Aggressive nutritional support should be initiated at diagnosis and continued throughout therapy due to high risk of protein-calorie malnutrition.
- Strongly recommend barrier techniques and frequent diaper changes. Consider placement of a Foley catheter during administration and urinary excretion of daunorubicin and high-dose MTX due to high risk of skin ulceration.
- In infants with extensive mucositis or diaper dermatitis:
  - Total parenteral nutrition (TPN) should be strongly considered due to increased risk of necrotizing enterocolitis (NEC) and intestinal perforation.
  - Strongly consider broad-spectrum antibiotics, antifungal therapy, and/or antiviral therapy based on clinical evaluation.

[1] Whitlock JA. Down syndrome and acute lymphoblastic leukaemia. Br J Haematol 2006;135:595-602.
[2] Izraeli S, Vora A, Zwaan CM, et al. How I treat ALL in Down's syndrome: pathobiology and management. Blood 2014;123:35-40.
[3] Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood 2019;133:205-214.

Note: All recommendations are category 2A unless otherwise indicated.

RISK STRATIFICATION DEFINITIONS[a]
INITIAL RISK GROUP STRATIFICATION

	Low Risk	Standard Risk	High Risk	Very High Risk
Children's Oncology Group (COG) (B-ALL only)	N/A	Aged 1 to <10 y and WBC count <50,000/mm^3	• Aged ≥10 y and/or WBC count ≥50,000/mm^3 • CNS-3/testicular disease[b] • *BCR::ABL1* is considered HR feature (PEDALL-5) • Steroid pretreatment	N/A
St. Jude Consortium	• B-ALL with DNA index ≥1.16, *ETV6::RUNX1* fusion OR • B-ALL with age 1–9.9 y and presenting WBC count <50,000/mm^3 • Absence of SR features	• B-ALL with age ≥10 years or presenting WBC count ≥50,000/mm^3 (not DNA index ≥1.16 or *ETV6::RUNX1* fusion) OR • B-ALL with the following features: ▸ CNS-3 status[b] ▸ Overt testicular leukemia ▸ Adverse genetic features[c] OR • T-ALL	N/A	
Dana-Farber Cancer Institute (DFCI) ALL Consortium[d]	N/A	• B-ALL • Aged 1 to <15 y and WBC count <50,000/mm^3 • Absence of HR/VHR adverse biologic features	• T-ALL • iAMP21 • *BCR::ABL1* is considered HR feature (PEDALL-5)	• *IKZF1* deletion • *KMT2A* rearrangement • Low hypodiploidy or near haploidy (ie, hypodiploidy <40 chromosomes) • *TCF3::HLF* (t[17;19])

Risk groups: standard risk (SR), high risk (HR), very high risk (VHR).

See PEDALL-F (2 of 3) for Post-Induction Therapy Risk Stratification Definitions

[a] For T-ALL risk stratification, see PEDALL-6. For infant risk stratification, see PEDALL-7.
[b] See Evaluation and Treatment of Extramedullary Involvement (PEDALL-D) for definition of CNS involvement.
[c] Adverse genetic risk features include *BCR::ABL1* fusion/t(9;22); *TCF3::PBX1* fusion/t(1;19); *KMT2Ar*; hypodiploidy; iAMP21; or *MEF2D* fusion.
[d] At Day 10 of Induction IA, based on results of FISH, karyotype, and targeted fusion sequencing panel, "Initial Risk Group" is assigned.

Note: All recommendations are category 2A unless otherwise indicated.

RISK STRATIFICATION DEFINITIONS[a]
POST-INDUCTION THERAPY RISK GROUP STRATIFICATION

	Favorable Risk	Average Risk	High Risk
COG[e] Initial Standard Risk (B-ALL only)	• NCI SR, favorable cytogenetics,[f] and CNS-1 or CNS-2[b] • Day 8 peripheral blood MRD <1%, Day 29 end of induction (EOI) bone marrow MRD <0.01%	• NCI SR, favorable cytogenetics,[f] and CNS-1 or CNS-2[b] • Day 8 peripheral blood MRD >1%, EOI bone marrow MRD <0.01% (*ETV6::RUNX1*), OR <0.1% DT OR • NCI SR • Neutral cytogenetics[g] • CNS-1[b] • EOI bone marrow MRD <0.01%	• NCI SR • CNS-2[b] • Neutral cytogenetics[g] • EOI bone marrow MRD (positive or negative) OR • NCI SR • CNS-1 or CNS-2[b] • Unfavorable cytogenetics[f] • EOI bone marrow MRD (positive or negative) OR • NCI SR • CNS-1 or CNS-2[b] • Any cytogenetics • EOI bone marrow MRD >0.01% or >0.1% (DT)
COG[e] Initial High Risk (B-ALL only)	• NCI HR but <10 y • Favorable cytogenetics[f] • CNS-1[b] • EOI bone marrow MRD <0.01%	• N/A	• NCI HR • CNS-1, CNS-2, or CNS-3[b] • Any cytogenetics • EOI bone marrow MRD (positive or negative) OR • NCI SR • CNS-3[b] or testicular disease • Any cytogenetics • EOI bone marrow MRD (positive or negative)

Risk groups: standard risk (SR), high risk (HR).

[a] For T-ALL risk stratification, see PEDALL-6. For infant risk stratification, see PEDALL-7.
[b] See Evaluation and Treatment of Extramedullary Involvement (PEDALL-D) for definition of CNS involvement.
[e] EOI risk assessment occurs after day 29 of bone marrow MRD assessment. MRD is determined by multiparameter flow cytometry.
[f] Genetic Risk Groups for B-ALL (PEDALL-B).
[g] Neither favorable nor unfavorable features. See Genetic Risk Groups for B-ALL (PEDALL-B).

Continued

Note: All recommendations are category 2A unless otherwise indicated.

RISK STRATIFICATION DEFINITIONS[a]
POST-INDUCTION THERAPY RISK GROUP STRATIFICATION

	Low Risk	Standard Risk	High Risk	Very High Risk
St. Jude Consortium	• B-ALL with DNA index ≥1.16, *ETV6::RUNX1* fusion OR • B-ALL with age 1–9.9 y with presenting WBC count <50,000/mm^3 AND • Absence of SR or HR features	B-ALL with age ≥10 y or presenting WBC count ≥50,000/mm^3 (not DNA index ≥1.16 or *ETV6::RUNX1* fusion) OR B-ALL with the following features: • CNS-3 status[b] • Overt testicular leukemia (evidenced by ultrasonogram) • Adverse genetic features[c] • Poor early response (≥1% MRD on Day 15 of remission induction or ≥0.01% MRD at the end of remission induction) OR • T-ALL • Absence of HR features	• MRD ≥1% at the end of remission induction • MRD ≥0.1% at the end of early intensification and inadequate decrease in MRD levels after 1–2 courses of consolidation treatment • Increasing MRD level at ≥0.01% after remission induction • Hypodiploid and MRD ≥0.01% at the end of remission induction • Re-emergence of leukemic lymphoblasts by MRD at ≥0.01% in patients previously MRD negative • Persistently detectable MRD at ≥0.01% after reinduction II	
DFCI ALL Consortium[h]	Initial SR with low MRD (<10^{-4}) at end-induction	Initial HR with low MRD (<10^{-4}) at end-induction	• Initial LR OR initial HR • High end-induction MRD (≥10^{-4}) but low MRD (<10^{-3}) end-IB phase	Any of the following: • Initial VHR biology regardless of MRD • Any initial risk group with high end-IB phase MRD (≥10^{-3}) • Patients with M2 marrow at end-induction but in morphologic CR at end-IB phase (regardless of end-IB phase MRD)

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

[a] For T-ALL risk stratification, see PEDALL-6. For infant risk stratification, see PEDALL-7.
[b] See Evaluation and Treatment of Extramedullary Involvement (PEDALL-D) for definition of CNS involvement.
[c] Adverse genetic risk features include *BCR::ABL1* fusion/t(9;22); *TCF3::PBX1* fusion/t(1;19); *KMT2Ar*; hypodiploidy; iAMP21; or *MEF2D* fusion.
[h] DFCI Final Risk Group is assigned based on MRD at end-induction (TP1) and end-IB phase (TP2). MRD is assessed by NGS assay (assessing *IgH, IgK/L, TCRβ,* and *TCRγ* clonal rearrangements that were identified in diagnostic specimen).

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY[a,b,c]

Regimens for *BCR::ABL1*-Negative B-ALL

Regimen Components and Risk Stratification Applications on PEDALL-G (3 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• Standard arm of COG AALL1731 regimen[b,d,e] (based on COG AALL0932 regimen[1]) • Standard arm of COG AALL1732 regimen[b,d,e] (based on COG AALL1131 regimen[2,3,4]) • DFCI ALL Protocol 16-001[e] (based on DFCI ALL protocol 11-001[5,6]) • Total Therapy XVII regimen[e] (based on Total Therapy XVI regimen[5])

Regimens for *BCR::ABL1*-Like B-ALL

Regimen Components and Risk Stratification Applications on PEDALL-G (4 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• COG AALL1131 regimen[b,d,2,3,4] + dasatinib[7] • COG AALL1521 regimen[b,d] ± ruxolitinib[e] • DFCI-ALL Protocol 16-001 + dasatinib[e] • Total Therapy XVII regimen + dasatinib[8] • Total Therapy XVII regimen ± ruxolitinib[e,8]

Regimens for *BCR::ABL1*-Positive B-ALL

Regimen Components and Risk Stratification Applications on PEDALL-G (5 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• Standard arm of COG AALL1631[b,d,e] (based on COG AALL1122/EsPhALL regimen): imatinib or dasatinib[e]; combined with a high-risk backbone of the Berlin-Frankfurt-Münster (BFM) regimen[9] • COG AALL0622 regimen[10]: dasatinib; post-induction intensified chemotherapy based on POG/CCG regimens[11,12] • Total Therapy XVII regimen plus dasatinib on day 15[e]

Continued

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; IT triple therapy [ITT] with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] Ongoing clinical trials from multi-institutional or cooperative group studies.

Note: All recommendations are category 2A unless otherwise indicated.

References

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

Regimens for T-ALL[f,g,h,i]

Regimen Components and Risk Stratification Applications on PEDALL-G (6 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• COG AALL1231 regimen[b,d,j,13] • COG AALL0434 regimen[b,d,j,14] • DFCI-ALL Protocol 16-001[e] (based on DFCI ALL protocol 11-001[5,6]) • SJCRH regimen based on Total Therapy XVII Regimen[e]

Regimens for Infant ALL[c]

Regimen Components and Risk Stratification Applications on PEDALL-G (6 of 13)

Preferred	Other Recommended Regimens
• Clinical trial	• Interfant regimens ± blinatumomab[15-19]

[a] All regimens include CNS prophylaxis with systemic therapy (MTX, cytarabine) and/or IT therapy (IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] Ongoing clinical trials from multi-institutional or cooperative group studies.
[f] Incorporation of nelarabine is reasonable post-induction for all patients with T-ALL, especially those who are MRD+ or have CNS disease at diagnosis. Strongly consider including nelarabine in post-induction therapy for patients who do not achieve CR after induction therapy.
[g] CNS-directed therapy with IT chemotherapy is recommended during all phases of therapy in all patients.
[h] Cranial radiation should be strongly considered for CNS-3 patients and is reasonable for other patients with high-risk T-ALL.
[i] The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[j] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,c,k]

The regimen components outlined in these tables represent the most recently published studies.

BCR::ABL1-Negative ALL	Induction	Consolidation
COG AALL0932 regimen[b,d,1,20] (SR)	SR arm: dexamethasone, vincristine, pegaspargase/calaspargase[l]; IT therapy: cytarabine then MTX	SR-low/avg arm: mercaptopurine,[b] vincristine; IT therapy: MTX
		SR-avg/high arm: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase[l]; IT therapy: MTX
COG AALL1131 regimen[b,d,2,3,4,21] (HR)	HR arm: prednisone or dexamethasone, vincristine, pegaspargase/calaspargase,[l] daunorubicin; IT therapy: cytarabine then MTX	HR arm: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase[l]; IT therapy: MTX
DFCI ALL Protocol 11-001 regimen[5,6]	Prednisone, vincristine, pegaspargase/calaspargase,[l] doxorubicin, IT cytarabine, then IT triple therapy (ITT)[a]	SR arm: high-dose MTX, vincristine, pegaspargase/calaspargase,[l] mercaptopurine,[b] dexamethasone; IT therapy: MTX or ITT[a]
		HR/VHR[m] arms: high-dose MTX, vincristine, pegaspargase/calaspargase,[l] mercaptopurine,[b] dexamethasone, doxorubicin, dexrazoxane; IT therapy: MTX or ITT[a]
Total Therapy XVI regimen[22]	Prednisone, vincristine, daunorubicin, pegaspargase /calaspargase,[l] cyclophosphamide, cytarabine, mercaptopurine (6-MP),[b] ITT[a]	LR arm: high-dose MTX, mercaptopurine,[b] ITT[a]
		SR/HR arm: high-dose MTX, mercaptopurine,[b] ITT[a]

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

[a] All regimens include CNS prophylaxis with systemic therapy (MTX, cytarabine) and/or IT therapy (IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[k] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see References.
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[m] VHR arm also includes cyclophosphamide, cytarabine, and etoposide.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,c,k]

BCR::ABL1-like B-ALL	Induction	Consolidation
COG AALL1131 regimen + dasatinib[b,d,e,2,4,7]	Vincristine, dexamethasone or prednisone, daunorubicin, pegaspargase/calaspargase[l]; IT therapy: cytarabine then MTX	For *CRLF2*- with *ABL* class kinase fusion: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase,[l] + dasatinib; IT therapy: MTX
COG AALL1521 regimen ± ruxolitinib[b,d,e,23]		For *CRLF2*+ or *CRLF2*- with *JAK2* fusions, *EPOR* rearrangements, *SH2B3* alterations, *IL7R* insertions/deletions: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase,[l] + ruxolitinib; IT therapy: MTX
DFCI-ALL Protocol 16-001 regimen + dasatinib[e,5,6]	For *ABL* class kinase fusion: DFCI-ALL Protocol 16-001 VHR arm: dexamethasone, vincristine, pegaspargase/calaspargase,[l] doxorubicin, cyclophosphamide, cytarabine, mercaptopurine[b] + dasatinib; IT therapy: cytarabine then ITT[a] or MTX	For *ABL* class kinase fusion: high-dose MTX, mercaptopurine,[b] dexamethasone, vincristine, cyclophosphamide, etoposide, high-dose cytarabine, pegaspargase/calaspargase,[l] doxorubicin + dasatinib; IT therapy: MTX
Total Therapy XVII regimen + dasatinib[8] or Total Therapy XVII regimen ± ruxolitinib[e,8]	For *ABL* class kinase fusion: Total Therapy XVII regimen + dasatinib[20]	For *ABL* class kinase fusion: Total Therapy XVII regimen (either LR or SR/HR arm) + dasatinib[7]
	For mutations associated with JAK-STAT pathway activation: Total Therapy XVII regimen ± ruxolitinib	For mutations that are associated with JAK-STAT pathway activation: Total Therapy XVII regimen (SR/HR arm) ± ruxolitinib

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

[a] All regimens include CNS prophylaxis with systemic therapy (MTX, cytarabine) and/or IT therapy (IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] Ongoing clinical trials from multi-institutional or cooperative group studies.
[k] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see References.
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,c,k]

BCR::ABL1-positive ALL	Induction	Consolidation
Standard arm of COG AALL1631[b,d,e] (based on COG AALL1122/EsPhALL regimen)	EsPhALL backbone (cyclophosphamide, mercaptopurine,[b] cytarabine, MTX) + imatinib[9]/ dasatinib[e]	Dexamethasone, vincristine, MTX, ifosfamide, cytarabine, pegaspargase/calaspargase,[l] cyclophosphamide, prednisone, daunorubicin, 6-TG,[b] imatinib/dasatinib
		HR patients (defined by high MRD after IB phase and/or after HR consolidation blocks): allogeneic HCT in CR1
COG AALL0622 regimen + dasatinib[10]	• Prednisone or dexamethasone, vincristine, pegaspargase/calaspargase,[l] daunorubicin or doxorubicin; IT therapy: MTX, hydrocortisone, cytarabine • Include TKI (imatinib or dasatinib) once *BCR::ABL* fusion identified or by Day 15 of induction[13,15]	High-dose MTX, vincristine, daunorubicin, cyclophosphamide, pegaspargase/calaspargase,[l] dexamethasone, cytarabine, dasatinib; ITT[a]
		HR patients (defined by high MRD at end-induction [≥1%] or after consolidation 2 [≥0.01%]): allogeneic HCT in CR1
Total Therapy XVII regimen[e] + dasatinib	Total XVII regimen: prednisone, vincristine, daunorubicin, pegaspargase/calaspargase,[l] cyclophosphamide, cytarabine, mercaptopurine,[b] ITT[a]; dasatinib on Day 15	LR arm: high-dose MTX, mercaptopurine,[b] dasatinib; ITT[a]
		SR/HR arm: high-dose MTX, pegaspargase/calaspargase,[l] mercaptopurine,[b] dasatinib; ITT[a]

Risk groups: low risk (LR), standard risk (SR), high risk (HR).

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).

[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.

[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673. Topp MS, et al. J Clin Oncol 2011;29:2493-2498. Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.

[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.

[e] Ongoing clinical trials from multi-institutional or cooperative group studies.

[k] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see References.

[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,i,k]

T-ALL	Induction	Consolidation
COG AALL1231 regimen[b,d,n,13]	Dexamethasone, vincristine, pegaspargase/calaspargase,[l] daunorubicin[n]; IT therapy: cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase/calaspargase,[l] vincristine[n]; IT therapy: MTX
COG AALL0434 regimen[b,d,14]	Prednisone, vincristine, pegaspargase/calaspargase,[l] daunorubicin; IT therapy: cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase/calaspargase,[l] vincristine, nelarabine; IT therapy: MTX
DFCI ALL 16-001[e] based on DFCI-ALL Protocol 11-001	Dexamethasone, vincristine, pegaspargase/calaspargase,[l] doxorubicin; IT therapy: cytarabine then ITT[a]	Cyclophosphamide, cytarabine, mercaptopurine,[b] IT therapy: MTX or ITT[a]
SJCRH regimen based on Total Therapy XVII regimen[e]	Prednisone, vincristine, pegaspargase/calaspargase,[l] cyclophosphamide, daunorubicin, mercaptopurine,[b] cytarabine[o]; ITT[a]	High-dose MTX, mercaptopurine,[b] pegaspargase/calaspargase[l]; ITT[a]

Infant ALL	Induction	Consolidation[p,q]
Interfant regimens[c,15-17]	Prednisone, dexamethasone, vincristine, cytarabine, daunorubicin, pegaspargase/calaspargase,[l] MTX; IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone) ± blinatumomab (*KMT2A* rearranged)	Intermediate-risk and HR arms: Chemotherapy consolidation: cyclophosphamide, mercaptopurine,[b] cytarabine, MTX, prednisone, pegaspargase/calaspargase[l,15] Post-consolidation, and HR arm not undergoing HCT: Dexamethasone, 6-TG,[b] vincristine, cytarabine, daunorubicin, pegaspargase/calaspargase,[l] cytarabine, prednisone, cyclophosphamide, MTX, mercaptopurine[b,15]
		LR arm: Identical approach as pediatric ALL risk-stratified chemotherapy based on genetics and MRD response (see PEDALL-J) or interfant consolidation (see above)

Risk groups: low risk (LR), high risk (HR).

Footnotes on PEDALL-G 6A

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).

[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.

[c] Blinatumomab may be incorporated into frontline therapy as a postremission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673; Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. Blood 2022;140(Suppl):Abstract LBA-1. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.

[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.

[e] Ongoing clinical trials from multi-institutional or cooperative group studies.

[i] The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).

[k] For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; IM I; and interim maintenance I and II, see References.

[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.

[n] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.

[o] Patients treated on the high-risk arm of St. Jude Children's Research Hospital (SJCRH) TXVII receive an intensification phase after induction prior to consolidation.

[p] IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone).

[q] For patients with MRD ≥5x10^{-4} at the EOI, myeloid type consolidation therapy (eg, ADE/MAE) can be considered (Stutterheim J, et al. J Clin Oncol 2021;39:652-662).

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[r,s]

BCR::ABL1-negative ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• UKALL R3 regimen[24] • COG AALL01P2 regimen[25] • ALL-REZ BFM 90 regimen[26] • COG AALL07P1 regimen[27] • COG AALL1331 regimen[t,28] • Blinatumomab[t,29-32] • Revumenib (*KMT2Ar* R/R *BCR::ABL*1-negative ALL)[u,33] • Tisagenlecleucel (refractory disease or ≥2 relapses)[v,w,34] ▸ Consider participation in a clinical trial for relapsed/refractory B-ALL targeting CD19, CD22, or other antigens, or for relapse following HCT ▸ Consider participation in a clinical trial with humanized or fully human CAR T-cell binding domains • Inotuzumab ozogamicin ± mini-hyper-CVD (cyclophosphamide, vincristine, dexamethasone)[x,35,36,37] • Clofarabine-containing regimens (eg, clofarabine, cyclophosphamide, etoposide)[38,39] • Fludarabine-based regimens: FLAG-IDA (fludarabine, cytarabine, G-CSF ± idarubicin)[40] • High-dose cytarabine-based regimens (eg, high-dose cytarabine, pegaspargase/calaspargase[l])[41] • Venetoclax-containing regimen: eg, venetoclax, vincristine, pegaspargase/calaspargase,[l] prednisone or dexamethasone[42]

Continued

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).

[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.

[r] Principles of Hematopoietic Cell Transplant (PEDALL-K).

[s] Guidelines for managing specific sites of extramedullary relapse (ie, testicular) are included in the protocols listed.

[t] Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.

[u] Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

[v] Tisagenlecleucel is associated with CRS, including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under REMS. For details, see: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

[w] Principles of Systemic Therapy - Immunotherapy (PEDALL-G [10 of 13]).

[x] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic SOS and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761040s003lbl.pdf. Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[r,s]
BCR::ABL1-positive ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• The regimens listed on PEDALL-G (7 of 13) for *BCR::ABL1*-negative ALL may be considered for *BCR::ABL1*-positive ALL with TKIs listed below.[y] ▸ TKIs to consider: ◊ Dasatinib ◊ Imatinib ◊ Ponatinib (category 2B) • Blinatumomab (TKI intolerant/refractory)[t,30-32,43] • Tisagenlecleucel (TKI intolerant/refractory disease or relapse post-HCT)[v,w,34] • Inotuzumab ozogamicin (TKI intolerant/refractory)[x,35,36] • Venetoclax-containing regimen: eg, venetoclax, vincristine, pegaspargase/calaspargase,[l] prednisone or dexamethasone[42]

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).

[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.

[r] Principles of Hematopoietic Cell Transplant (PEDALL-K).

[s] Guidelines for managing specific sites of extramedullary relapse (ie, testicular) are included in the protocols listed.

[t] Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557Orig1s028Correctedlbl.pdf.

[v] Tisagenlecleucel is associated with CRS, including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under REMS. For details, see: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

[w] Principles of Systemic Therapy - CD19-targeting CAR T-Cell Therapy (PEDALL-G [10 of 13]).

[x] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic SOS and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761040s003lbl.pdf. Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.

[y] HCT should be considered after CR is achieved.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[r,s]
T-ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• Nelarabine-containing regimen: eg, nelarabine, cyclophosphamide, and etoposide[44] • Bortezomib-containing regimen: eg, bortezomib, vincristine, doxorubicin, pegaspargase/calaspargase,[l] and prednisone or dexamethasone[27] • UKALL R3 Block 1: dexamethasone, mitoxantrone, pegaspargase/calaspargase,[l] and vincristine[24] • BFM Intensification Block 1: high-dose MTX, high-dose cytarabine, dexamethasone, vincristine, pegaspargase/calaspargase,[l] and cyclophosphamide[26] • Venetoclax-containing regimen: eg, venetoclax, vincristine, pegaspargase/calaspargase,[l] and prednisone or dexamethasone[42,45] • Daratumumab-containing regimen: eg, daratumumab, vincristine, pegaspargase/calaspargase,[l] doxorubicin, and prednisone or dexamethasone[z] • Revumenib (*KMT2Ar* R/R T-ALL)[u,33] • Consider TKI-based regimen if *ABL*-class translocation

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[r] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[s] Guidelines for managing specific sites of extramedullary relapse (ie, testicular) are included in the protocols listed.
[u] Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
[z] Clinical trial recently completed and full manuscript is pending publication [Hogan LE, et al. J Clin Oncol 2022;40(Suppl):Abstract 10001].

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF SYSTEMIC THERAPY
CD19-targeting CAR T-Cell Therapy

Tisagenlecleucel[v]

- **The FDA label indication for the use of tisagenlecleucel is for patients <26 years of age and CD19+ B-ALL that is refractory or with ≥2 relapses. Of note, there has been limited published experience with the use of CAR T-cell therapy in infants <12 mo of age.**
  - **Relapse includes medullary and/or extramedullary disease. CAR T cells have shown activity against extramedullary disease.**
- **Prior to apheresis for T-cell collection, consider avoidance of agents that may significantly impact the absolute lymphocyte count and/or T-cell function.**
- **The following lymphodepletion regimen is suggested prior to infusion of tisagenlecleucel (with alternatives allowed):**
  - **Fludarabine (30 mg/m^2 IV daily for 4 days)**
  - **Cyclophosphamide (500 mg/m^2 IV daily for 2 days starting with first dose of fludarabine)**
  - **Infuse tisagenlecleucel 2 to 14 days after completion of the lymphodepleting chemotherapy. Recommend evaluation of response 28 days after tisagenlecleucel infusion.**
- **Recommendations for toxicity management of CRS or neurotoxicity are included in the tisagenlecleucel package insert. Tocilizumab and corticosteroids are the main options used to manage CRS and neurotoxicity.[46,47] See the American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT) consensus grading[48] and CARTOX management guidelines[49] for detailed CAR T-cell toxicity grading, monitoring, and management.**
- **Hypogammaglobulinemia: Monitor IgG levels after treatment with tisagenlecleucel and replace with IV or subcutaneous Ig per standard guidelines (generally accepted to replete for IgG <400 mg/dL).**
- **Patients may be monitored for B-cell aplasia as a surrogate measure of functional CAR T-cell persistence.**
- **The role of consolidative allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel (persistence of B-cell aplasia) and negative NGS MRD have been associated with durable clinical responses without subsequent HCT.[34,50]**
- **There is no consensus on the role of subsequent vaccination in patients with functional persistence of CAR T cells.**
- **Encourage patient participation in the Center for International Blood and Marrow Transplant Research (CIBMTR) Cellular Therapy Registry.[aa]**
- **Strongly consider NGS-based MRD testing post CAR T-cell therapy.[50]**

[v] Tisagenlecleucel is associated with CRS, including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under REMS. For details, see: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

[aa] The CIBMTR tracks safety and efficacy data following commercial CAR T-cell therapy. For details and cellular therapy data collection forms, see https://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES

[1] Angiolillo AL, Schore RJ, Kairalla JA, et al. Excellent outcomes with reduced frequency of vincristine and dexamethasone pulses in standard-risk B-lymphoblastic leukemia: Results from Children's Oncology Group AALL0932. J Clin Oncol 2021;39:1437-1447.
[2] Burke MJ, Salzer WL, Devidas M, et al. Replacement of cyclophosphamide/cytarabine/mercaptopurine with cyclophosphamide/etoposide during consolidation/delayed intensification does not improve outcome for pediatric B-ALL: a report from the COG. Haematologica 2019;104:986-992.
[3] Salzer WL, Burke MJ, Devidas M, et al. Toxicity associated with intensive postinduction therapy incorporating clofarabine in the very high-risk stratum of patients with newly diagnosed high-risk B-lymphoblastic leukemia: A report from the Children's Oncology Group study AALL1131. Cancer 2018;124:1150-1159.
[4] Salzer WL, Burke MJ, Devidas M, et al. Impact of intrathecal triple therapy versus intrathecal methotrexate on disease-free survival for high-risk B-lymphoblastic leukemia: Children's Oncology Group Study AALL1131. J Clin Oncol 2020;38:2628-2638.
[5] Vrooman LM, Blonquist TM, Supko JG, et al. Efficacy and toxicity of pegaspargase and calaspargase pegol in childhood acute lymphoblastic leukemia/lymphoma: Results of DFCI 11-001. J Clin Oncol 2019;37:10006.
[6] Burns MA, Place AE, Stevenson KE, et al. Identification of prognostic factors in childhood T-cell acute lymphoblastic leukemia: Results from DFCI ALL Consortium Protocols 05-001 and 11-001. Pediatr Blood Cancer 2021;68:e28719.
[7] Reshmi SC, Harvey RC, Roberts KG, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. Blood 2017;129:3352-3361.
[8] Inaba H, Azzato EM, Mullighan CG. Integration of next-generation sequencing to treat acute lymphoblastic leukemia with targetable lesions: The St. Jude Children's Research Hospital approach. Front Pediatr 2017;5:258.
[9] Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol 2012;13:936-945.
[10] Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: Results of Children's Oncology Group Trial AALL0622. J Clin Oncol 2018;36:2306-2314.
[11] Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-5181.
[12] Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014;28:1467-1471.
[13] Teachey DT, Devidas M, Wood BL, et al. Children's Oncology Group trial AALL1231: a phase III clinical trial testing bortezomib in newly diagnosed T-cell acute lymphoblastic leukemia and lymphoma. J Clin Oncol 2022;40:2106-2118.
[14] Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. Pediatr Blood Cancer 2015;62:1176-1183.
[15] Pieters R, De Lorenzo P, Ancliffe P, et al. Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the Interfant-06 Protocol: Results from an international phase III randomized study. J Clin Oncol 2019;37:2246-2256.
[16] Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet 2007;370:240-250.
[17] Salzer WL, Jones TL, Devidas M, et al. Decreased induction morbidity and mortality following modification to induction therapy in infants with acute lymphoblastic leukemia enrolled on AALL0631: a report from the Children's Oncology Group. Pediatr Blood Cancer 2015;62:414-418.
[18] Van Der Sluis IM, De Lorenzo P, Kotecha RS, et al. A phase 2 study to test the feasibility, safety and efficacy of the of the addition of blinatumomab to the Interfant06 backbone in infants with newly diagnosed KMT2A-rearranged acute lymphoblastic leukemia. a collaborative study of the Interfant Network. Blood 2021;138:361.
[19] Tomizawa D, Miyamura T, Imamura T, et al. A risk-stratified therapy for infants with acute lymphoblastic leukemia: a report from the JPLSG MLL-10 trial. Blood 2020;136:1813-1823. Blood 2022;139:2848.
[20] Maloney KW, Devidas M, Wang C, et al. Outcome in children with standard-risk B-cell acute lymphoblastic leukemia: Results of Children's Oncology Group Trial AALL0331. J Clin Oncol 2020;38:602-612.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES

[21] Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: A report from Children's Oncology Group Study AALL0232. J Clin Oncol 2016;34:2380-2388.
[22] Jeha S, Pei D, Choi J, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total Therapy Study 16. J Clin Oncol 2019;37:3377-3391.
[23] Tasian SK, Assad A, Hunter DS, et al. A phase 2 study of ruxolitinib with chemotherapy in children with Philadelphia chromosome-like acute lymphoblastic leukemia (INCB18424-269/AALL1521): Dose-finding results from the Part 1 safety phase [abstract]. Blood 2018;132(Suppl):Abstract 555.
[24] Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet 2010;376:2009-2017.
[25] Raetz EA, Borowitz MJ, Devidas M, et al. Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study [corrected]. J Clin Oncol 2008;26:3971-3978.
[26] Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol 2010;28:2339-2347.
[27] Horton TM, Whitlock JA, Lu X, et al. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. Br J Haematol 2019;186:274-285.
[28] Hogan LE, Brown PA, Ji L, et al. Children's Oncology Group AALL1331: Phase III trial of blinatumomab in children, adolescents, and young adults with low-risk B-Cell ALL in first relapse. J Clin Oncol. 2023;41:4118-4129.
[29] Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376:836-847.
[30] von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016;34:4381-4389.
[31] Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: A randomized clinical trial. JAMA 2021;325:833-842.
[32] Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: A randomized clinical trial. JAMA 2021;325:843-854.
[33] Issa GC, Aldoss I, Thirman MJ, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). J Clin Oncol 2024:JCO2400826.
[34] Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-448.
[35] Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia 2019;33:884-892.
[36] Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375:740-753.
[37] Jabbour EJ, Sasaki K, Ravandi F, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-HCVD) with or without blinatumomab versus intensive chemotherapy (HCVAD) as frontline therapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: A propensity score analysis. Cancer 2019;125:2579-2586.
[38] Hijiya N, Thomson B, Isakoff MS, et al. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Blood 2011;118:6043-6049.
[39] Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. Leuk Lymphoma 2012;53:1693-1698.
[40] Gabriel MA, O'Brien TA, Tapp H, et al. Fludarabine, idarubicin and high dose cytarabine (FLAG-IDA) followed by allogeneic transplantation: A successful strategy for remission re-induction in high risk pediatric patients with relapsed, refractory and secondary acute leukemias. Blood 2006;108:3145.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES

[41] Harris RE, Sather HN, Feig SA. High-dose cytosine arabinoside and L-asparaginase in refractory acute lymphoblastic leukemia: the Children's Cancer Group experience. Med Pediatr Oncol 1998;30:233-239.
[42] Place AE, Karol SE, Forlenza CJ, et al. Pediatric patients with relapsed/refractory acute lymphoblastic leukemia harboring heterogeneous genomic profiles respond to venetoclax in combination with chemotherapy. Blood 2020;136:37-38.
[43] Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: Results from a phase II, single-arm, multicenter study. J Clin Oncol 2017;35:1795-1802.
[44] Whitlock J, dalla Pozza L, Goldberg JM, et al. Nelarabine in combination with etoposide and cyclophosphamide is active in first relapse of childhood T-acute lymphocytic leukemia (T-ALL) and T-lymphoblastic lymphoma (T-LL). Blood 2014;124:795.
[45] Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2020;20:212-218.
[46] Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321-3330.
[47] Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47-62.
[48] Lee DW, Santomasso B, Locke F, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-638.
[49] Mahadeo KM, Khazal SJ, Abdel-Azim H, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol 2019;16:45-63.
[50] Pulsipher MA, Han X, Maude SL, et al. Next-generation sequencing of minimal residual disease for predicting relapse after tisagenlecleucel in children and young adults with acute lymphoblastic leukemia. Blood Cancer Discov 2022;3:66-81.

Note: All recommendations are category 2A unless otherwise indicated.

PHARMACOGENOMICS[1-5]

- **Genetic polymorphisms of genes involved with drug metabolism can significantly influence the toxicity profile of many different chemotherapeutic agents. Sufficient data exist for two genes involved in thiopurine metabolism—*TPMT* and nudix hydrolase 15 (*NUDT15*)—to help guide decisions regarding drug dosing.**
- **Genetic testing for no function alleles of *TPMT* and *NUDT15* should be considered prior to the initiation of thiopurine therapy, or if excessive toxicity is encountered following treatment with thiopurines.**
- **The most commonly encountered no function alleles for *TPMT* are: *2, *3A, *3B, *3C, and *4.**
- **Intermediate metabolizers of *TPMT* carry one normal function allele (*1) and one no function allele (eg, *2, *3A, *3C). Estimated frequency is 3%–14% of patients.**
- **Poor metabolizers of *TPMT* carry two no function alleles (eg, *2, *3A, *3C). Estimated frequency is 0.03%–0.5% of patients.**
- **Dosing recommendations for patients who are intermediate or poor metabolizers of *TPMT* are shown in Table 1.**
- **For patients who are normal metabolizers of *TPMT* or *NUDT15* who do not appear to tolerate thiopurines, consider measuring erythrocyte thiopurine metabolites and/or erythrocyte *TPMT* activity. Genetic testing may not identify rare or previously undiscovered no function alleles.**

Table 1: Dosing Guidelines for Thiopurines Based on *TPMT* Phenotype[a,b]

TPMT Phenotype/Genotype	Dosing Recommendations for 6-MP	Dosing Recommendations for 6-TG
Normal metabolizer (eg, *1/*1); Homozygous for normal function alleles	Starting dose should be based on treatment protocol. Allow 2 weeks to achieve steady state prior to making any dose adjustments.	Starting dose should be based on treatment protocol. Allow 2 weeks to achieve steady state prior to making any dose adjustments.
Intermediate metabolizer (eg, *1/*2, *1/*3A, *1/*3B, *1/*3C, or *1/*4); Heterozygous for no function alleles[c]	Start at 30%–80% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2–4 weeks to achieve steady state prior to making any dose adjustments.	Start at 50%–80% of full dose.[c] Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2–4 weeks to achieve steady state prior to making any dose adjustments.
Poor metabolizer (eg, *2/*3A, *3A/*3C); Homozygous for no function alleles	Start at ~10% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 4–6 weeks to achieve steady state prior to making any dose adjustments.	Start at ~10% of full dose as dictated by protocol. Allow 4–6 weeks to achieve steady state prior to making any dose adjustments.

[a] Adapted from Relling M, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.

[b] The recommendations for dose reductions may differ based on the treatment regimen.

[c] For patients who are *TPMT* intermediate metabolizers who are already receiving reduced starting doses of thiopurines (<75 mg/m^2/day of 6-MP or <40 mg/m^2/day of 6-TG) further dose reduction may not be needed.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PHARMACOGENOMICS[1-5]

- **The most commonly encountered no function alleles for *NUDT15* are: *2, *3, and *9.**
- **Intermediate metabolizers of *NUDT15* carry one normal function allele (*1) and one no function allele (eg, *2, *3, *9). Estimated frequency ranges from 0.8%–17% of patients.**
- **Poor metabolizers of *NUDT15* carry two no function alleles (eg, *2, *3, *9). Estimated frequency ranges from 0.2%–0.9% of patients.**
- **Up to 25% of patients of Asian and Native American ancestry will carry a no function *NUDT15* allele. Patients of other ancestries may also carry a *NUDT15* no function allele but at a lower frequency.**
- **Dosing recommendations for patients who are intermediate or poor metabolizers of *NUDT15* are shown in Table 2.**

Table 2: Dosing Guidelines for Thiopurines Based on *NUDT15* Phenotype[a,b]

NUDT15 Phenotype/Genotype	Dosing Recommendations for 6-MP	Dosing Recommendations for 6-TG
Normal metabolizer (eg, *1/*1); Homozygous for normal function alleles	Starting dose should be based on treatment protocol. Allow 2 weeks to achieve steady state prior to making any dose adjustments.	Starting dose should be based on treatment protocol. Allow 2 weeks to achieve steady state prior to making any dose adjustments.
Intermediate metabolizer (eg, *1/*2, *1/*3, *1/*9); Heterozygous for no function allele[d]	Start at 30%–80% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2–4 weeks to achieve steady state prior to making any dose adjustments.	Start at 50%–80% of full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 2–4 weeks to achieve steady state prior to making any dose adjustments.
Poor metabolizer (eg, *2/*3); Homozygous for no function alleles	Start at 10 mg/m^2/day. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 4–6 weeks to achieve steady state prior to making any dose adjustments.	Start at 25% full dose. Adjust dose based on degree of myelosuppression as dictated by protocol. Allow 4–6 weeks to achieve steady state prior to making any dose adjustments.

[a] Adapted from Relling M, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.
[b] The recommendations for dose reductions may differ based on the treatment regimen.
[d] For patients who are intermediate metabolizers of *NUDT15* who are already receiving reduced starting doses of thiopurines (<75 mg/m^2/day of 6-MP or <40 mg/m^2/day 6-TG), further dose reduction may not be needed.

References

Note: All recommendations are category 2A unless otherwise indicated.

PHARMACOGENOMICS – REFERENCES

[1] Relling M, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for thiopurine dosing based on *TPMT* and *NUDT15* genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.
[2] Moriyama T, Nishil R, Perez-Andreu V, et al. *NUDT15* polymorphisms alter thiopurine metabolism and hematopoietic toxicity. Nat Genet 2016;48:367-373.
[3] Yi E, Choi Y, Choi R, et al. *NUDT15* variants cause hematopoietic toxicity with low 6-TGN levels in children with acute lymphoblastic leukemia. Cancer Res Treat 2018;50:872-882.
[4] Lee SHR, and Yang JJ. Pharmacogenomics in acute lymphoblastic leukemia. Best Pract Res Clin Haematol 2017;30:229-236.
[5] Al-Mahayri ZN, Patrinos GP, and Ali BR. Pharmacogenomics in acute lymphoblastic leukemia: promises and limitations. Pharmacogenomics 2017;18:687-699.

Note: All recommendations are category 2A unless otherwise indicated.

RESPONSE ASSESSMENT

Response Criteria for Blood and Bone Marrow:

- **CR**
  - **No circulating blasts or extramedullary disease**
    - ◊ **No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement**
  - **Marrow with trilineage hematopoiesis (TLH) and <5% blasts (M1) or <1% blasts by flow or molecular testing[a]**
  - **With blood count recovery = ANC >1000/µL and platelets >100,000/µL**
  - **No recurrence for 4 weeks**
- **CR with incomplete blood count recovery (CRi)**
  - **Meets all criteria for CR except platelet count and/or ANC**
- **Overall response rate (ORR = CR + CRi)**
  - **NOTE: MRD assessment is not included in morphologic assessment and should be obtained (PEDALL-J)**
- **Refractory disease**
  - **CR not achieved at the EOI**
- **Progressive disease (PD)**
  - **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% (M2 or greater) or >1% with previous/supportive molecular findings or in any extramedullary site after a CR**

Response Criteria for CNS Disease:

- **CNS remission: Achievement of CNS-1 status (PEDALL-D) in a patient with CNS-2 or CNS-3 status at diagnosis.**
- **CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation. New development of CNS-2 status on two consecutive LPs (between 2–4 weeks apart) with confirmation by immunophenotyping or other molecular testing methods.**

[a] Molecular testing includes: Flow cytometry, PCR, NGS, and FISH. If there are any equivocal results, repeat in 2–4 weeks given the high suspicion for relapse.

Note: All recommendations are category 2A unless otherwise indicated.

MINIMAL RESIDUAL DISEASE

- **MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.**
- **MRD is an essential component of patient evaluation over the course of sequential therapy. If a validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests.**
- **Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risk for relapse, as well as the prognostic significance of MRD measurements during and after initial induction therapy.[1]**
- **There are data to support the importance of MRD testing in T-ALL (all immunophenotypes),[2,3] de novo[4,5] and relapsed B-ALL,[6-8] and infant ALL.[9]**
- **The most frequently employed methods for MRD assessment include flow cytometry assays[10,11,12] specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative PCR (RQ-PCR) assays (eg, clonally rearranged Ig, T-cell receptor [TCR] genes), reverse transcriptase quantitative PCR (RT-qPCR) assays (eg, *BCR::ABL1*), and NGS-based assays to detect fusion genes or clonal rearrangements in Ig and TCR loci (does not require patient-specific primers).**
  - **Prior treatment with immunotherapy or HCT can affect interpretation of flow cytometry-based MRD results. MRD should be performed in a laboratory with experience performing MRD in this setting.**
- **The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate.**
- **Current flow cytometry[10,11] or PCR methods can detect leukemic cells at a sensitivity threshold of at least $1x10^{-4}$ (<0.01%) bone marrow mononuclear cells (MNCs).[13,14] PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ (<0.0001%) bone marrow MNCs. The concordance rate for detecting MRD between these methods is generally high. Methods not achieving these sensitivity levels are not recommended.**
  - **Timing of MRD assessment:**
    - ◊ **Upon completion of induction (de novo or relapse).**
    - ◊ **End of consolidation.**
    - ◊ **Prior to HCT.**
    - ◊ **Additional time points should be guided by the regimen used.**
    - ◊ **Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.**
    - ◊ **For some techniques, a baseline sample (ie, prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment.**
- **MRD quantification can be affected by bone marrow aplasia and some protocols require count recovery prior to sending MRD. MRD sent during aplasia may need to be repeated after count recovery.**
- **Infants with high MRD after the EOI may benefit from AML-like consolidation.[15]**

References

Note: All recommendations are category 2A unless otherwise indicated.

MINIMAL RESIDUAL DISEASE
REFERENCES

[1] Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult lymphoblastic leukemia. JAMA Oncol 2017;3:e170580.
[2] Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood 2011;118:2077-2084.
[3] Wood BL, Winter SS, Dunsmore KP, et al. T-lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value of end-induction minimal residual disease (MRD) in Children's Oncology Group (COG) Study AALL0434. Blood 2014;124:1.
[4] Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 2008;111:5477-5485.
[5] Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115:3206-3214.
[6] Eckert C, von Stackelberg A, Seeger K, et al. Minimal residual disease after induction is the strongest predictor of prognosis in intermediate risk relapsed acute lymphoblastic leukaemia—long-term results of trial ALL- REZ BFM P95/96. Eur J Cancer 2013;49:1346-1355.
[7] Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol 2009;27:377-384.
[8] Eckert C, Hagedorn N, Sramkova L, et al. Monitoring minimal residual disease in children with high-risk relapses of acute lymphoblastic leukemia: prognostic relevance of early and late assessment. Leukemia 2015;29:1648-1655.
[9] Van der Velden VH, Corral L, Valsecchi MG, et al. Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol. Leukemia 2009;23:1073-1079.
[10] Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. Haematologica 2012;97:1582-1593.
[11] Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2013;27:635-641.
[12] Cherian S, Soma LA. How I diagnose minimal/measurable residual disease in B lymphoblastic leukemia/lymphoma by flow cytometry. Am J Clin Pathol 2021;155:38-54.
[13] Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia 2010;24:521-535.
[14] Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010;2010:7-12.
[15] Stutterheim J, van der Sluis IM, de Lorenzo P, et al. Clinical implications of minimal residual disease detection in infants with KMT2A-rearranged acute lymphoblastic leukemia treated on the Interfant-06 protocol. J Clin Oncol 2021;39:652-662.

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Indications for HCT (B-cell) in First Remission

- Unfavorable cytogenetics
  - Consider HCT if *MLL/KMT2A* mutation (<6 months in age) with high-risk features (PEDALL-7).[a,1]
- MRD
  - Consider HCT if MRD ≥0.01% post-consolidation (week 9–12 from diagnosis).[b,2]
- Other considerations
  - The role of HCT for patients with hypodiploid ALL in CR1 has not yet been established, even in patients who are MRD-positive at end-induction.[3-8]
    - ◊ HCT for hypodiploid ALL may be considered in the setting of a clinical trial.
  - HCT is not routinely indicated for *BCR::ABL1*+ ALL in CR1 (while on TKI plus systemic chemotherapy) provided that the patient has achieved MRD negativity (<0.01%) post-consolidation and is being treated on an intensive pediatric regimen plus TKI. Consider HCT (for *BCR::ABL1*+ ALL) if relapse (any time point), or MRD ≥0.01% (by week 9–12).[9,10]
  - For patients who are MRD positive (≥0.01%) at end-induction, there is insufficient evidence to suggest a survival advantage for HCT, even in patients with kinase activating mutations (ie, *IKZF1, CDKN2A/B, PDGFRB, ABL1, ABL2, CSF1R, JAK2, CRLF, EPOR*) or iAMP21.

Indications for HCT (B-cell) in Non-First Remission Settings

- Induction failure (M3 marrow): Recommend HCT after achieving MRD-negative status.
- CR2: Consider HCT based upon timing of relapse (or refractory disease) and leukemic phenotype; see PEDALL-K (2 of 5).
- CR3: Recommend HCT.
- For a patient with CNS involvement at the time of relapse (or refractory disease), consider a CNS boost at the time of administration of TBI. For those without CNS involvement at the time of relapse (or refractory disease), there is no clear evidence that CNS boost will prevent subsequent CNS relapse.[11,12]
- For relapsed/refractory disease, see PEDALL-K (2 of 5).

Indications for HCT (T-cell)

- HCT should be considered for:
  - Patients with MRD positivity (>0.1%) at completion of consolidation. Additional therapy should be given prior to HCT to achieve MRD negativity. See PEDALL-G (9 of 13).
  - Induction failure (M3 marrow).[13]
  - Patients with medullary or extramedullary relapse (any time point).[14] See PEDALL-K (2 of 5).
- For relapsed/refractory disease, see PEDALL-K (2 of 5).

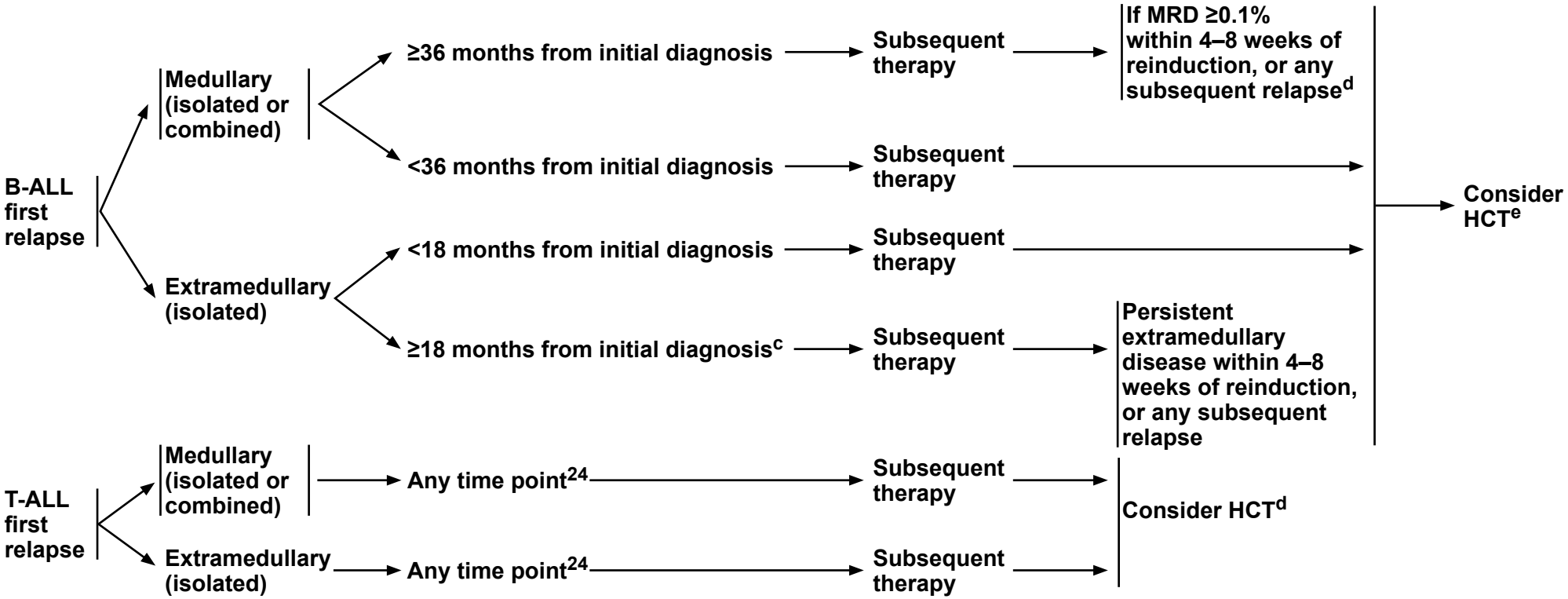
[a] The Interfant-99 study noted a potential benefit for HCT in children aged <6 months with *MLL* rearrangements plus either poor day 8 (induction) response to systemic corticosteroids, or WBC count at initial diagnosis >300 x 10^9/L.
[b] MRD based upon flow cytometry, PCR, or NGS.

Note: All recommendations are category 2A unless otherwise indicated.

Continued
References

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

TIME TO RELAPSE[15-23]



[c] For late bone marrow or isolated extramedullary relapses, if patient achieves MRD-negative CR2 with reinduction/therapy for relapsed disease, no HCT is indicated.
[d] The recommendations may differ based on the treatment regimen. Consideration of HCT can also be made in the setting of MRD of 0.01%–0.09% given an increased risk of relapse. Hogan LE, et al. J Clin Oncol 2023;41:4118-4129; Parker C, et al. Lancet 2010;376:2009-2017.
[e] Consideration for HCT depends upon donor availability and patient's clinical status at the time of potential HCT.

Continued
References

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PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Donor Type

- Unrelated vs. related donor
  - In children/young adults undergoing HCT for ALL, there is no survival advantage (event-free survival [EFS] or overall survival [OS]) by donor type when comparing use of matched unrelated donors to matched related donors.[25]
- Umbilical cord blood (UCB)[26-28]
  - Allows rapid procurement and more lenient human leukocyte antigen (HLA) matching.
    - ◊ No outcome differences are noted in HCT for childhood leukemia when comparing UCB versus matched related/matched unrelated donors.[26]
    - ◊ There are possible lower relapse rates using UCB versus matched unrelated donor if the patient achieves MRD positivity pre-HCT.[27]
    - ◊ There is no survival advantage for double (vs. single) UCB HCT in children/young adults, when a single cord unit with adequate cell dose is available.[28]
- The role of haploidentical transplants for childhood leukemia has been examined in several single and multicenter studies, with potential efficacy and favorable toxicity profiles. Haploidentical transplants (with post-transplant cyclophosphamide or αβ-depletion) may be considered as an alternative donor source, especially if no HLA-matched donor is available.[29,30,31,32]

Donor Cell Source

- When comparing bone marrow to peripheral blood stem cells (PBSCs) as the donor cell source, there is no survival advantage for use of PBSCs in matched unrelated donor transplantation. Higher graft-versus-host disease (GVHD) rates with equivalent survival are noted with PBSCs (vs. marrow) in recipients of matched unrelated donor transplants. The optimal donor cell source (marrow vs. PBSCs) has not been clearly defined with either matched related donor or haploidentical donor transplants. Due to increased risks of acute and chronic GVHD with PBSCs, the use of PBSCs should be considered with caution for HCT in children/young adults with ALL.[33,34]

Conditioning Regimen

- Both TBI and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL.[35,36,37] Non-TBI–containing regimens are under current investigation.
- The use of TBI in conditioning regimens for ALL demonstrated a disease-free survival advantage seen regardless of donor source (matched related vs. unrelated HCT).[37]
- For infants: If donor available, prefer non–TBI-based prep regimen and age ≥6 months at time of HCT.[38] See PEDALL-G, 2 of 13.

Impact of Pre-HCT MRD Status

- An increased risk of relapse has been noted in children with ≥0.1% MRD pre-HCT for ALL, suggesting the need to attain an MRD level <0.1% prior to HCT.[39,40] An increased risk of relapse has also been noted in children with an MRD of 0.01%–0.09%.[41,42]
- The absence of detectable MRD by NGS before and after HCT may be associated with favorable outcomes.[43]

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT
REFERENCES

[1] Mann G, Attarbaschi A, Schrappe M, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. Blood 2010;116:2644-2650.
[2] Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood 2015;126:964-968.
[3] Mulligan CG, Jeha S, Pei D, et al. Outcome of children with hypodiploid ALL treated with risk-directed therapy based on MRD levels. Blood 2015;126:2896-2899.
[4] Heerema NA, Nachman JB, Sather HN, et al. Hypodiploidy with less than 45 chromosomes confers adverse risk in childhood acute lymphoblastic leukemia: a report from the children's cancer group. Blood 1999;94:4036-4045.
[5] Nachman JB, Heerema NA, Sather H, et al. Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. Blood 2007;110:1112-1115.
[6] Harrison CJ, Moorman AV, Broadfield ZJ, et al. Three distinct subgroups of hypodiploidy in acute lymphoblastic leukaemia. Br J Haematol 2004;125:552-559.
[7] Pui CH, Rebora P, Schrappe M, et al. Outcome of children with hypodiploid acute lymphoblastic leukemia: A retrospective multinational study. J Clin Oncol 2019;37:770-779.
[8] McNeer J, Devidas M, Dai Y, et al. Hematopoietic stem-cell transplantation does not improve the poor outcome of children with hypodiploid acute lymphoblastic leukemia: A report from Children's Oncology Group. J Clin Oncol 2019;37:780-789.
[9] Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014;28:1467-1471.
[10] Fielding A. Philadelphia-positive acute lymphoblastic leukemia-is bone marrow transplant still necessary? Biol Blood Marrow Transplant 2011;17:S84-S88.
[11] Hiniker SM, Agarwal R, Modlin LA, et al. Survival and neurocognitive outcomes after cranial or craniospinal irradiation plus total-body irradiation before stem cell transplantation in pediatric leukemia patients with central nervous system involvement. Int J Radiat Oncol Biol Phys 2014;89:67-74.
[12] Alexander BM, Wechsler D, Braun TM, et al. Utility of cranial boost in addition to total body irradiation in the treatment of high risk acute lymphoblastic leukemia. Int J Radiat Oncol Biol Phys 2005;63:1191-1196.
[13] Schrappe M, Hunger SP, Pui CH et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med 2012;366:1371-1381.
[14] Raetz EA, Teachey DT. T-cell acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2016;2016:580-588.
[15] Locatelli F, Schrappe M, Bernardo ME, et al. How I treat relapsed childhood acute lymphoblastic leukemia. Blood 2012;120:2807-2816.
[16] Oliansky DM, Camitta B, Gaynon P, et al. Role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. Biol Blood Marrow Transplant 2012;18:505-522.
[17] Urdezo C, Valsecchi MG, Bacigalupo A, et al. Treatment of childhood acute lymphoblastic leukemia in second remission with allogeneic bone marrow transplantation and chemotherapy: ten-year experience of the Italian Bone Marrow Transplantation Group and the Italian Pediatric Hematology Oncology Association. J Clin Oncol 1995;13:352-358.
[18] Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Münster Group 87. J Clin Oncol 2005;23:7942-7950.
[19] Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia 2008;22:2142-2150.
[20] Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol 2010;28:2339-2347.
[21] Gaynon PS, Qu RP, Chappell RJ, et al. Survival after relapse in childhood acute lymphoblastic leukemia: impact of site and time to first relapse-the Children's Cancer Group Experience. Cancer 1998;82:1387-1395.
[22] Borgmann A, von Stackelberg A, Hartmann R, et al. Unrelated donor stem cell transplantation compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission: a matched-pair analysis. Blood 2003;101:3835-3839.
[23] Parker C, Krishnan S, Hamadeh L, et al. Outcomes of patients with childhood B-cell precursor acute lymphoblastic leukaemia with late bone marrow relapse: long-term follow-up of the ALLR3 open-label randomised trial. Lancet Haematol 2019;6:e204-e216.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT
REFERENCES

[24] Burke MJ, Verneris MR, La Rademacher J, et al. Transplant outcomes for children with T-cell acute lymphoblastic leukemia in second remission: a report from the Center for International Blood and Marrow Transplant Research. Biol Blood Marrow Transplant 2015;21:2154-2159.
[25] Peters C, Schrappe M, von Stackelberg A, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: A prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. J Clin Oncol 2015;33:1265-1274.
[26] Lou X, Zhao C, Chen H. Unrelated donor umbilical cord blood transplant versus unrelated hematopoietic stem cell transplant in patients with acute leukemia: A meta-analysis and systematic review. Blood Rev 2018;32:192-202.
[27] Milano F, Gooley T, Wood B, et al. Cord-blood transplantation in patients with minimal residual disease. N Engl J Med 2016;375:944-953.
[28] Michel G, Galambrun C, Sirvent A, et al. Single- vs double-unit cord blood transplantation for children and young adults with acute leukemia or myelodysplastic syndrome. Blood 2016:127:3450-3457.
[29] Xue YJ, Cheng YF, Lu AD, et al. Allogeneic hematopoietic stem cell transplantation, especially haploidentical, may improve long-term survival for high-risk pediatric patients with Philadelphia chromosome-positive acute lymphoblastic leukemia in the tyrosine kinase inhibitor era. Biol Blood Marrow Transplant 2019;25:1611-1620.
[30] Wagner JE, Ballen KK, Zhang MJ, et al. Comparison of haploidentical and umbilical cord blood transplantation after myeloablative conditioning. Blood Adv 2021;5:4064-4072.
[31] Ruggeri A, Galimard JE, Paina O, et al. Outcomes of unmanipulated haploidentical transplantation using post-transplant cyclophosphamide (PT-Cy) in pediatric patients with acute lymphoblastic leukemia. Transplant Cell Ther 2021;27:424.e1-424.e9.
[32] Merli P, Algeri M, Galaverna F, et al. TCRalphabeta/CD19 cell-depleted HLA-haploidentical transplantation to treat pediatric acute leukemia: updated final analysis. Blood 2024;143:279-289.
[33] Keesler DA, St Martin A, Bonfim C, et al. Bone marrow versus peripheral blood from unrelated donors for children and adolescents with acute leukemia. Biol Blood Marrow Transplant 2018;24:2487-2492.
[34] Anesetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med 2012;367:1487-1496.
[35] Davies S, Ramsay NK, Klein JP, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol 2000;18:340-347.
[36] Bunin N, Aplenc R, Kamani N et al. Randomized trial of busulfan vs total body irradiation containing regimens for children with acute lymphoblastic leukemia. A Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant 2003;32:543-548.
[37] Peters C, Dalle J-H, Locatelli F, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: A multinational, randomized, noninferiority phase III study. J Clin Oncol 2021;39:295-307.
[38] Tomizawa D, Miyamura T, Imamura T, et al. A risk-stratified therapy for infants with acute lymphoblastic leukemia: a report from the JPLSG MLL-10 trial. Blood 2020;136:1813-1823.
[39] Pulsipher MA, Langholz B, Wall DA, et al. The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and Marrow Transplant Consortium trial. Blood 2014;123:2017-2025.
[40] Bader P, Kreyenberg H, Henze GH, et al. ALL-REZ BFM Study Group. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol 2009;27:377-384.
[41] Hogan LE, Brown PA, Ji L, et al. Children's Oncology Group AALL1331: Phase III trial of blinatumomab in children, adolescents, and young adults with low-risk B-Cell ALL in first relapse. J Clin Oncol 2023;41:4118-4129.
[42] Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet 2010;376:2009-2017.
[43] Pulsipher MA, Carlson C, Langholz B, et al. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. Blood 2015;125:3501-3508.

Note: All recommendations are category 2A unless otherwise indicated.

ABBREVIATIONS

AFB	acid-fast bacilli
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AVN	avascular necrosis
AYA	adolescent and young adult
B-ALL/LL	B-cell acute lymphoblastic leukemia/lymphoma
BFM	Berlin-Frankfurt-Münster
CAR	chimeric antigen receptor
CBC	complete blood count
CLIA	Clinical Laboratory Improvement Amendments
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRi	complete response with incomplete blood count recovery
CRRT	continuous renal replacement therapy
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
DIC	disseminated intravascular coagulation
DT	double trisomy
EBV	Epstein-Barr virus
EFS	event-free survival
EOI	end of induction
ETP	early T-cell precursor
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GVHD	graft-versus-host disease
H&E	hematoxylin and eosin
H&P	history and physical
HCT	hematopoietic cell transplant
HLA	human leukocyte antigen
HSV	herpes simplex virus
iAMP21	intrachromosomal amplification of chromosome 21
ICC	International Consensus Classification
Ig	immunoglobulin
ITT	intrathecal triple therapy
IVIG	intravenous immunoglobulin
LDA	low-density array
LDH	lactate dehydrogenase
LFT	liver function test
LL	lymphoblastic lymphoma
LOH	loss of heterozygosity
LP	lumbar puncture
MNC	mononuclear cell
MPAL	mixed phenotype acute leukemia
MRD	minimal residual disease
NEC	necrotizing enterocolitis
NGS	next-generation sequencing
NOS	not otherwise specified
NSAID	nonsteroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival

ABBREVIATIONS

PALS	Pediatric Advanced Life Support
PBSC	peripheral blood stem cell
PCR	polymerase chain reaction
PD	progressive disease
PPI	proton pump inhibitor
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RQ-PCR	real-time quantitative polymerase chain reaction
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase-polymerase chain reaction
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
SAA	serum asparaginase activity
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SNP	single nucleotide polymorphism
SOS	sinusoidal obstructive syndrome
T-ALL	T-cell acute lymphoblastic leukemia
T-LL	T-cell lymphoblastic lymphoma
TBI	total body irradiation
TCR	T-cell receptor
TDM	therapeutic drug monitoring
TKI	tyrosine kinase inhibitor
TLH	trilineage hematopoiesis
TLS	tumor lysis syndrome
TPN	total parenteral nutrition
UCB	umbilical cord blood
ULN	upper limit of normal
VOD	veno-occlusive disease
VRE	vancomycin-resistant enterococci
VZV	varicella zoster virus
WBC	white blood cell

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Note: All recommendations are category 2A unless otherwise indicated.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pediatric Acute Lymphoblastic Leukemia

Discussion

This discussion corresponds to the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia. Last updated: December 16, 2024.

Table of Contents

Overview

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The age-adjusted incidence rate of ALL in the United States is 1.38 per 100,000 individuals per year,[1] with approximately 6550 new diagnoses and 1330 deaths estimated in 2024.[2] It is also the most common pediatric malignancy, representing 75% to 80% of acute leukemias among children. In contrast, ALL represents approximately 20% of all leukemias among adults.[3,4] The median age of diagnosis for ALL is 15 years,[5] with 55.4% of patients being diagnosed at <20 years of age.[6] In contrast, 28% of patients are diagnosed at ≥45 years and approximately 12.3% of patients are diagnosed at ≥65 years.[6] ALL is divided into 2 major subtypes, B-ALL and T-ALL, with B-ALL accounting for approximately 80% of pediatric ALL.[7-9]

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.[10] Improvements are largely owed to advances in the understanding of the molecular genetics and pathogenesis of the disease, the incorporation of risk-adapted therapy, the advent of new targeted agents, the use of allogeneic hematopoietic cell transplantation (HCT), and improvements in supportive care. Analyses from the SEER database have shown improvements in survival for children and adolescent and young adult (AYA) patients with 5-year overall survival (OS) rates of 89% and 61%, respectively.[10,11] However, survival rates for adult patients remain low at approximately 20% to 40%.[12-15] Although the exact OS percentage can vary based on how the age range is defined for pediatric, AYA, and adult patients, the trend is nonetheless clear that OS decreases substantially with increased age.[13,16] The exception is infants <1 year of age, which is an age group that has not seen any improvement in survival over the last 30 years with a 6-year OS rate of 58.2%.[17] Nevertheless, recent data from the Interfant group incorporating immunotherapy into frontline cytotoxic chemotherapy treatment demonstrated very promising 2-year disease-free survival (DFS) rates (81.6%) in a small number of patients (n = 30) treated in a pilot study, raising optimism that cure rates may improve in the modern era.[18] Historically, outcomes for children with T-ALL were worse than outcomes for children with B-ALL; however, with modern intensive T-ALL–focused chemotherapy backbones, the prognoses for childhood T-ALL and B-ALL are nearly equivalent.[7-9]

Cure rates for AYA patients with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the adoption of pediatric treatment regimens.[19] AYA patients represent a unique population, because they may receive treatment based on either a pediatric or an adult protocol, depending on local referral patterns and institutional practices.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia were developed as a result of meetings convened by a multidisciplinary panel of pediatric ALL experts, with the goal of providing recommendations on standard treatment approaches based on current evidence. The NCCN Guidelines focus on risk assessment and stratification of risk-adapted therapy; treatment strategies for *BCR::ABL1* (Philadelphia chromosome [Ph])-positive and *BCR::ABL1*-negative B-cell lineage [B-ALL], T-cell lineage [T-ALL], and infant ALL); and supportive care considerations. Given the complexity of ALL treatment regimens and the required supportive care measures, the NCCN Pediatric ALL Panel recommends that patients be treated at a specialized cancer center with expertise in the management of ALL.

The Panel considers the term “pediatric” to include any patient aged ≤18 years and certain AYA patients >18 years of age. Across treatment centers, practice patterns vary with regard to AYA patients in terms of whether patients with ALL are treated primarily by pediatric or adult

oncologists. These Guidelines are intended to apply to AYA patients treated in a pediatric oncology setting, and may include patients up to age 30 years. The NCCN Guidelines for Acute Lymphoblastic Leukemia are intended to apply to AYA patients treated in an adult oncology setting.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Pediatric Acute Lymphoblastic Leukemia, an electronic search of the PubMed database was performed to obtain key literature in pediatric acute lymphoblastic leukemia published since the previous Guidelines update, using the following search terms: acute lymphoblastic leukemia and pediatric or childhood or infant. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[20] Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis

Clinical Presentation

Patients with ALL develop symptoms related to the infiltration of blasts in the bone marrow, lymphoid system (including thymus presenting as a mediastinal mass in T-ALL), and extramedullary sites (including the central nervous system [CNS] and testicles).[3,8] These symptoms may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding.[4,21] Among children, pain in the extremities or joints may be the only presenting symptom.[4] The presence of lymphadenopathy, splenomegaly, and/or hepatomegaly on physical examination may be found. Chin numbness or facial palsy may result from cranial nerve or CNS involvement.[22,23] Abdominal masses from gastrointestinal (GI) involvement are more suggestive of mature B-cell ALL (Burkitt lymphoma).[4]

Compared to patients with B-ALL, individuals with T-ALL generally present at older ages, are more likely to be male (3:1 male:female predominance), and are more likely to self-identify as Black or African American. Individuals with T-ALL are also more likely to present with a higher white blood cell (WBC) count and are more likely to have extramedullary disease, including lymphadenopathy, mediastinal mass, and CNS involvement. Mediastinal mass is present in >50% of patients with T-ALL and can compress adjacent organs such as the trachea and blood vessels (eg, superior vena cava), causing dyspnea/airway obstruction and venous obstruction/facial edema/thrombosis (also known as superior vena cava syndrome), respectively. In addition to mediastinal mass, pleural and cardiac effusions can be seen.[7-9]

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. A value of ≥25% marrow blasts is often used in treatment protocols to define leukemia.[24] Unlike with myeloid leukemia, there is no clear lower limit for the proportion of blasts required to establish an ALL diagnosis. In general, it is uncommon to observe presentations of ALL with low blast counts and the diagnosis of ALL should be avoided when there are <20% marrow blasts. In addition, there is no compelling evidence that not treating a patient when there are <20% marrow blasts has an adverse effect on outcome.[24] In clinical situations that preclude bone marrow aspirate and biopsy, such as hyperleukocytosis (eg, ≥100,000 leukocytes per microliter) and/or mediastinal mass, peripheral blood may be substituted for bone marrow provided there is a significant amount of circulating disease,[25,26] with the NCCN Pediatric ALL Panel suggesting a general guide of ≥1000 circulating lymphoblasts per microliter or ≥20% lymphoblasts.

The 2022 WHO classification lists ALL and lymphoblastic lymphoma (LL) as the same entity, distinguished only by the primary location of the disease.[24] When the disease is restricted to a mass lesion primarily involving nodal (including thymus for T-ALL) or extranodal sites with no or minimal involvement in blood or bone marrow (generally defined as <20% lymphoblasts in the marrow), the case would be consistent with a diagnosis of LL.[24] However, based on morphologic, genetic, and immunophenotypic features, LL is indistinguishable from ALL. Patients with LL generally benefit from treatment with ALL-like regimens versus traditional lymphoma therapy[27,28] and should be treated in a center that has experience with LL.

Hematopathology evaluations should include morphologic examination of malignant lymphocytes using Wright-Giemsa–stained slides and hematoxylin and eosin–stained core biopsy and clot sections; comprehensive immunophenotyping with flow cytometry and/or immunohistochemistry (see *Immunophenotyping*); and baseline characterization of leukemic clone(s) by flow cytometry or molecular assay (eg, immunoglobulin [Ig] or T-cell receptor [TCR] gene rearrangements) to facilitate subsequent analysis of minimal (or “measurable”) residual disease (MRD).

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry and/or immunohistochemistry to determine the presence of cell surface or intracellular antigens on lymphocytes. ALL can be broadly classified into two groups based on immunophenotype, which include precursor B-cell ALL and T-cell ALL.[4,29] Among children, B-ALL constitutes approximately 80% of ALL diagnoses and T-ALL constitutes approximately 10% to 15%.[30-32] In adult patients, subtypes of B-ALL represent approximately 75% of ALL diagnoses, whereas the remaining 25% comprise T-ALL.[32,33] Within the B-cell lineage, the profile of cell surface markers differs according to the stage of B-cell maturation, which includes early precursor B-cell (early pre–B-cell) and pre–B-cell ALL. Early pre–B-cell ALL is

characterized by the presence of terminal deoxynucleotidyl transferase (TdT), the expression of CD19/CD22/CD79a, and the absence of CD10 (formerly termed common ALL antigen) or surface Igs. CD10 negativity correlates with *KMT2A* rearrangement and poor prognosis.[34,35] Pre–B-cell ALL is characterized by the presence of cytoplasmic Igs and CD10/CD19/CD22/CD79a expression and was previously termed "common B-ALL" due to the expression of CD10 at diagnosis.[4,24] The definition of CD20 positivity is unclear, though most studies use ≥20% of blasts expressing CD20.[36,37] CD20 may be expressed in approximately 50% of B-ALL in children, with a higher frequency in patients between 1 and 10 years of age compared to patients <1 or >10 years.[37] In some cases, *CRLF2* overexpression detected via flow cytometry may be used as a surrogate for genomic alterations of the *CRLF2* gene in pediatric B-ALL, including *P2RY8::CRLF2* and *IGH::CRLF2*.[38]

T-ALL is typically associated with the presence of cytoplasmic CD3 (T-cell lineage blasts) or cell surface CD3 (mature T cells) in addition to variable expression of CD2/CD5/CD7; variable expression of markers of T cell progenitors CD1a, CD99, CD117 (KIT), and CD34 (in approximately 1/3 of cases); and expression of TdT.[24] CD4 and CD8 are frequently coexpressed (in approximately 46% of cases), and CD10 may be positive (in approximately 40% of cases). Previous classifications of T-ALL were based on intrathymic staging according to antigens expressed, and included these notations: pro-T/T-I, pre-T/T-II, cortical T/T-III, and medullary T/T-IV.[24,39] Most cases previously classified as pro-T or pre-T now meet the criteria for early T-cell precursor (ETP) ALL.[24] ETP ALL represents a distinct biologic subtype of T-ALL that accounts for 12% of pediatric T-ALLs (and about 2% of ALL) and is characterized by: the absence of CD1a/CD8, weak expression of CD5 (<75% positive lymphoblasts), and the presence of ≥1 myeloid or stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65) on at least 25% of lymphoblasts.[24,40] [24,40] When CD5 is expressed at a higher level, it is called near-ETP ALL. Initial reports demonstrated that ETP ALL was associated with unfavorable outcomes[40-42]; however, with modern more intensive therapies, multiple groups have reported similar outcomes among ETP ALL, near-ETP ALL, and non-ETP T-ALL.[43-45]

Hematologic malignancies related to ALL include acute leukemias of ambiguous lineage (ALALs), such as the mixed phenotype acute leukemias (MPALs).[46,47] MPALs include bilineage leukemias, in which two distinct populations of lymphoblasts are identified, with one meeting the criteria for acute myeloid leukemia (AML). Biphenotypic MPAL is defined as a single population of lymphoblasts that expresses markers consistent with B-cell or T-cell ALL, in addition to expressing myeloid or monocytic markers.[47] Notably, myeloid-associated markers such as CD13 and CD33 may be expressed in ALL, and the presence of these markers does not exclude the diagnosis of ALL, nor is it associated with adverse prognosis.[47] The initial immunophenotyping panel should be sufficiently comprehensive to establish a leukemia-associated phenotype that may include expression of nonlineage antigens; these are useful in classification, particularly for MPAL. In the 2022 update of the WHO classification of hematolymphoid tumors (WHO 5th ed) and by the ICC (International Consensus Classification 2022), ALALs/MPALs were separated into those with defining genetic abnormalities and those defined based on immunophenotyping alone.[47] Lineage assignment criteria were refined to highlight principles of intensity and pattern. Two new subtypes of ALAL were also added: MPAL with *ZNF384* rearrangement and with *BCL11B* rearrangement.[47]

Genetic Abnormalities and Molecular Subtypes

Identification of specific recurrent genetic abnormalities is critical for disease evaluation, optimal risk stratification, and treatment planning. Subtypes of B-ALL with recurrent genetic abnormalities include the following: hyperdiploidy (51–67 chromosomes); hypodiploidy (<44

chromosomes); iAMP21; t(9;22)(q34.1;q11.2), *BCR::ABL1*; t(v;11q23.3); *BCR::ABL1*-like features; *KMT2A* rearranged; t(12;21)(p13.2;q22.1), *ETV6::RUNX1*; *ETV6*::*RUNX1*-like features; t(1;19)(q23;p13.3), *TCF3::PBX1*; t(5;14)(q31.1;q32.1), *IL3::IGH;* t(17;19)(q22;p13.3)[*TCF3*::*HLF*]; t(17;18)(q22;q21.2)[*TCF4::HLF*]; and with other defined genetic abnormalities that include rearrangements of *DUX4, MEF2D*, *ZNF384*, *MYC*, and *NUTM1;* and *PAX5alt, PAX5* p.P80R, *IKZF1* p.N159Y, and *CDX2::UBTF*.[24] Of note, in cases of poor response to ALL therapy for ALL with *IG::MYC* rearrangement, therapy for mature B-cell lymphoma may be considered.

In the Guidelines, the NCCN Panel for Pediatric ALL has delineated the features that are commonly associated with favorable or unfavorable outcomes in B-ALL (see *Genetic Risk Groups for B-ALL* in the algorithm). A brief summary is also provided in this discussion for genetic features associated with T-ALL.

Favorable-Risk Features

Among children, the most common chromosomal abnormality associated with ALL is hyperdiploidy (51–67 chromosomes) as seen in 25% of cases of B-ALL compared to 7% in the adult ALL patient population.[32,48] The *ETV6::RUNX1* subtype (also within the B-cell lineage) resulting from chromosomal translocation t(12;21) is also among the most commonly occurring subtypes in childhood ALL (25%) compared to adults (2%).[32,48] Both hyperdiploidy and *ETV6::RUNX1* subtypes are associated with favorable outcomes in pediatric ALL,[49] and occur less frequently among AYA patients compared with younger children.[48] In contrast, *DUX4r* is a favorable-risk feature that occurs more frequently among AYA patients compared with younger children[50,51] and *NUTM1* is a favorable-risk feature that occurs more frequently among infants with ALL.[52,53]

Intermediate-Risk Features

Several chromosomal abnormalities are now recognized as markers of intermediate-risk disease,[51,54] including *MEF2Dr*, *ZNF384r*, *PAX5alt*, *PAX5* P80R, *ETV6::RUNX1*-like, and *TCF3::PBX1* although further confirmatory studies are necessary to assess the risk associated with these alterations.

Unfavorable-Risk Features

Several chromosomal abnormalities are well-recognized prognostic biomarkers of high-risk disease at all ages, including hypodiploidy (<44 chromosomes [alternatively defined as low hypodiploidy (32–39 chromosomes), near haploidy (24–31 chromosomes), or high hypodiploidy (40–43 chromosomes)]), *KMT2A* (*MLL*) translocations, t(17;19)/*TCF3::HLF,* t(17;18)/*TCF4::HLF*, *BCR::ABL1, and BCR::ABL1*-like.[55,56] Hypodiploidy is associated with poor prognosis and is observed in 1% to 2% of pediatric patients.[57-59] Of note, low hypodiploid ALL is often associated with *TP53* pathogenic mutations, half of which are observed germline and associated with Li-Fraumeni syndrome.[60,61] In addition, it is worth noting that masked hypodiploidy, which results from a doubling of hypodiploid clones, needs to be distinguished from true hyperdiploidy to allow appropriate risk stratification and treatment selection. Single nucleotide polymorphism (SNP) array or whole genome sequencing to look for loss of heterozygosity (LOH) can distinguish true hyperdiploidy from masked hypodiploidy.[56]

The prevalence of chromosomal rearrangements involving the *KMT2A* gene, previously referred to as the human mixed lineage leukemia (*MLL*), is approximately 5% in pediatric ALL, with a higher incidence in infant ALL(~70%–80%).[62-65] These *KMT2A* rearrangements, including cases with t(4;11) translocation, are associated with poor outcomes, especially in infant ALL.[35,66,67] The translocation t(17;19)(q22;p13), resulting in the fusion gene *TCF3::HLF*, defines a rare subtype of pediatric ALL (<1%) and is associated with poor outcomes.[68,69] Conversely, another translocation

t(1;19) that results in the fusion gene *TCF3::PBX1* has an incidence of approximately 5% in pediatric ALL, and is associated with intermediate outcomes.[68,70]

B-ALL with *iAMP21* is characterized by amplification of a portion of chromosome 21, detected by fluorescence in situ hybridization (FISH) with a probe for the *RUNX1* gene.[71,72] Occurring in approximately 2% of children with ALL, B-ALL with *iAMP21* is associated with adverse prognosis when treated with low-intensity regimens.[71,72] Children with *iAMP21* are typically older, with a median age of 9 years, and have low platelet counts and low WBC counts.[73]

BCR::ABL1-positive ALL is associated with poor prognosis and is relatively uncommon among childhood ALL (2%), whereas this subtype is more common among adults (25%).[32,48] The frequency of *BCR::ABL1*-positive ALL increases with age, and younger children (1–9 years) with *BCR::ABL1*-positive ALL have a better prognosis than adolescents with this subtype.[74,75]

In pediatric B-ALL, the prevalence of mutations in the Ikaros gene (*IKZF1*) is approximately 15% to 20%[76,77] and these mutations occur at a higher frequency of >75% in the setting of *BCR::ABL1* positivity.[76,78] In many studies, *IKZF1* mutations are associated with a poor prognosis and a greater incidence of relapse.[78,79] *IKZF1* deletions with co-occurring deletions in *CDKN2A*, *CDKN2B* (homozygous), *PAX5*, or *PAR1* in the absence of *ERG* deletion, which are called *IKZF1*plus, as well as those with concomitant 22q11.22 deletions, are especially associated with worse outcomes in pediatric patients with B-ALL. However, *DUX4* rearrangements with *IKZF1* alterations do not confer poor prognosis.[78,80,81] Emerging data suggest that an intragenic *ERG* deletion is associated with favorable outcomes in pediatric B-ALL, and in this context, co-occurring *IKZF1* deletions do not affect prognosis.[82,83]

BCR::ABL1-like ALL is a subgroup of B-ALL associated with unfavorable prognosis, with a prevalence of approximately 15% in pediatric ALL.[84-86] A study using gene expression signatures to classify pediatric patients with ALL into subtypes estimated the 5-year DFS in the *BCR::ABL1*-like ALL group to be 60%.[86] In adult patients with *BCR::ABL1*-like ALL, the 5-year event-free survival (EFS) is significantly lower (22.5%; 95% CI, 14.9%–29.3%) compared to patients with non-*BCR::ABL1*-like ALL (49.3%; 95% CI, 42.8%–56.2%).[87] Although this subgroup is *BCR::ABL1*-negative, there is an otherwise similar genetic profile to the *BCR::ABL1*-positive ALL subgroup including an *IKZF1* mutation.[78] A study evaluating the relationship between *BCR::ABL1*-like and *IKZF1* in children with B-cell precursor ALL showed that 40% had co-occurrence of these mutations.[88] The presence of the *BCR::ABL1*-like signature and an *IKZF1* deletion were indicative of poor prognosis independent of conventional risk factors.[88] Genomically, the *BCR::ABL1*-like subtype is typically associated with gene fusions and mutations that activate tyrosine kinase pathways as the common mechanism of transformation. These gene fusions and mutations include ABL-class rearrangements (ie, *ABL1*, *ABL2, PDGFRA, PDGFRβ*, *FGFR1*), *JAK-STAT* rearrangements and/or mutations (ie, *CRLF2,*[89] *EPOR*, *JAK1, JAK2*, *JAK3, TYK2, SH2B3*, *IL7R*), and other rearrangements in *FLT3*, *NTRK3*, *LYN*, and *PTK2B* genes.[86,90,91] Genomic profiling studies have found that at least 80% of pediatric patients with *BCR::ABL1*-like ALL have cytokine receptor- or kinase-activating alterations, suggesting potential for ABL-class tyrosine kinase inhibitors (TKIs) or JAK small molecule inhibitors to significantly improve patient outcomes in this subgroup.[90-92]

Genetic Abnormalities Associated with T-ALL

T-ALL is characterized by activating mutations of *NOTCH1*, and rearrangements of transcription factors *TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *LYL1*, *TAL1*, and *KMT2A*.[85,93] The prevalence of activating *NOTCH1* mutations is over 50% in T-ALL., The prevalence of mutations in the

NOTCH1-targeting E3 ligase *FBXW7*, which leads to prolonged *NOTCH1* activation, is approximately 10% to 15%.[94-96] In patients with T-ALL, *NOTCH1* and *FBXW7* mutations have generally been associated with favorable prognosis and lower MRD levels.[97-99] However, it is unclear if these mutations are independent predictors of outcome, or if there needs to be concurrent absence of *RAS* or *PTEN* mutations.[100-102]

Integrated analysis of whole genome, exome, and transcriptome sequencing of T-ALL was performed in samples from children and adolescents treated in the AALL0434 study. The analysis identified 15 subtypes with distinct expression patterns, leukemic drivers, and outcomes as described in the *Prognostic Factors and Risk Stratification* section.[103]

The hematopathology review and molecular characterization studies described above allow determination of the WHO and ICC ALL subtypes and cytogenetic and clinical risk groups (see *ALL Subtypes* in the algorithm).[24,46]

NCCN Recommendations for Genetic Characterization

The presence of recurrent genetic abnormalities should be evaluated using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics), interphase FISH assays, reverse transcriptase-polymerase chain reaction (RT-PCR) testing, and next-generation sequencing (NGS) methods. FISH probes and RT-PCR primers should include those capable of detecting major recurrent genetic abnormalities. RT-PCR should measure and quantify transcript sizes (ie, p190 vs. p210) of *BCR::ABL1* in B-ALL. If samples are *ETV6::RUNX1* and *BCR::ABL1*-negative, testing for other gene fusions and mutations associated with *BCR::ABL1*-like ALL is encouraged, as it will aid in risk stratification. Recurrent gene fusions and mutations that activate tyrosine kinase pathways and are associated with *BCR::ABL1*-like ALL include: gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, *LYN*, *PDGFRB*, *NTRK3*, *PTK2B*, *FLT3*, and *FGFR1* and mutations involving *CRLF2*, *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions).[91,104] Low-density arrays (LDAs),[105] NGS-based assays, and multiplex RT-PCR are typically used to detect signature or cryptic rearrangements and mutations characteristic of *BCR::ABL1*-like ALL. Additional FISH probes that may be useful to consider include: centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; dual-color probe set to detect cryptic t(12;21), which will also allow detection of iAMP21 (when ≥5 copies of the *RUNX1* gene are detected); *CDKN2A* at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) *IGH::CRLF2* rearrangements; and probes to detect *JAK2* rearrangements.[106] In cases of aneuploidy or inadequate karyotype, additional assessment may include a microarray comparative genomic hybridization (aCGH) and/or NGS. Whole transcriptome sequencing can be used to identify B-ALL/LL subtypes defined by gene expression profile (ie, *ETV6::RUNX1*-like, *PAX5alt*, *MYCr*).

Workup

The initial workup for ALL should include a thorough medical history and physical examination, along with laboratory and imaging studies, including chest x-ray, and, if LL is suspected, CT or PET/CT. Laboratory studies should include a complete blood count (CBC) with platelets and differential, a blood chemistry profile, liver function tests, and disseminated intravascular coagulation panel (including measurements for D-dimer, fibrinogen, prothrombin time, and partial thromboplastin time). The blood chemistry panel should include a tumor lysis syndrome (TLS) panel (including measurements for serum lactate dehydrogenase [LDH], uric acid, potassium, phosphates, and calcium), especially for those with hyperleukocytosis and large leukemia burden, such as mediastinal mass. Patients of childbearing potential should undergo pregnancy testing, and patients with testes should be evaluated for testicular involvement of

disease, including a scrotal ultrasound as indicated. Testicular involvement is rare in ALL, with a prevalence of 1%–2% in males with ALL, but is slightly more common in T-ALL than B-ALL. For patients with T-LL and mediastinal mass, a multidisciplinary approach is necessary for obtaining biopsy specimen if peripheral blood and bone marrow are negative for blasts, and examination of pleural fluid, if present, by thoracentesis can be diagnostic, which also can alleviate respiratory symptoms.

Pediatric and AYA patients treated with cytotoxic chemotherapy, radiation therapy, and/or HCT may be at increased risk for infertility. Fertility counseling and/or preservation options should be presented to all patients (see NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology). Fertility preservation techniques such as sperm cryopreservation, oocyte cryopreservation, harvesting of ovarian or testicular tissue for cryopreservation, or embryo cryopreservation utilizing are options for some patients. Referral to a fertility preservation/reproductive health program should be considered for eligible patients prior to initiation of chemotherapy.[107,108] Counseling on cessation of smoking, drugs/illicit substances, vaping, and alcohol is also encouraged for AYA patients (see NCCN Guidelines for Smoking Cessation). Psychosocial assessment is also encouraged (see NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology).

Appropriate imaging studies should also be performed to detect meningeal disease, chloromas, or CNS bleeding for patients with major neurologic signs or symptoms at diagnosis. If neurologic symptoms are observed, a CT/MRI scan of the head with contrast is recommended. To rule out mediastinal masses and/or pleural effusion, a chest x-ray should be performed. If LL is suspected, a whole-body PET/CT scan is the recommended imaging modality; however, PET/MRI scans are being used at more centers to reduce radiation exposure. For centers without access to PET imaging, a CT scan suffices to identify areas of disease involvement. CNS involvement should be evaluated through lumbar puncture at timing that is consistent with the treatment protocol. Pediatric-inspired regimens typically include lumbar puncture and prophylactic intrathecal (IT) chemotherapy at the time of diagnostic workup. The NCCN Pediatric ALL Panel recommends that the first IT therapy be performed at the time of initially scheduled lumbar puncture unless directed by symptoms to perform earlier, although the procedure may be delayed in the presence of hyperleukocytosis and/or mediastinal mass (see *NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement*).

All patients should be evaluated for opportunistic infections as appropriate. In addition, an echocardiogram or cardiac scan should be considered for all patients due to the use of anthracyclines as the backbone of nearly all treatment regimens. Assessment of cardiac function is particularly important for patients with mediastinal mass, cardiomegaly, pleural effusion, prior cardiac history, prior anthracycline exposure, or clinical symptoms suggestive of cardiac dysfunction. To appropriately tailor doses of select components of chemotherapy including thiopurines and minimize adverse effects during treatment, pharmacogenomic testing for thiopurine methyltransferase (*TPMT*) and nucleoside diphosphate–linked moiety X-type motif (nudix hydrolase 15, *NUDT15*) should be considered. For dosing guidelines for thiopurines based on *TPMT* and *NUDT15* phenotype, see *Pharmacogenomics* in the algorithm.

During the workup, it is important to consider the potential influence of any ALL predisposition syndromes. A growing number of pathologic germline variants associated with ALL risk have been reported.[109] Importantly, children with Down syndrome are at an increased risk for the development of ALL.[110] For non-Down syndrome–related ALL, most patients do not have an identifiable leukemia predisposition syndrome. An exception is

low-hypodiploid (32–39 chromosomes) ALL where pathologic germline *TP53* variants are common and testing should be considered.[60] Other pathologic germline variants associated with ALL risk have been reported, particularly *PAX5, ETV6,* and *IKZF1*.[109] A complete family history can help identify risk for a cancer predisposition syndrome, although de novo mutations have been reported. There are increasing data to suggest that ALL can present as a second malignancy.[111] For patients with possible cancer predisposition syndromes, principles of cancer risk assessment and counseling should be taken into consideration (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate).

It should be noted that the recommendations included in the guidelines represent a minimum set of workup considerations, and that other evaluations or testing may be needed based on clinical symptoms. Procurement of cells should be considered for purposes of future research (in accordance with institutional practices or policies).

Prognostic Factors and Risk Stratification

Various disease-related and patient-specific factors may have prognostic significance in patients with ALL. In particular, patient age, WBC count, immunophenotypic/cytogenetic/genetic subtype, presence of CNS disease, and response to therapy have been identified as important factors in defining risk and assessing prognosis for both childhood and adult ALL.

Initially, risk assessment for childhood ALL was individually determined primarily by the institution, complicating the interpretation of data. However, in 1993, the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) established a common set of risk criteria.[112] In this system, two risk groups were designated: standard risk and high risk. Standard risk was assigned to patients aged 1 to <10 years and with a WBC count <50 × 10^9 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk.[59]

Different cooperative groups have used a combination of clinical, biologic, and response variables to allocate patients into risk groups based on outcome.[59,106,113] Some cooperative groups subdivide patients into five or more different risk groups that are used to tailor therapy. In B-ALL, patients with high-risk or very-high-risk disease have been found to have any of the following characteristics: t(9;22) chromosomal translocation (ie, *BCR::ABL1*-positive ALL) and/or presence of *BCR::ABL1* fusion gene; hypodiploidy (<44 chromosomes)[114]; *BCR::ABL1*-like[90]; *iAMP21*[71,115]; patients <1 year of age with *KMT2A* gene rearrangement[63,115]; or inability to achieve remission with induction therapy.[59] Conversely, criteria were refined for patients with lower risk and included hyperdiploidy—especially with simultaneous trisomies of chromosomes 4, 10, and 17[59,116]—and the t(12;21) chromosomal translocation (*ETV6::RUNX1* subtype).[117] The presence or absence of extramedullary disease and the early response to treatment (eg, MRD) also modified risk.

Risk stratification of T-ALL has been challenging, because other than MRD measurements, the clinical variables used to classify risk in B-ALL, including age and WBC counts, are not independently prognostic in T-ALL.[44] Although T-ALL is often categorized as high risk depending on the institution, newer treatment options have resulted in improved survival outcomes for these patients.[43,44,118,119] Furthermore, the identification of genetic mutations and the use of targeted therapies may change the way T-ALL is treated and ultimately how these patients are assessed for risk. Through a comprehensive analysis of genome and transcriptome sequencing of both tumor and remission samples from children with T-ALL (n = 1300), genomic features associated with clinical outcome have been identified.[103] This comprehensive genomic analysis could divide T-ALL into

15 subtypes with distinct expression patterns, leukemic drivers, and outcomes. Notably, in ~60% of cases the primary leukemic driver was due to genetic alterations in noncoding regions, requiring whole genome sequencing in >25% of cases. A higher risk of MRD positivity (MRD ≥ .01%) was noted in the setting of alterations in JAK-STAT and RAS signaling pathways as well as in the setting of ETP-like drivers and co-lesions, including *ETV6*, *H2B3*, *NRAS*, and *WT1*. Conversely, alterations in NOTCH, ribosome, and PI3K pathways as well as *CCN3D*, *LEF1*, *PI3K*, and *USP7* lesions were associated with lower risk of MRD positivity. Subtypes associated with poor EFS, DFS, and OS outcomes included SPI1, MLLT10, HOXA1, NKX2-5, and LMO2γδ-like subtypes. While the ETP-like KMT2A subtype was associated with poor outcomes, the non–ETP-like KMT2A subtype was associated with more favorable prognosis, despite higher MRD. Similarly, the ETP-like MLLT10 subtype was associated with worse prognosis than the non–ETP-like MLLT10 subtype, and the TLX3 immature subtype had worse prognosis than the TLX3 DP-like subtype. Similarly to the non-ETP like KMT2A subtype, the ZFP36L2 subtype was associated with favorable outcomes despite higher rates of MRD, suggesting that MRD status alone should not be the only factor in treatment decisions such as allogeneic HCT. Of note, these results should be validated in an independent cohort and require whole genome and/or whole transcriptome sequencing to identify many prognostic genomic features.

The POG and CCG have since merged to form the Children's Oncology Group (COG) and subsequent risk assessment has produced additional risk factors to further refine therapy.[115] In the United States, other groups have also developed standards for risk-stratified treatment approaches, including the St. Jude Consortium[120-122] and the Dana-Farber Cancer Institute (DFCI) ALL Consortium.[113,123,124] Initial risk stratification for these cooperative groups integrates the NCI criteria, such that patients are classified as having low-, standard-, high-, or very-high-risk disease (see *Risk Stratification Definitions, Initial Risk Group Stratification* in the algorithm). After induction remission therapy, each group applies additional risk-stratified criteria (see *Risk Stratification Definitions, Post-Induction Therapy Risk Group Stratification* in the algorithm). The Berlin-Frankfurt-Münster (BFM) Group categorizes risk based on several factors, including MRD, poor prednisone response, evidence of *MLL*/*AF4*, and hypodiploidy.[125,126]

COG Approach

In the COG approach, patients with B-ALL are initially classified as having standard-risk disease (ie, aged 1 to <10 years and WBC count <50 × 10^9 cells/L) or high-risk disease [ie, aged ≥10 years and/or WBC count >50 × 10^9 cells/L, CNS-3/testicular disease, t(9;22) chromosomal translocation (ie, *BCR::ABL1*-positive ALL and/or presence of *BCR::ABL1* fusion protein, and have received steroid pre-treatment)].[115] After induction, a critical measure used to ascribe risk is MRD,[115] and patients are classified as having favorable-, average-, or high-risk disease within initial standard- or high-risk classifications. The threshold for end-of-induction (EOI) MRD has decreased from ≥0.1% to ≥0.01%, and peripheral blood MRD is assessed at day 8 instead of day 8/day 15 bone marrow aspirates for morphology.[115] Risk stratification for T-ALL in the COG approach is primarily dependent on extramedullary disease and MRD status at both day 29 of induction as well as end of consolidation (EOC) for those patients who do not achieve remission at the EOI.[44] For patients requiring an EOC MRD assessment, the threshold between intermediate and very high risk is ≥0.1%.[44]

St. Jude Consortium Approach

In the St. Jude Consortium approach, patients with ALL are initially classified as having low-risk disease if they present with the following features: B-ALL with DNA index ≥1.16 or the *ETV6::RUNX1* fusion; or B-ALL with age 1–9.9 years and WBC count <50 × 10^9 cells/L. Patients

with standard-risk features include: patients with B-ALL aged ≥10 years or presenting with WBC count ≥50 × 10^9 cells/L (not including DNA index ≥1.16 or the presence of the *ETV6::RUNX1* fusion); patients with B-ALL with CNS-3 status, overt testicular leukemia, or adverse genetic features including *BCR::ABL1* fusion/t(9;22), *TCF3::PBX1* fusion/t(1;19), *KMT2A* rearrangement, hypodiploidy, *iAMP21*, or *MEF2D* fusion; patients with T-ALL; or patients with ALL that lacks low-risk features.[122] After induction, the same criteria hold true for low-risk and standard-risk groups, with an addition to the latter that estimates poor early response based on MRD (≥1% MRD on day 15 of remission induction, or ≥0.01% MRD at the EOI). Patients are categorized as having high-risk disease post-induction if MRD is detectable (≥1% MRD at the EOI or ≥0.1% MRD at the early intensification therapy and increasing) and/or persistent.

DFCI ALL Consortium Approach

In the DFCI ALL Consortium approach, patients with ALL are initially assigned to risk groups at day 10 of induction IA, based on the results of FISH, karyotype, and a targeted fusion NGS panel.[127] The initial grouping includes: standard risk (ie, aged 1 to <15 years, WBC count <50 × 10^9 cells/L, and lacking high-risk or very-high-risk adverse biologic features); high risk (ie, disease expressing *BCR::ABL1* and *iAMP21*, or if patients have T-ALL); or very high risk (ie, B-ALL with these features: *IKZF1* deletion, *KMT2A* rearrangement, low hypodiploidy or near haploidy, or *TCF3::HLF*/t[17;19]).[113] After induction, patients are classified as being at: low risk if they were initially at standard risk and have low MRD (<10^{-4}) at the EOI; or standard risk if they were initially at high risk and have low MRD at the EOI. In addition, high EOI MRD and persistent MRD are features of high-risk and very-high-risk disease.

For AYA patients treated in an adult setting, see the NCCN Guidelines for Acute Lymphoblastic Leukemia for additional risk stratification recommendations.

Treatment Considerations: Phases and Agents

The treatment approach to ALL represents one of the most complex and intensive programs in cancer therapy. Although the specific treatment regimens and selection of drugs, dose schedules, and treatment durations differ among pediatric, AYA, and adult patients, and among different subtypes of ALL, the basic treatment principles are similar. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance; however, these general treatment phases are further broken down into more detailed phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification (DI); continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance (IM) I and II. All treatment regimens for ALL include CNS prophylaxis and/or treatment. Some treatment plans may involve targeted agents and HCT.

Induction

Remission induction is the first block of chemotherapy with the intent of reducing tumor burden by clearing as many leukemic cells as possible from the bone marrow.[30] Induction regimens are typically based on a backbone that includes a combination of vincristine, corticosteroids (eg, prednisone, dexamethasone), and asparaginase with or without anthracyclines (eg, daunorubicin, doxorubicin).[29,30,120,128]

The BFM/COG regimens are mainly based on a 4-drug induction regimen that includes a combination of vincristine, an anthracycline, a corticosteroid, and asparaginase.[126,129-132] In the COG, patients classified as having NCI standard-risk disease are treated with a 3-drug induction that does not include anthracyclines. Some studies from the Cancer and Leukemia Group B (CALGB) have utilized a 5-drug regimen in AYA and adult patients, which adds cyclophosphamide to the above 4-drug combination.[133] The majority of protocols for patients with T-ALL use a 4-drug regimen.

Randomized studies comparing the use of dexamethasone versus prednisone as part of induction therapy in children with ALL showed that dexamethasone significantly decreased the risk of isolated CNS relapse and improved EFS outcomes compared with prednisone.[134,135] The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone into the CNS.[136] Although dexamethasone is reported to significantly reduce the risks for CNS relapse and improve EFS rates compared to prednisone, significant toxicities are associated with dexamethasone, especially used at high doses (eg, 10 mg/m^2 per day), including osteonecrosis and infection,[137,138] and an advantage for OS has yet to be conclusively shown, except in the subset of patients with T-ALL with prednisone good response in the AIEOP-BFM ALL 2000 study.[137] COG uses a dexamethasone schedule of 6 mg/m^2 per day for 28 days (instead of 10 mg/m^2 per day for 21 days used in the AIEOP-BFM ALL 2000 study) that was derived from studies from the Medical Research Council (MRC) of the United Kingdom.

Several different agents exist for asparagine depletion, including calaspargase, pegaspargase, and asparaginase *Erwinia chrysanthemi* (recombinant)-rywn (ERW-rywn). Compared to native *Escherichia coli*-derived L-asparaginase, pegaspargase has a longer half-life and decreased immunogenicity.[30,139] Calaspargase is an asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability and increases its half-life relative to pegaspargase.[140] As of December 1, 2022, pegaspargase can only be ordered for patients <1 month (31 days) or ≥21.5 years in the United States,[141] limiting its use in the pediatric population; thus, calaspargase is the preferred formulation if available for patients >1 month through 21.5 years. Calaspargase is not available in many countries and pegaspargase is the most commonly used product. ERW-rywn is typically given to patients who have experienced an allergic reaction to calaspargase or pegaspargase, and it requires a more frequent administration schedule (see prescribing information for further details). The U.S. Food and Drug Administration (FDA) approved an intramuscular dosing schedule for ERW-rywn of 25 mg/m^2 Monday/Wednesday and 50 mg/m^2 Friday based on a positive risk:benefit ratio from a phase 2/3 study,[142] in addition to 25 mg/m^2 administered intramuscularly every 48 hours.[143] Moreover, *E. coli*-derived L-asparaginase is currently not available in the United States and has been discontinued by the manufacturer.

Post-Induction Therapy Including Consolidation

The intent of post-induction that includes consolidation is to eliminate any leukemic cells potentially remaining after induction therapy, further eradicating residual disease. This phase of treatment may involve four to six cycles of therapy, and in some settings may occur over a duration of up to 8 months.[120] The consolidation phase is the treatment phase most affected by risk stratification, such that patients with lower-risk disease receive less intensive consolidation and patients with higher-risk disease receive consolidation that is more intensive.

Italian Association of Pediatric Hematology and Oncology (AIEOP)/BFM protocols use consolidation regimens with cyclophosphamide, cytarabine, and mercaptopurine (6-MP), and COG and others intensify therapy by adding vincristine and asparaginase (augmented BFM regimen) for patients with high-risk B-ALL and T-ALL. For T-ALL, nelarabine can also be added.[30,120,128,131,132] Thereafter, patients receive *IM therapy* and *DI therapy* (also known as *reinduction therapy*). Methotrexate (MTX) is crucial for controlling systemic leukemia as well as CNS and testicular disease. IM therapy includes high-dose MTX (HD-MTX) with leucovorin rescue plus 6-MP, Capizzi-MTX (escalating intermediate doses of MTX without leucovorin rescue plus vincristine and asparaginase), or escalating-MTX (escalating intermediate doses of MTX without leucovorin rescue plus vincristine) based on the treatment risk or leukemia cell lineage. The DI phase may vary among studies but can comprise combinations of drugs similar to those used during the induction and consolidation phases. In

COG protocols, thioguanine (6-TG) is primarily incorporated into DI,[144-152] and is also part of reinduction I and II in COG AALL1122.[153]

Maintenance

The goal of extended maintenance or continuation therapy is to prevent disease relapse after post-induction therapy. Most maintenance regimens are based on a backbone of daily 6-MP and weekly MTX (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.[30,120,128] Factors that affect the bioavailability of 6-MP can significantly impact patient care. Oral 6-MP can have highly variable drug and metabolite concentrations among patients.[154,155] Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.[156-158] The efficacy of maintenance therapy is determined by the metabolism of 6-MP to the antimetabolite chemotherapeutic agent 6-TG; however, other pathways compete for 6-MP, thereby reducing the amount of active metabolite produced. The four enzymes that metabolize 6-MP are xanthine oxidase (XO), hypoxanthine-guanine phosphoribosyltransferase (HPRT), TPMT, and NUDT15. Heterozygosity at the *TPMT* gene locus occurs in 5% to 10% of the population and has been shown to have intermediate enzyme activity.[159-161] NUDT15 deficiency, which is more prevalent in patients of East Asian descent and patients of Hispanic ethnicity, is also associated with 6-MP intolerance.[162] Therefore, determining a patient's *TPMT* and *NUDT15* genotype is recommended to optimize 6-MP dosing, especially in patients who experience myelosuppression at standard doses.[162] For dosing guidelines for thiopurines based on *TPMT* and *NUDT15* phenotype, see *Pharmacogenomics* in the algorithm.

Nonadherence also results in undertreatment, particularly in the AYA population. Adherence issues should be addressed for patients without cytopenia. If increasing doses of 6-MP are given during maintenance but no drop in the counts is observed, this may be indicative of nonadherence.[163] Quantification of 6-MP metabolites can be very useful in determining whether the lack of myelosuppression is due to nonadherence or hypermetabolism. Clinicians can also take a detailed history and perform pill counts to confirm adherence.

A systematic review and meta-analysis evaluated the benefit of periodic vincristine and corticosteroid by comparing contemporary studies with a reduced pulse frequency to those with a high pulse frequency in patients with B-ALL.[164] There was no benefit in OS or relapse risk with high pulse frequency, which was associated with a higher rate of grade 3+ nonhepatic adverse events.

Extramedullary Disease Prophylaxis and Treatment

The goal of CNS prophylaxis and/or treatment is to prevent CNS disease or relapse by clearing leukemic cells within sites that cannot be readily accessed with systemic chemotherapy because of the blood-brain barrier. CNS3 disease is associated with worse outcomes compared with CNS1 or CNS2 disease.[165] Patients with CNS2 also have worse outcome than those with CNS1 in B-ALL.[166] CNS-directed therapy may include IT therapy (eg, IT MTX with or without cytarabine and corticosteroid), cranial irradiation, and/or systemic chemotherapy (eg, dexamethasone, HD-MTX, intermediate-/high-dose cytarabine, asparaginase).[30,120,128,136,167] Cranial irradiation is often avoided in favor of IT therapy and systemic chemotherapy when possible due to concern for late adverse effects, particularly in patients with CNS1 or CNS2 status. CNS prophylaxis is typically given to all patients throughout the entire course of ALL therapy, from induction, to consolidation, to the maintenance phases of treatment. Patients with testicular disease at diagnosis that is not resolved by the EOI therapy may receive radiation to the testes.

Hematopoietic Cell Transplantation

Allogeneic HCT has demonstrated improved clinical outcomes in pediatric patients with ALL with evidence of certain high-risk features and/or

persistent disease.[120,168,169] In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, umbilical cord blood, or haploidentical donor).[169-171] Both total body irradiation (TBI) and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL.[171-173] Non-TBI–containing regimens are currently under investigation. The benefit of allogeneic HCT in infants with ALL is controversial, although some studies have demonstrated a role in patients with high-risk disease with *KMT2A* rearrangements and other poor-risk factors.[120,174,175] Based on the data, it is reasonable to consider HCT in first remission (CR1) for certain patients as described in the HCT sections throughout the discussion.

Targeted Agents

The emergence of targeted therapies for hematologic malignancies, including the treatment of *BCR::ABL1*-positive disorders with TKIs, represents an important advancement in ALL therapy.[176-180] Clinicians should be aware of variation among the TKIs relating to absorption from the GI tract. Additionally, histamine-2 antagonist or proton pump inhibitors (PPIs) can affect the bioavailability of some TKIs. In instances of *BCR::ABL1*-like ALL harboring *CRLF2* and *JAK* alterations, the utility of Janus kinase inhibitors is being explored.[181] The purine nucleoside analog nelarabine has been approved for the treatment of relapsed or refractory (R/R) T-ALL or LL.[182] Monoclonal antibodies to surface antigens such as CD19, CD20, CD22, CD38, and CD52 have been used in unconjugated form (eg, rituximab, epratuzumab, daratumumab), conjugated to immunotoxins or chemotherapeutic agents (moxetumomab, inotuzumab ozogamicin [InO]), or in the form of a bispecific antibody (blinatumomab).[120,183-185] Chimeric antigen receptor (CAR) T cells that target CD19 have demonstrated durable remissions in pediatric and AYA patients with R/R B-ALL.[186] Revumenib, an oral, small molecule *KMT2A* inhibitor, has been approved for the treatment of R/R acute leukemia, including ALL.[187]

Overall, these agents may be incorporated as part of frontline induction, consolidation, and/or maintenance regimens during the course of initial ALL therapy, and/or in R/R disease settings.

Treatment Considerations: AYA Patients

Historically, the AYA population has been treated on either a pediatric or an adult ALL regimen, depending on referral patterns and the institution. Several retrospective studies from both the United States and Europe have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved EFS compared to same-aged patients treated on adult ALL regimens.[19,128] Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense IT chemotherapy regimens.[188,189] Adult protocols also entail a greater use of allogeneic HCT compared to pediatric protocols, but the benefits of HCT in the AYA population have not been sufficiently studied, and the available data have conflicting findings.[190-194] However, this is a significant difference between the way adults and pediatric patients are treated and may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

Despite improved outcomes for AYA patients treated on pediatric-inspired regimens versus adult ALL regimens, studies have shown poorer outcomes among patients in the AYA group compared with children <10 years.[195] This may be attributed to factors that are based on biology and social differences. Compared to the pediatric population, AYA patients have a lower frequency of favorable chromosomal or cytogenetic abnormalities, such as hyperdiploidy or *ETV6::RUNX1*[196]; a greater incidence of poor-risk cytogenetics, including *BCR::ABL1*-positive ALL,

hypodiploidy, and complex karyotype[197]; and a higher incidence of ETP-ALL.[40,198] Furthermore, the positive prognostic values of the *ETV6::RUNX1* mutation and hyperdiploidy are greater in the pediatric population, suggesting that the benefits decline with age.[196]

The effects of the treatment are also shown to be different in the AYA population compared to the pediatric population. *In vitro* studies showed that ALL cells from children >10 years are more resistant to chemotherapy compared to the cells from children <10 years.[199] The COG AALL0232 study reported an initial delay in response to induction therapy in AYA patients aged 16 to 30 years compared to younger patients (aged 1–15 years).[200] The number of patients who had negative end-induction MRD was significantly lower in the cohort aged 16 to 30 years compared to the younger cohort (59% vs. 74%; $P < .0001$), with fewer patients achieving M1 marrow on day 15 of induction (67% vs. 80%, respectively; $P = .0015$). In addition to the biological differences, the social component of treating AYA patients is important. Enrollment in clinical trials has been shown to improve patient outcomes[201]; however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.[202] Pediatric patients have been shown to be more adherent to treatment protocols compared to AYA patients,[203] which may be due to greater parental supervision of the treatment and better health insurance coverage.[204]

Treatment Considerations: Vulnerable Populations

Infant ALL (<12 months of age) makes up 2% to 5% of pediatric ALL and represents a high-risk ALL group due to lack of response to treatment and treatment-related complications.[30,205] This is due in part to a high incidence of early bone marrow, CNS, and extramedullary relapse.[206] Infants with ALL also have an increased incidence of poor prognostic features, including high initial WBC count, massive organomegaly, thrombocytopenia, CNS leukemia at diagnosis, or *KMT2A* gene rearrangements at chromosome band 11q23—which is the most common molecular genetic rearrangement in infant ALL.[30,206,207]

Children with trisomy 21 (Down syndrome) have an increased risk of ALL, although the basis for this increased risk is unknown.[30,110,208] ALL in children with Down syndrome is associated with unique features, including the absence of ALL in patients <1 year of age; a lower incidence of favorable and unfavorable cytogenetics; increased sensitivity to MTX; and an increased susceptibility to infections.[208] Some reports have determined that ALL in children with Down syndrome frequently expresses *CRLF2*, which is associated with mutated *JAK2*.[209,210] Historically, children with ALL and Down syndrome have been shown to have poorer outcomes relative to non-Down syndrome–related ALL.[211] These differences may be due to poor adherence of physicians to protocol guidelines,[212] and an increased susceptibility to treatment-related toxicities and infections. In biologically defined subsets, current data suggest that the outcomes for children with ALL and Down syndrome are comparable to those of non-Down syndrome–related ALL.[208,213] For both infants and children with Down syndrome with ALL, it is essential to use protocols that have demonstrated safety in these patient populations and that incorporate aggressive and tailored supportive care measures (see *Special Considerations for Patients with Down Syndrome and Infants* in the algorithm).

Minimal Residual Disease

MRD in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods. Numerous studies in childhood ALL have shown the prognostic importance of post-induction and/or post-consolidation MRD measurements in predicting the likelihood of disease relapse.[214-223]

The most frequently used methods for MRD quantification include multiparameter flow cytometry (eg, 6-color or higher) to detect

leukemia-associated immunophenotypes, PCR assays to detect fusion genes (eg, *BCR::ABL1*), and clonal rearrangements in Ig and/or TCR genes.[224-231] New multiplexed PCR and NGS for MRD are emerging methodologies. Of note, there are limited data on the accuracy of NGS MRD in T-ALL, and NGS is not FDA approved for MRD detection in T-ALL.

Current multiparameter flow cytometry methods or PCR methods can detect leukemic cells at an optimal/maximal sensitivity threshold of at least 10^{-4} (<0.01%) bone marrow mononuclear cells (MNCs), and NGS methods can detect leukemic cells at an optimal/maximal sensitivity threshold of 10^{-6} (0.0001%) bone marrow MNCs, respectively.[225,227,229,230,232,233] The concordance rate for quantifying MRD between these methods is generally high at disease burdens 10^{-4} (>0.01%), but NGS is able to detect MRD at lower thresholds.[226,228,230,234-236] The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.[227,234,237] However, this practice could lead to an increase in cost without a clear directive in terms of modification of treatment.

MRD assessments at early time points in the course of treatment (eg, during or at the EOI and EOC) have been shown to be highly predictive of outcomes in children with ALL. In a study conducted by the COG for children with B-ALL (n = 2143), the prognostic impact of MRD was evaluated by flow cytometry in the peripheral blood at day 8, and in marrow at end-induction (day 29) and end-consolidation.[216] The presence of MRD in day 8 blood and day 29 marrow was associated with shorter EFS in all risk groups (NCI standard- and high-risk), and end-induction MRD predicted early relapses (within 3 years) and late relapses. The early relapse-free survival (RFS) rates in the setting of MRD negativity versus MRD positivity (>0.01%) were 6.8% and 28%, respectively ($P < .001$). In addition, the late RFS rates in the setting of MRD negativity versus MRD positivity were 4.6% and 24%, respectively ($P < .001$).[216] In a study of pediatric patients with ALL enrolled in Total Therapy studies at the St. Jude Children's Research Hospital (n = 158), patients with detectable MRD (flow cytometry optimal sensitivity level of 1×10^{-4}) at the EOI therapy had a significantly higher 3-year cumulative incidence of relapse than those who achieved MRD negativity (33% vs. 7.5%; $P < .001$).[238] Subsequent studies confirmed these findings.[239] In another study of pediatric patients with ALL enrolled in Total Therapy studies, nearly 50% of patients achieved MRD clearance (MRD $<1 \times 10^{-4}$ by flow cytometry) before day 19 of induction therapy (about 2–3 weeks from initiation of induction); the 5-year cumulative incidence of relapse was significantly higher among patients with MRD at day 19 of treatment than those without detectable MRD (33% vs. 6%; $P < .001$).[240]

MRD also emerged as a highly prognostic factor in the COG AALL0232 trial, in which pediatric patients with ALL (n = 2479 evaluable) were randomized in a 2 x 2 factorial design to receive either HD-MTX or Capizzi escalating-dose MTX during IM or prednisone or dexamethasone during induction.[241] MRD was assessed by 6-color flow cytometry, and patients with end-induction MRD <0.01% had a 5-year EFS of 87% ± 1% versus patients with an end-induction MRD ranging from 0.01% to 0.1% with a 5-year EFS of 74% ± 4%.[241] Patients who converted from MRD-positive to MRD-negative status by EOC had a favorable 5-year DFS rate compared to patients with MRD ≥0.01% (79% ± 5% vs. 39 ± 7%, respectively).[241] Although HD-MTX was superior to Capizzi-MTX, MRD retained prognostic significance in both groups.[241]

In the AIEOP-BFM ALL 2000 study, children with *BCR::ABL1*-negative B-ALL (n = 3184 evaluable) were risk stratified according to MRD status (PCR optimal sensitivity level $\leq 10^{-4}$) at two time points (days 33 and 78), which were used to guide post-induction treatment.[217] Patients were grouped into an MRD standard-risk arm if MRD was negative (with a

sensitivity of ≤10^{-4}) on day 33 and day 78, an MRD intermediate-risk arm if MRD was positive on either day 33 or 78 and <10^{-3} on day 78, and an MRD high-risk arm if MRD was ≥10^{-3} on day 78. The 5-year EFS rate was 92% for patients categorized as being at standard risk (n = 1348), 78% for those at intermediate risk (n = 1647), and 50% for those at high risk (n = 189), resulting in a statistically significant difference among the groups (*P* < .001); the 5-year OS rates were 98%, 93%, and 60%, respectively. Importantly, in this study, MRD remained a significant and independent prognostic factor for relapse in the overall population.[217] Data from the UKALL trial have also demonstrated that treatment intensity can be modified in children and young adult patients with ALL according to MRD at the EOI.[242,243]

The AIEOP-BFM ALL 2000 study also investigated the prognostic value of MRD by PCR for Ig and TCR gene rearrangements in children with T-ALL (n = 464).[220] The 7-year EFS rate was 91.1% for patients categorized as being at standard risk (n = 75), 80.6% for intermediate risk (n = 292), and 49.8% for high risk (n = 97), resulting in a statistically significant difference among the groups (*P* < .001). MRD negativity at day 33 was the most favorable prognostic factor. Importantly, MRD ≥10^{-3}% on day 78 was the most important predictive factor for relapse and, if MRD on day 78 was negative (48% of all patients), early MRD levels on day 33 were irrelevant for outcomes, highlighting the significance of later MRD assessments (EOC) on outcomes in pediatric T-ALL.

In the COG AALL0434 trial, most children with T-ALL (n = 1256) were classified by flow cytometry as having ETP, near-ETP, or non-ETP.[45] MRD was assessed by flow cytometry in peripheral blood on day 8, in the bone marrow on days 15 and 29 (EOI) and, for patients with high-risk disease (EOI M2 marrow or MRD ≥1.0%) or lack of response to induction (EOI M3 marrow), in the bone marrow on approximately day 57 (EOC). The risk-stratification grouping included MRD assessment by flow cytometry using the following cutoffs: low risk, <0.1%; intermediate risk, <1%; and high risk, >1%. Patients with ETP and near-ETP ALL were more likely to have high end-induction MRD levels, with a 5 times higher rate of lack of response to induction than those with non-ETP ALL. Interestingly, there were no differences in EFS or OS among the three groups, suggesting that patients with ETP and near-ETP experienced response to post-induction and/or off-protocol treatment. There was no difference in EFS or OS between patients with a day 29 MRD <0.01% and 0.01% to 0.1%. However, both near-ETP and non-ETP groups with day 29 MRD ≥0.1% had inferior EFS and OS, but this was not observed for those with ETP. A Day 29 MRD ≥10% was a significant predictor of inferior outcomes in all patients, and for patients with non-ETP with day 29 MRD ≥1%, end-consolidation MRD ≥0.01% was an important predictor of inferior EFS.

In a study conducted by the International BFM study group, MRD by flow cytometry on day 15 was included as part of risk stratification, with patients with day 15 MRD ≥10% included in the high-risk group and patients with day 15 MRD <0.1% included in the standard risk group. Other criteria for high risk included prednisone-poor response, *BCR::ABL1* or *KMT2A::AFF1*, hypodiploidy (≤44 chromosomes), or lack of complete response (CR) by day 33. Other criteria for standard risk included prednisone-good response, age >1 year and <6 years, lack of *BCR::ABL1* or *KMT2A::AFF1*, WBC <20 x 10^9/L at diagnosis, and achievement of CR by day 33. All other patients were included in an intermediate-risk group.[244] Patients at intermediate or high risk were also randomized to an augmented IB versus a standard IB regimen to evaluate whether increased early intensification impacted survival. MTX dose was also evaluated, with those in the intermediate-risk arm randomized to 2 g/m^2 versus 5 g/m^2. MRD was found to be prognostic, as 5-year EFS and OS were superior in the standard-risk group. EFS and OS rates for the standard-, intermediate-, and high-risk groups were 90.7% ± 1.4% and 94.7% ± 1.1%; 77.9% ± 0.7% and 85.7% ± 0.6%, and 60.8% ± 1.5% and

68.4% ± 1.4%, respectively. There was no significant difference in 5-year EFS among those who received augmented IB versus standard IB (*P* = .55). And the lower MTX dose of 2 g/m^2 was not found to be inferior to MTX 5 g/m^2 in terms of 5-year EFS (78.8% ± 1.4% vs. 78.9% ± 1.4% respectively; *P* = .84).

To examine the impact of integrating the assessment of genetic abnormalities with MRD, samples from a pediatric ALL cohort treated in the UKALL 2003 trial were analyzed (n = 3113).[245] MRD was measured at the EOI for 86% of the patients (n = 2678) by PCR analysis of Ig/TCR rearrangements. In tandem, patients were assigned to a genetic subtype based on immunophenotype, cytogenetics, and FISH.[245] Patients with disease with good-risk cytogenetics (*ETV6::RUNX1*, high hyperdiploidy [51–65 chromosomes]) demonstrated the fastest disease clearance, whereas patients with disease with high-risk genetics (*KMT2A* fusions, near haploidy, low hypodiploidy [<40 chromosomes], *iAMP21*, *TCF3::HLF*), and T-ALL demonstrated slower responses.[245]

In an analysis of 10-year outcomes of the UKALL 2003 trial, MRD was categorized into MRD low-risk (MRD <0.01% at EOI and undetectable prior to IM) and MRD high-risk (MRD ≥0.01% at EOI).[246] Patients with low-risk MRD were randomly assigned to receive one versus two cycles of standard DI while patients with high-risk MRD were randomly assigned to standard versus intensified post-induction therapy. In the low-risk group, 10-year EFS and OS rates were comparable with one versus two cycles of DI (EFS, 92.1% vs. 93.8%; *P* = .4; OS, 97.3% vs. 97.7%; *P* = .5) In the high-risk group, the 10-year EFS rate was higher with intensified therapy (87.2%) compared to standard therapy (82.3%), though not statistically significant (*P* = .09). High-risk group OS rates were similar with standard therapy versus intensified therapy (88.2% vs. 90.9%, respectively; *P* = .3)

Another study investigated the value of MRD in infants with *KMT2A*-rearranged ALL treated in the Interfant-06 protocol and found that EOI and EOC MRD levels predicted outcomes.[247] The 6-year DFS rates were 60.2%, 45%, and 33.8% for infants with negative, intermediate, and high EOI MRD levels, respectively (*P* = .0039). Positive MRD at EOC predicted dismal outcomes. The 6-year DFS rates were 68.2%, 40.1%, and 11.9% for infants with negative, intermediate, and high EOC MRD levels, respectively (*P* < .0001).

Stratification based on MRD may also indicate which patients should undergo allogeneic HCT versus continued chemotherapy. In the ALL-Relapse Study of the BFM Group (ALL-REZ BFM) 2002, children with an intermediate risk of relapse based on MRD were stratified based on a cutoff MRD level of 10^{-3}.[248] Patients with MRD ≥10^{-3} were allocated to receive HCT (n = 99). In this group, 83% had donors and underwent HCT versus 17% who had no suitable donor and therefore continued chemotherapy. The EFS was higher for patients receiving HCT (64% ± 5%) versus patients remaining on chemotherapy (24% ± 10%). Patients who had a low level of MRD (<10^{-3}) were directed to receive continued chemotherapy (n = 109). Within this cohort, 83 patients received either chemotherapy or radiotherapy alone and 22 patients received an allogenic HCT. There was no significant difference in EFS between these two groups (66% ± 6% vs. 80% ± 9%; *P* = .45). Results indicate that MRD can be useful to further risk stratify patients with intermediate risk of relapse to the appropriate treatment regimen. Of note, the study acknowledges that MRD cutoff values are regimen dependent and not necessarily applicable to other protocols. The ALL R3 and COG AALL1331 trials used a lower MRD optimal threshold (10^{-4}) to stratify patients for HCT, which may be reflective of the intensity of the induction regimens used.[249,250] Therefore, MRD levels may influence treatment decisions, but the application of this prognostic factor must be carefully evaluated on a regimen-by-regimen basis.

For children and adolescents with T-LL who were treated on the COG A5971 trial (n = 99), submicroscopic systemic disease (minimal disseminated disease) of T-LL cells was evaluated by flow cytometry.[251] In 71.7% (71 of 99) of the bone marrow samples obtained at initial diagnosis, T-LL cells made up 0.01% to 31.6% (median, 0.22%) of MNCs. Patients with stage II/III T-LL accounted for 57 of these 71 samples. Two-year EFS was significantly worse in patients with ≥1% and ≥5% of minimal disseminated disease than in those with <1% and <5%, respectively. The presence of T-LL cells in peripheral blood significantly correlated with that in the bone marrow. However, with more intensive therapy backbones in the AALL0434 trial, minimal disseminated disease was no longer prognostic.[252] In patients with T-LL treated on the COG AALL1231 trial, 86 of the 209 patients (41%) underwent bone marrow MRD assessment at the EOI.[253] MRD <0.1% (n = 75) was associated with a significantly better 4-year EFS compared to MRD ≥0.1% (n = 11) (89% ± 4.4% vs. 63.6% ± 17.2%; P = .025), though MRD was not associated with a significant difference in OS.

Up to 20% of children treated with intensive therapies for ALL will experience disease relapse.[254] MRD assessment may play a prognostic role in the management of relapsed disease.[255-257] Several studies suggest early assessment of MRD during induction treatment for initial relapse (eg, day 15 from initiation of treatment) may be highly predictive of subsequent relapse in children with ALL.[258,259] This raises the possibility of identifying patients with high-risk disease who may potentially benefit from earlier intensification or tailoring of treatment regimens, or for potentially allowing less-intensive treatments to be administered in patients at low risk for relapse based on early MRD measurements. Large trials are warranted to address these possibilities, although serial MRD measurements may likely be needed to monitor leukemic cell kinetics during the long course of treatment.

NCCN Recommendations for MRD Assessment

Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies.[214,217-222,241] The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate. If a validated MRD assessment technology with appropriate sensitivity (at least 10^{-4}) is not available locally, there are commercially available tests. Current flow cytometry assays or PCR methods can detect leukemic cells at an optimal sensitivity threshold of at least 1×10^{-4} (<0.01%) bone marrow MNCs,[225,227,232,233] and NGS methods can detect leukemic cells at an optimal/maximal sensitivity threshold of 10^{-6} (<0.0001%) bone marrow MNCs, respectively.[225,227,229,230,232,233] As noted previously, NGS methods are FDA approved to detect MRD in B-ALL but not in T-ALL. A baseline sample to characterize the leukemic clone should be obtained to facilitate interpretation of future MRD assessments.

MRD quantification can be affected by bone marrow aplasia, and some protocols require count recovery prior to sending MRD samples. Therefore, if an MRD sample is sent for analysis during aplasia, a subsequent MRD assessment may be needed after count recovery. In addition, prior treatment with immunotherapy or HCT can affect the interpretation of flow cytometry-based MRD results and should be assessed by a laboratory with experience in this setting. Strong consideration should be made for NGS-based MRD testing following CAR T-cell therapy, as detectable bone marrow MRD by NGS has been shown to be highly predictive of relapse following tisagenlecleucel in patients with ALL.[260]

The timing of MRD assessment varies depending on the ALL treatment protocol used, and may occur during or after completion of initial induction therapy. Negative MRD at the EOI is associated with excellent outcomes

and could be used to identify patients at low risk of relapse. The kinetics of MRD response are different between B-ALL and T-ALL, and in T-ALL MRD after consolidation therapy has been shown to be an important prognostic factor regardless of MRD status at the EOI.[45,220,245] Therefore, it is recommended that measurement be performed upon completion of induction therapy (during treatment of *de novo* or relapsed disease), EOC, and prior to HCT; additional time points for MRD evaluation should be guided by the treatment protocol or regimen used.[232,233] Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden. In general, MRD positivity at the EOI in B-ALL and EOC in T-ALL predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD prior to allogeneic HCT should be considered.

Management of *BCR::ABL1*-Negative or *BCR::ABL1*-Like B-ALL

Front-Line Management of *BCR::ABL1*-Negative or *BCR::ABL1*-Like ALL

The management of *de novo BCR::ABL1*-negative and *BCR::ABL1*-like B-ALL is complex and current regimens are based on a number of completed or ongoing trials referenced in the algorithm, which are summarized below.

COG AALL0331 and AALL0932

The COG AALL0331 trial helped establish the benefit of intensifying therapy for patients with EOI MRD >0.01%, which is now part of all COG protocols. This trial enrolled 5377 patients with standard-risk B-ALL and used a 3-drug induction without anthracyclines (ie, dexamethasone, vincristine, and pegaspargase), with post-induction assignment into refined risk groups based on genetics and early response (ie, standard-risk low, standard-risk average, and standard-risk high).[261] At the EOI, patients were randomized to receive standard consolidation (6-MP, vincristine, and IT MTX) versus intensified consolidation (cyclophosphamide, cytarabine, 6-MP, vincristine, pegaspargase, and IT MTX).[261] The 6-year EFS and OS for all evaluable patients with standard-risk disease were 89% and 96%, respectively, and intensified consolidation did not significantly improve outcomes for patients with standard-risk–average disease.[261] Patients with standard-risk–high disease (day 15 bone marrow ≥5% blasts and/or day 29 MRD ≥0.1%) were non-randomized to intensified consolidation and two intensified IM and DI phases, resulting in 6-year continuous CR and OS rates of 86% and 93% of patients, respectively.[261]

Due to the intensification of pre-maintenance therapy and modern risk stratification, the COG AALL0932 study, a randomized phase III trial, was designed to optimize maintenance therapy in newly diagnosed pediatric B-ALL by asking two questions: 1) Will a higher dose (40 mg/m^2/dose) for weekly oral MTX be superior to standard dose (20 mg/m^2/dose)?; and 2) Will a reduced frequency of vincristine and dexamethasone pulses (from every 4 weeks to every 12 weeks) impact outcomes? The 5-year DFS (95.1% [95% CI, 93.3%–96.8%] vs. 98.8% [95% CI, 97.9%–99.7%]; *P* = .92) and OS rates (94.2% [95% CI, 92.2%– 96.1%] vs. 98.1% [95% CI, 97.0%–99.2%]; *P* = .89) for patients with average-risk disease who received oral MTX 20 mg/m^2/dose versus 40 mg/m^2/dose were similar, suggesting that higher MTX starting dose does not improve outcomes.[145] The 5-year DFS for patients with average-risk disease randomized to receive vincristine and dexamethasone pulses every 4 weeks versus every 12 weeks was 94.1% (95% CI, 92.2%–96.0%) versus 95.1% (95% CI, 93.3%–96.9%) (*P* = .86). The 5-year OS for the every-4-week versus every-12-week regimens was 98.3% (95% CI, 97.2%–99.4%) versus 98.6% (95% CI, 97.7%–99.6%) (*P* = .69).[145] This study highlighted excellent outcomes in patients randomized to vincristine/dexamethasone pulses every 12 weeks, despite receiving one third of the amount of pulses used in standard of care in COG trials.

COG AALL0232 and AALL1131

The AALL0232 trial enrolled 2154 patients between the ages of 1 and 30 years who were diagnosed with high-risk B-cell ALL.[262] In this study patients were randomly assigned to receive dexamethasone versus prednisone during induction and HD-MTX versus Capizzi-MTX plus pegaspargase during IM1. HD-MTX showed improved 5-year EFS (79.6% vs. 75.2%; *P* = .008) and OS (88.9% ± 1.2% vs. 86.1% ± 1.4%; *P* = .025) rates compared to Capizzi-MTX. No statistically significant difference was reported in the occurrence of mucositis, neurotoxicity, osteonecrosis, or other toxicities. The ALL0232 trial compared dexamethasone 10 mg/m^2/day for 14 days to prednisone 60 mg/m^2/day for 28 days. Dexamethasone showed improved outcomes during induction in patients <10 years of age; however, it was associated with a higher risk of osteonecrosis in patients ≥10 years of age. These data suggest that age may be an important factor for the selection of a corticosteroid.[262]

Relative to pediatric patients with standard-risk B-ALL, patients with high-risk B-ALL experience high relapse rates and worse clinical outcomes.[178,241] Some approaches to combat this are investigating the integration of new agents into treatment after induction. The COG AALL1131 study was a phase III trial for patients aged 1 to 30 years with newly diagnosed high-risk B-ALL.[147,263,264] Patients enrolled in this trial received a standard 4-drug induction (dexamethasone/prednisone, vincristine, daunorubicin, and pegaspargase). The high-risk stratum of this study was designed to compare post-induction CNS prophylaxis with standard-of-care IT MTX versus triple IT therapy including MTX, hydrocortisone, and cytarabine.[264] Randomization was closed early after a futility boundary had been crossed, concluding that triple IT therapy was not superior to IT MTX. Neither 5-year post-induction DFS or OS rates statistically favored triple IT therapy over standard MTX; thus, IT MTX remains standard-of-care CNS prophylaxis in this setting. Another experimental arm of this study was designed to evaluate the safety and efficacy of clofarabine, cyclophosphamide, and etoposide as part of multiagent chemotherapy.[263] However, infectious toxicities precipitated the closure of this study arm. Another experimental arm investigated whether substituting post-induction chemotherapy (cyclophosphamide, cytarabine, and 6-MP) with cyclophosphamide and etoposide would improve the 4-year DFS of pediatric patients with very-high-risk B-ALL.[147] This substitution was not superior to the control arm. Given this experience, future therapeutic approaches will examine the utility of targeted agents. In this context, the COG has investigated the incorporation of dasatinib for newly diagnosed patients with high-risk *BCR::ABL1*-like B-ALL harboring *ABL*-class lesions (AALL1131),[90] and is investigating ruxolitinib for newly diagnosed patients with high-risk *BCR::ABL1*-like ALL harboring *CRLF2* rearrangements and/or a mutation that activates the JAK-STAT pathway (AALL1521).[148,265] In addition, ongoing trials are investigating whether the combination of immunotherapies with chemotherapy improves outcomes in certain subsets of patients (blinatumomab in standard-risk B-ALL: COG AALL1731; InO in high-risk B-ALL: COG AALL1732).

DFCI ALL Protocols 05-001, 11-001, and 16-001

The DFCI ALL Consortium Protocol 05-001 enrolled 678 children and adolescent patients (aged 1–18 years) with newly diagnosed *BCR::ABL1*-negative B-ALL, and tested a new risk stratification system.[113] At study entry, patients were classified as having standard-risk or high-risk disease and a 4-drug induction was used (prednisone, vincristine, doxorubicin, and pegaspargase).[113] After achieving CR, patients with high EOI MRD (≥10^{-3} via PCR analysis of patient-specific Ig or TCR rearrangements) and/or adverse cytogenetics (*KMT2A* rearrangement or hypodiploidy) were reclassified as having very-high-risk disease and received intensified therapy.[113] Among all patients, the 5-year EFS and OS rates were 87% (95% CI, 84%–89%) and 93% (95% CI, 90%–94%), respectively. The 5-year DFS rates for the standard-risk (n = 407),

high-risk (n = 176), and very-high-risk (n = 65) groups were 94%, 84%, and 79%, respectively.

To refine risk classification for future trials, the prognostic significance of alternative age and WBC count thresholds, alternative EOI MRD levels, and *IKZF1* deletion status were examined. The *IKZF1* deletion was associated with inferior 5-year EFS and higher cumulative incidence of relapse, including among patients with low MRD.[113] Further analysis of outcome by age demonstrated that patients with *BCR::ABL1*-negative B-ALL aged 10 to 14.99 years had similar EFS to those <10 years of age, whereas those ≥15 years of age had a significantly worse outcome.[113] In an ongoing trial, DFCI protocol 16-001 will incorporate some changes to risk stratification for B-ALL, including the use of: 1) 15 years as a cut-off to distinguish standard risk versus high risk; 2) prospective determination of *IKZF1* deletion status; and 3) assessment of MRD via NGS assay to identify patients with very-high-risk disease.[113]

The DFCI ALL Consortium Protocol 11-001 evaluated the efficacy and toxicity of calaspargase compared to standard pegaspargase in pediatric patients (aged 1–21 years) with newly diagnosed ALL or LL (n = 239).[140] Patients were randomized to receive IV standard pegaspargase (n = 120) or calaspargase (n = 119) and EOI MRD was assessed in patients with ALL by real-time quantitative PCR. Of 230 evaluable patients, 99% of patients in the standard pegaspargase group and 95% of patients in the calaspargase group achieved a CR (*P* = .12), and there was no difference in the frequency of EOI MRD between the two groups. In addition, a 3-week dosing schedule of calaspargase and a 2-week dosing schedule of standard pegaspargase had similar safety profiles and nadir serum asparaginase activity (SAA). The 5-year EFS (± standard error [SE]) was 84.9% (± 3.4%) for pegaspargase and 88.1% (± 3.0%) for calaspargase (*P* = .65).

St. Jude Total Therapy XV–XVII Studies

In the St. Jude Total XV study, 498 evaluable patients with newly diagnosed ALL (aged 1–18 years) were enrolled, with study aims of determining whether prophylactic cranial irradiation could be safely omitted in all patients and determining the impact on overall EFS.[121] Induction was comprised of multiagent chemotherapy (prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, and 6-MP), and upon hematopoietic recovery, MRD was assessed prior to intensified consolidation/continuation therapy according to risk-stratified groups. Of 498 patients, 492 (98.8%) entered CR (low risk, 99.6%; standard risk, 99.5%; and high risk, 90.4%). The 5-year EFS and OS estimates were 85.6% and 93.5%, respectively.[121] This study demonstrated that prophylactic cranial irradiation could be omitted without compromising OS.

In the Total XVI study, investigators evaluated whether a higher dose of pegaspargase (3500 U/m^2 vs. 2500 U/m^2) and early intensification of triple IT therapy would improve systemic and CNS control in pediatric patients with ALL (n = 598).[266] Patients with features associated with increased risk of CNS relapse received two extra doses of IT therapy during the first 2 weeks of remission induction. The 5-year EFS and OS rates were 88.2% and 94.1%, respectively, with a cumulative risk of any CNS relapse of 1.5%.[266] Higher doses of pegaspargase did not affect treatment outcome, and patients with features associated with increased risk for CNS relapse experienced significantly lower CNS relapse than patients with similar features in the Total XV study.[266]

The ongoing Total XVII study will incorporate novel precision medicine strategies based on genomic features and targeted treatment.[106] Some of these approaches include the use of NGS-based diagnostics. In addition, the Total XVII study will investigate the use of dasatinib in patients with disease with *ABL*-class chimeric fusions identified by RNA sequencing,

and ruxolitinib in patients with disease with alterations that activate the JAK-STAT signaling pathway.[106]

Blinatumomab

Blinatumomab is a bispecific T-cell–engaging antibody that directs CD3-positive effector memory T cells to CD19-positive target cells, inducing cell death.[267,268] Blinatumomab first showed promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al[185] evaluated the efficacy of blinatumomab in patients with MRD-positive *BCR::ABL1*-negative B-ALL (n = 21; age range, 20–77 years). MRD positivity was defined as never having achieved MRD negativity before blinatumomab or having experienced a hematologic remission with MRD ≥10^{-4}. After blinatumomab treatment, 16 of 20 evaluable patients achieved MRD negativity at a detection threshold of 10^{-4}.[185] After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.[269] Gökbuget et al[270] examined the efficacy of blinatumomab in an expanded cohort (n = 116; age range, 18–76 years) using a higher threshold for MRD positivity (hematologic CR with MRD ≥10^{-3}). After one 28-day cycle of blinatumomab, 88 of 113 evaluable patients achieved a complete MRD response, and the RFS rate at 18 months was 54%.[270] In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT, establishing blinatumomab as an effective “bridge to transplant” in patients with MRD positivity. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in pediatric and adult patients with R/R B-precursor ALL.[184,271-273] In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR (CR2) with MRD defined as disease ≥0.1% (see *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL* for discussion of studies related to blinatumomab use in R/R B-ALL).

More recently, the efficacy of 4 cycles of intensive chemotherapy (hyper-CVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone] alternating with HD-MTX and cytarabine) followed by 4 cycles of blinatumomab consolidation and maintenance alternating between 3 cycles of POMP (6-MP, vincristine, MTX, and prednisone) and 1 cycle of blinatumomab is being evaluated in an ongoing single-arm, phase II trial.[274] In this trial, which is enrolling patients ≥14 years of age with newly diagnosed *BCR::ABL1*-negative B-ALL, the estimated 3-year RFS was 73%, with no patients relapsing >2 years following the start of treatment.

In contrast to prior studies investigating blinatumomab as a means of eradicating MRD during or after multiagent therapy, the phase III ECOG-ACRIN E1910 trial investigated whether blinatumomab could improve outcomes in patients receiving chemotherapy who had achieved MRD negativity (<0.01%).[275] Patients with newly diagnosed Ph-negative B-ALL between the ages of 30 to 70 years initially received multiagent induction therapy with a BFM-like regimen adapted from E2993/UKALLXII. Polyethylene glycol (PEG) was added for patients <55 years of age and rituximab was added for CD20 positivity. Following induction, patients who achieved a CR/CR with incomplete count recovery (CRi) remained on study and proceeded to intensification with HD-MTX and pegaspargase for CNS prophylaxis. Thereafter, MRD status was assessed by 6-color flow cytometry. Patients were randomized to receive either 4 cycles of consolidation chemotherapy or 2 cycles of blinatumomab followed by 2 cycles of consolidation chemotherapy, followed by a third cycle of blinatumomab, followed by another cycle of consolidation chemotherapy, and finally a fourth cycle of blinatumomab. However, following the FDA approval of blinatumomab for patients with MRD-positive disease, those with MRD positivity in the trial were no longer randomized and assigned to the blinatumomab arm. All patients received POMP maintenance therapy for a total of 2.5 years. Patients were referred for allogeneic HCT at

provider discretion. For the entire cohort, CR/CRi rate following induction was 81%. For those who achieved MRD negativity, the addition of blinatumomab led to significant improvement in 3-year OS and RFS (85% and 80% for the blinatumomab arm versus 68% and 64%, respectively; *P* = .002 for OS).

Based on data from the ECOG-ACRIN E1910 trial[275] and a phase III randomized trial from Locatelli and associates investigating blinatumomab consolidation in children with relapsed B-ALL[276] (see Management of Relapsed or Refractory *BCR::ABL1*-Negative or *BCR::ABL1*-like ALL), the FDA approved blinatumomab for adult and pediatric patients ≥1 month with *BCR::ABL1*-negative B-ALL in the consolidation phase of multiphase chemotherapy.[277]

Hematopoietic Cell Transplant

For pediatric and AYA patients with *BCR::ABL1*-negative ALL in CR1, allogeneic HCT may be considered for patients who: 1) have persistent MRD positivity at EOC (regardless of genetic features); or 2) have high-risk genetic features and have persistent MRD positivity at the EOI.[241] In the latter group, it should be noted that some studies have examined the role of HCT in pediatric patients with hypodiploid B-ALL, and it is unclear whether HCT improves outcomes when given in CR1 in patients with MRD positivity at the EOI.[278-281] However, HCT for hypodiploid ALL may be considered in the context of a clinical trial.

Management of Relapsed or Refractory *BCR::ABL1*-Negative or *BCR::ABL1*-Like ALL

The outcomes of pediatric patients with R/R B-ALL have been historically poor. In addition, the number of previous regimens utilized in the relapsed/refractory setting and duration of CR1 impact outcomes.[254,282,283] In the guidelines, early relapse is defined as disease that recurs <36 months from initial diagnosis for isolated or combined bone marrow relapse or <18 months from initial diagnosis for isolated extramedullary relapse. Late relapse is defined as disease that recurs ≥36 months from initial diagnosis for isolated or combined bone marrow relapse or ≥18 months from initial diagnosis for isolated extramedullary relapse. In general, HCT is the only known curative therapy for early relapse of B-ALL. For patients with late relapses of B-ALL or late isolated CNS relapses of T-ALL, chemotherapy alone may be sufficient.[249,282] It has also been reported that patients who received CAR T cells can maintain long-term remission without subsequent HCT.[186] Several trials referenced in the algorithm have developed regimens that are currently used to treat R/R B-ALL, and these studies are summarized below.

ALL-REZ BFM 90

The ALL Relapse BFM 90 (ALL-REZ BFM 90) trial was designed to improve prognosis for pediatric patients with relapsed ALL (<19 years of age; n = 525) through additional multi-chemotherapy blocks.[284] The patients were stratified into three risk groups: A (early bone marrow relapses; n = 126); B (late bone marrow relapses; n = 183); and C (isolated extramedullary relapses; n = 64). Patients with early bone marrow or T-ALL relapse (poor prognosis group/PPG; n = 152) were eligible for experimental regimens. After treatment with this regimen, 440 patients (84%) achieved CR2, 25 patients died during induction, and 60 patients (11%) did not experience a response. A majority of patients in each group achieved CR2 (Group A: 83%; Group B: 94%; and Group C: 100%).[284] In addition, 117 patients received HCT in CR2. Significant differences existed between strategic groups: probability of EFS (pEFS)(A) = .17 ± .03; pEFS(B) = .43 ± .04; pEFS(C) = .54 ± .06; pEFS(PPG) = .15 ± .03; log-rank *P* < .001.[284] Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HCT.[284]

COG AALL01P2

In the COG AALL01P2 study, 124 pediatric patients aged 1 to 21 years with relapsed ALL were treated with 3 blocks of reinduction chemotherapy, with an upfront randomization in block order (arm A = blocks 1, 2, 3; arm B = blocks 1, 3, 2).[285] Patients with CNS leukemia were nonrandomly assigned to arm B to allow early introduction of high-dose cytarabine, and patients with mature B-ALL and Down syndrome were excluded.[285] In addition, patients with *BCR::ABL1*-positive ALL received imatinib with all chemotherapy blocks. Of 117 patients evaluable for response in block 1, 81.2% achieved a CR2. For early relapses (defined as recurrence <36 months after initial diagnosis) versus late relapses (defined as recurrence ≥36 months after initial diagnosis), the CR2 rates were 68% ± 6% and 96% ± 3% (P < .0001), respectively.[285] One objective of this study was to determine the feasibility of measuring MRD in a single COG central reference laboratory at the completion of each block to monitor the kinetics of response. The absence of MRD at the end of the first month of reinduction therapy was associated with better outcomes in all patients.[285] In addition, subsequent blocks of therapy reduced the MRD burden in 40 (71%) of 56 patients with MRD positivity after block 1.

UKALL R3

The UKALL R3 trial investigated the outcomes of pediatric patients with relapsed ALL aged 1 to 18 years (n = 239).[249] Patients were stratified into standard-, intermediate-, or high-risk groups based on the duration of CR1, site of relapse, and immunophenotype. In addition, patients were randomized to receive mitoxantrone or idarubicin on days 1 and 2 of induction.[249] After three blocks of therapy, all patients in the high-risk group and patients in the intermediate-risk group with post-induction high MRD (≥10^{-4} cells) received HCT. The estimated 3-year PFS and OS rates in the mitoxantrone versus idarubicin groups were 64.6% versus 35.9% (P = .0004) and 69% versus 45.2% (P = .004), respectively.[249] After a median follow-up of 84 months, PFS of all randomly assigned patients was 60% (95% CI, 54%–70%). Of 92 patients who received HCT, 58 (63%) remained in CR2, 13 (14%) died of complications, and 21 (23%) relapsed after HCT.[282] Of 70 patients who continued on chemotherapy, 49 (70%) remained in CR2, 2 (3%) died of complications, and 19 (27%) relapsed. At 5 years, the PFS was 56% (95% CI, 46%–65%) in patients with high MRD and 72% (95% CI, 60%–81%) in patients with low MRD (<10^{-4} cells; P = .0078).[282]

COG AALL07P1

Bortezomib is a proteasome inhibitor that has demonstrated some activity in relapsed pediatric ALL.[286-288] The COG AALL07P1 phase II study tested the hypothesis that adding bortezomib to reinduction chemotherapy in pediatric patients experiencing first relapse would increase CR2 rates.[286,289] Of the evaluable patients treated with bortezomib and chemotherapy (n = 135; B-ALL, n = 103; T-ALL, n = 22; T-LL, n = 10), overall CR2 rates were 68% ± 5% for patients with precursor B-ALL (<21 years of age), 63% ± 7% for very early relapse (<18 months from diagnosis), and 72% ± 6% for early relapse (18–36 months from diagnosis).[286] The CR2 rate for patients with relapsed T-ALL was 68% ± 10%.

Clofarabine-Based Regimens

Clofarabine is a second-generation purine analog that has demonstrated single-agent activity in R/R pediatric ALL[290,291] and is approved by the FDA as monotherapy for pediatric patients aged 1 to 21 years with R/R ALL treated with at least two previous regimens. Other clinical studies have evaluated its use in combination with chemotherapy.[292,293] A phase II study evaluated the efficacy and safety of clofarabine, etoposide, and cyclophosphamide in pediatric patients with R/R ALL (aged 1–21 years; n = 25).[292] The overall response rate (ORR) was 44% (7 CR, 4 CR with partial recovery) with a 67.3-week median duration of remission censored at last follow-up.[292]

Fludarabine-Based Regimens

A regimen of high-dose cytarabine and fludarabine followed by granulocyte colony-stimulating factor (G-CSF) (ie, FLAG alone) or combined with idarubicin (FLAG-IDA) yields response rates ranging from 39% to 83% in adult patients with R/R ALL.[294-297] In a study by Gabriel et al, 32 pediatric patients (median age, 10.4 years; range, 1.7–15.5 years) with high-risk leukemias, including relapsed ALL (n = 13), primary refractory ALL (n = 3), relapsed AML (n = 13), primary refractory AML (n = 1), and secondary AML (n = 2), were given the FLAG-IDA regimen.[298] Overall, 23 (71.9%) of 32 patients achieved a CR after a single course of FLAG-IDA. In patients with relapsed ALL, 10 (76.9%) of 13 achieved a CR, and in patients with primary refractory ALL, 2 of 3 achieved a CR—1 after a second course of FLAG-IDA and both had *BCR::ABL1*-positive disease.[298] Overall, 22 of the 23 patients who achieved remission (10 AML and 12 ALL) proceeded to HCT after further consolidation with 2 to 3 courses of the FLAG regimen.

High-Dose Cytarabine-Based Regimens

In a study by the CCG, 52 pediatric patients with R/R ALL received high-dose cytarabine and L-asparaginase.[299] By day 28, 10 patients had died from the disease and treatment-related complications. Of the 42 evaluable patients, 22 (42% of all patients) achieved CR2.[299] However, 16 of the 22 patients who entered CR2 subsequently relapsed, and the median duration of CR2 was 3 months (range, 0.7–19 months).[299]

Venetoclax-Based Regimens

In a phase I open-label study, the safety and efficacy of venetoclax combined with chemotherapy was evaluated in patients <25 years of age with R/R ALL.[300] ORR was 56% with venetoclax combined with dexamethasone, vincristine, and pegaspargase. The combination was well tolerated and responses were seen in patients with a variety of mutations, including *KMT2A* rearrangements.

Blinatumomab

Blinatumomab is a component of the growing arsenal of immunotherapies for cancer treatment, and is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (69%; including rapid MRD-negative responses) in AYA and adult patients with R/R B-precursor ALL (n = 25).[273,301] Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 AYA and adult patients with R/R *BCR::ABL1*-negative B-cell ALL that demonstrated a CR or CR without platelet recovery in 43% of patients within the first 2 cycles of treatment.[272,302] In a follow-up prospective, multicenter, randomized, phase III trial, patients with R/R B-cell precursor ALL (n = 405) were assigned to receive either blinatumomab (n = 271) or standard chemotherapy (n = 134).[271] The OS was longer in the blinatumomab group, with median OS at 7.7 months, compared to the standard chemotherapy group, with median OS at 4.0 months (95% CI, 0.55–0.93; P = .01).[271] Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard chemotherapy group with respect to both CR with full hematologic recovery (CR, 34% vs. 16%; P < .001) and CR with full, partial, or incomplete hematologic recovery (CR, CR with partial hematologic recovery [CRh], or CRi, 44% vs. 25%; P < .001).[271] Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.[271]

In a phase I/phase II open-label study, the safety and efficacy of blinatumomab was evaluated in children <18 years of age with R/R B-ALL.[184] Based on phase I data, the recommended dosage of blinatumomab was 5 µg/m^2/day for the first 7 days, followed by 15 µg/m^2/day afterwards.[184] Of the 70 patients who received this dosage, 27 (39%) achieved CR within the first 2 cycles, 14 (52%) of whom achieved complete MRD response.[184]

In a phase III trial, COG AALL1331, the efficacy of blinatumomab versus chemotherapy was evaluated in pediatric patients (aged 1–30 years) with intermediate- or high-risk B-ALL in first relapse (n = 208).[303] In this study, after re-induction chemotherapy (Block 1 of UKALLR3), patients were randomized to receive either two intensive chemotherapy blocks (arm A; n = 103) or two 4-week blocks of blinatumomab (arm B; n = 105). Randomization was halted early, not due to the triggering of the pre-defined DFS stopping rule, but due to the combination of higher DFS and OS, lower rates of serious adverse events, and higher rates of MRD negativity with blinatumomab compared to chemotherapy. At a median of 2.9 years, DFS favored the blinatumomab group, but was not statistically significant (54.4% vs. 39.0%; HR, 0.70; 95% CI, 0.47–1.03; *P* = .06), though the study was limited by early termination of randomization. The 2-year OS rate was statistically significant in favor of blinatumomab (71.3% vs. 58.4% in the chemotherapy group; HR, 0.62; 95% CI, 0.39–0.98; *P* = .04). In addition, a greater percentage of patients in the blinatumomab arm achieved MRD negativity after the first cycle of randomized therapy (75% vs. 32% in the chemotherapy group; *P* < .001), and this significant difference persisted following the second cycle of randomized therapy (66% vs. 32% in the chemotherapy group; *P* < .001). A higher percentage of patients in the blinatumomab arm were able to proceed to HCT (70% vs. 43% in the chemotherapy group; *P* < .001).

In another randomized phase III trial,[276] after induction therapy and two rounds of consolidation chemotherapy, 108 pediatric patients with high-risk B-ALL in first relapse were randomized to 1 cycle of blinatumomab versus chemotherapy for third consolidation prior to HCT. The 24-month EFS rate was 66.2% (95% CI, 50.1%–78.2%) in the blinatumomab arm compared to 27.1% (95% CI, 13.2%–43.0%) in the consolidation chemotherapy arm (HR, 0.33; 95% CI, 0.18–0.61; *P* < .001). Benefit for blinatumomab was seen across all specified subgroups and was independent of MRD status at the EOI or before the start of therapy. There was not a significant benefit in OS with blinatumomab compared to consolidation chemotherapy (HR, 0.43; 95% CI, 0.18–1.01). MRD remission by PCR was observed in a higher proportion of patients in the blinatumomab arm compared to the consolidation chemotherapy arm (90% vs. 54%, absolute percentage difference, 35.6% [95% CI, 15.6%–52.5%]). This benefit was also seen in the subgroup of patients with detectable MRD at baseline (93% vs. 24%, absolute percentage difference, 69.1% [95% CI, 45.4%–85.5%]). A total of 88.9% of patients in the blinatumomab arm proceeded to HCT compared to 70.4% in the consolidation chemotherapy arm. A post hoc analysis of the study reported similar findings, with more patients achieving MRD $<10^{-4}$ by PCR following third consolidation with blinatumomab compared to chemotherapy (81.5% vs. 48.1%, respectively; *P* = .0367).[304] Among patients with baseline MRD $\geq 10^{-4}$ (at end of second consolidation) who achieved MRD negativity after blinatumomab, 91% achieved MRD $<10^{-4}$ by day 15.

There are significant and unique side effects to blinatumomab treatment compared to the current standard-of-care regimens. In addition, blinatumomab requires prolonged exposure for efficacy due to a short half-life (mean ± standard deviation [SD]) of 1.25 ± 0.63 hours.[305] The most significant toxicities noted in clinical studies are CNS events and cytokine release syndrome (CRS). Neurologic toxicities have been reported in 50% of patients (median onset, 7 days) and grade 3 or higher neurologic toxicities, including encephalopathy, convulsions, and disorientation, have occurred in 15% of patients. CRS typically occurs within the first 2 days following initiation of blinatumomab infusion (see prescribing information for further details). Symptoms of CRS include pyrexia, headache, nausea, asthenia, hypotension, increased transaminases, and increased total bilirubin. The incidence of adverse events can be reduced with monitoring for early intervention at onset of symptoms. However, the serious nature of

these events underscores the importance of receiving treatment in a specialized cancer center that has experience with blinatumomab.

An arm of the phase III COG AALL1331 trial investigated the survival benefit of adding blinatumomab to chemotherapy in 255 patients (aged 1–30 years) with low-risk B-ALL in first relapse.[250] Following reinduction, patients were randomized to receive chemotherapy alone versus chemotherapy intercalated with three 4-week cycles of blinatumomab. While there was no significant DFS or OS benefit with the addition of blinatumomab for the overall cohort, blinatumomab did improve outcomes in patients with bone marrow relapse, with or without extramedullary relapse. For this specific patient cohort, the 4-year DFS and OS rates for those who received chemotherapy plus blinatumomab compared to chemotherapy alone were 72.7% ± 5.8% versus 53.7% ± 6.7 (*P* = .015) and 97.1% ± 2.1% versus 84.8% ± 4.8% (*P* = .020), respectively. However, for patients with isolated extramedullary relapse, 4-year DFS was poor for both arms, at 36.6% ± 8.2% for blinatumomab versus 38.8% ± 8.0% for chemotherapy (*P* = .62). Four-year OS rates were also similar for those with isolated extramedullary relapse, at 76.5% ± 7.5% for blinatumomab versus 68.8% ± 8.6% for chemotherapy (*P* = .53).

CAR T Cells

One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft-versus-leukemia effect through allogeneic HCT or donor lymphocyte infusions. However, this method resulted in a significant risk of graft-versus-host disease (GVHD). To circumvent this issue, current advances are focused on the use of one's own T cells to target the B-ALL cells. The generation of CAR T cells to treat B-ALL is a significant advancement in the field.[186,306-308] The treatment of patients with CAR T cells has served as a bridge for transplant, enabling patients who were formerly unable to receive a transplant due to poor remission status to achieve a CR and ultimately transplantation. It is also reported that patients who received CAR T cells can maintain long-term remission without subsequent HCT.[186] In a systematic review and meta-analysis of 38 studies utilizing CD19-directed CAR T-cell therapy in both children and adults (n = 2134) with R/R B-ALL, median EFS and OS were 13.3 months and 36.2 months, respectively, with an ORR of 76%.[309] CAR T-cell therapy relies on the genetic manipulation of a patients' T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.[310] Briefly, T cells from the patient are harvested and engineered to express a chimeric T-cell receptor that targets a cell surface tumor antigen (eg, CD19 on B-ALL cells). CAR T cells can be engineered to target any cell-surface antigen on leukemic cells, and even more than one antigen, which may help avoid the issue of tumor evasion via receptor down regulation. Studies of CAR T cells targeting antigens other than CD19 are ongoing.[310] The manufacturing of CAR T cells currently requires ex vivo viral transduction, activation, and expansion over several days to weeks to produce a sufficient cell number to engender disease response.[311] Following infusion, debulking of tumors occurs in less than a week and these CAR T cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

A study of 25 children and 5 adults infused with autologous T cells transduced with a CD19-directed CAR (CTL019) lentiviral vector showed a morphologic CR in 90% (27 out of 30) of patients within a month of treatment and an OS of 78% (95% CI, 65%–95%) and EFS of 78% (95% CI, 51%–88%) at 6 months.[312] There were 19 patients in sustained remission, 15 of whom received no further therapy.

The pivotal phase II ELIANA trial investigated the use of the CD19-directed CAR T-cell therapy tisagenlecleucel in 75 children and young adults with R/R B-ALL and demonstrated an overall remission rate

of 81% within 3 months of infusion, all of which were notably MRD negative.[186] This high response rate was associated with OS rates of 90% and 76% at 6 and 12 months, respectively. As with blinatumomab, T-cell activation was accompanied by severe CRS and neurologic toxicity, as well as higher infectious risks—though treatment-related mortality remained low.[186] Given these data, CTL019/tisagenlecleucel was recommended for accelerated approval by the FDA oncologic drug advisory committee in July 2017 and fully approved by the FDA in August 2017 for the treatment of patients aged <26 years with R/R precursor B-cell ALL. Recent long-term follow-up data, with a median follow-up of 38.8 months, demonstrated an overall remission rate of 82%.[313] Three-year EFS and OS rates were 44% and 63%, respectively. Estimated 3-year RFS rates were 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT.

A systematic review compared the efficacy of tisagenlecleucel to historical standard-of-care R/R regimens for children and AYA patients with R/R B-ALL.[314] In the intention-to-treat analysis, tisagenlecleucel was associated with significantly higher ORR ($P < .001$), lower hazard of death ($P < .001$), and higher adjusted OS probability at 4 years (44.05% vs. 32.86%) when compared to historical standard of care.

In a pilot clinical trial, 74 children and AYA patients (age range 1–29 years) with R/R B-ALL or B-LL were treated with huCART19, a humanized CD19 CAR T-cell product.[315] There were two cohorts: those with prior CAR exposure (retreatment cohort, n = 33) and those without prior CAR exposure (CAR-naïve cohort, n = 41). ORR was 98% for the CAR-naïve cohort (100% for patients with B-ALL) and 68% for the retreatment cohort at one month post infusion. RFS for the CAR-naïve cohort at 12 and 24 months was 85% and 74%, respectively, compared to 74% and 58% in the retreatment cohort. This study highlighted durable remissions in children and AYA patients with R/R B-ALL, even after previous CAR T-cell therapy.

The side effect profile of CAR T cells differs substantially from those observed with standard therapies (ie, chemotherapy, HCT). While side effects from CAR T cells may be severe, they have been reversible. Adverse events are attributed to CRS and macrophage activation that occur in direct response to adoptive cell transplant resulting in high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic complications. Tocilizumab, a monoclonal antibody against interleukin-6 receptor; siltuximab, an antagonist of interleukin-6; and corticosteroids are the main options used to manage CRS and neurotoxicity symptoms.[316,317] Several groups have developed comprehensive guidelines regarding grading systems for and management of CAR T-cell–associated toxicities.[318,319]

A post-hoc analysis of pooled data from five clinical trials that included 195 patients between the ages of 1 to 29 years with R/R CD19-positive ALL or lymphocytic lymphoma compared the safety and efficacy of CD19-directed CAR T-cell therapy in those with and without CNS involvement at relapse.[320] There was no significant difference in rates of CR at 28 days post infusion (97% vs. 94%; $P = .74$), RFS (60% vs. 60%; $P = .50$), or OS at 2 years (83% vs. 71%; $P = .39$) between the CNS-positive and CNS-negative cohorts. Additionally, the incidence and severity of CRS and neurotoxicity were not significantly different between the two groups, though the study required control of CNS disease both at time of enrollment and CAR T-cell infusion.

A phase II trial evaluated the safety and efficacy of the coadministration of CD19- and CD22-directed CAR T cells in patients ≤20 years with R/R B-ALL, including those with extramedullary relapse.[321] Ninety-nine percent of patients with hematologic relapse or refractory disease achieved MRD-negative CR. The 12-month EFS among this entire cohort was 73.5%, improved to 85% among those who proceeded to HCT. Among patients with isolated testicular and CNS relapse, 12-month EFS was 95% and

68.6%, respectively. Eighty-eight percent of patients experienced CRS and 20.9% of patients experienced neurotoxicity. Neurotoxicity was associated with three deaths.

Another phase II study evaluated the administration of sequential CD19-directed and CD22-directed CAR T-cell therapies in patients aged 1 to 18 years with R/R B-cell ALL. Patients first received CD19-directed CAR T-cell therapy, followed by CD22-directed CAR T-cell therapy upon achievement of CRi or MRD negative CR. Among patients who received the target dose of 0.5 x 10^6 to 5.0 x 10^6 cells/kg, including two patients who did not receive CD22-directed cells, 97% achieved an objective response at the 3-month mark. Eighteen-month EFS and DFS (censored for transplant) were 79% and 80%, respectively, with an OS of 96%. Nineteen percent of patients experienced grade 3–4 CRS while 5% of patients experienced grade 3–4 neurotoxicity. B-cell aplasia was noted in 45% of patients with evaluable data at data cutoff.

Inotuzumab Ozogamicin

InO is a calicheamicin-based antibody-drug conjugate targeting CD22. Following the generation of encouraging single-agent phase II data,[322] a randomized study was conducted comparing InO with standard intensive chemotherapy regimens in *BCR::ABL1*-negative or *BCR::ABL1*-positive ALL in first or second relapse, defined as >5% marrow blasts (n = 326). Compared to standard therapy, InO produced a significantly higher CR/CRi rate (80.7% vs. 29.4%; *P* < .001) and higher MRD-negative rates (78.4% vs. 28.1%; *P* < .001).[323] Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with *BCR::ABL1*-positive leukemia. The overall incidence of severe adverse events was similar across treatment arms, with a higher incidence of hepatic veno-occlusive disease observed in the InO group, related in part to dual alkylator-based transplant conditioning administered in remission. These data translated into a significant benefit in the median duration of remission (4.6 vs. 3.1 months; *P* = .03), median PFS (5 vs. 1.8 months; *P* < .001), and mean OS (13.9 vs. 9.9 months; *P* = .005).[323] In August 2017, InO received full approval from the FDA for the treatment of adults with R/R precursor B-cell ALL.

In an analysis of patients ≥60 years of age with newly diagnosed *BCR::ABL1*-negative ALL who were treated on phase II clinical trials with either intensive hyper-CVAD versus the combination of InO and mini-hyper-CVD (mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone), with or without blinatumomab, there was a trend for higher CR rate and lower rate of death in the InO plus mini-hyper-CVD arm. The 3-year EFS rate for InO plus mini-hyper-CVD was 49% compared to 29% for hyper-CVAD (*P* = .001). The 3-year OS rates were 54% versus 32%, respectively (*P* = .002).[324]

The phase II COG trial AALL1621 assessed the safety and efficacy of InO in 48 pediatric and AYA patients aged 1 to 21 years with R/R CD22-positive B-ALL.[325] CR/CRi was 58.3% and 66.7% of patients with CR or CRi had MRD <0.01%. Of patients who subsequently proceeded to HCT, 28.6% developed grade 3 sinusoidal obstruction syndrome (SOS).

Another phase II study assessed the safety and efficacy of InO in pediatric patients aged ≥1 to <18 years with R/R CD22-positive B-ALL.[326] Of the 27 evaluable patients, estimated ORR (including CR, CR with insufficient platelet recovery [CRp], and CRi) was 81.5%, with 81.8% of patients with response achieving MRD negativity. One-year EFS was 36.7% and OS was 55.1%, with a median follow-up of 16 months. Eighteen patients received subsequent consolidation therapy (14 with HCT, 2 with CAR T-cell therapy, and 2 with CAR T-cell therapy followed by HCT). Seven patients developed SOS, of which 6 were ≥ grade 3.

While pediatric experience with InO is relatively limited, based on available data, InO was FDA approved for pediatric patients aged ≥1 year with relapsed/refractory CD22-positive B-ALL on March 6, 2024. InO is also

associated with potentially fatal or life-threatening hepatic SOS, especially after HST,[327,328] as well as an increased risk of post-HCT non-relapse mortality (see prescribing information for further details). Ursodiol prophylaxis can be considered for prevention of SOS with use of InO.[329]

Revumenib

In the ongoing phase II AUGMENT-101 study, the safety and efficacy of the oral menin inhibitor revumenib was evaluated in adult and pediatric patients ≥30 days old (n = 94; 57 with efficacy-evaluable data; age range 1.3-75 years) with primary refractory or relapsed *KMT2Ar* acute leukemia, including 14 patients with ALL.[187] Many patients (43.6%) had received ≥3 prior lines of therapy and 50% of patients had undergone prior allogeneic HCT.

Patients received revumenib 163 mg (or 95 mg/m^2 for those weighing <40 kg) every 12 hours in 28-day continuous cycles. Dose of revumenib could be increased to 276 mg (or 160 mg/m^2 if weight <40 kg) if no concomitant strong CYP3A4 inhibitor was being utilized; however, this did not occur on study and is rare in R/R acute leukemia, as most patients require fungal prophylaxis with azoles. Among patients with evaluable data, the CR/CRh rate was 22.8%. ORR was 63.2% with 68.2% of patients with evaluable data achieving MRD negativity. Among those who achieved response, 38.9% were able to proceed to allogeneic HCT and half of these patients receive revumenib maintenance therapy following HCT.

The most common adverse effects were nausea/vomiting/diarrhea, febrile neutropenia (grade ≥3 febrile in 37.2% of patients, and edema. Grade ≥3 differentiation syndrome occurred in 16% of patients and grade ≥3 QTc prolongation occurred in 13.8% of patients.

Based on this data, the FDA approved revumenib for R/R acute leukemia with a *KMT2A* translocation in adult and pediatric patients ≥1 year.

Hematopoietic Cell Transplant

For patients with early relapse of B-ALL, HCT is the only currently established curative modality. The CIBMTR group conducted an analysis of outcomes of patients with ALL (n = 582; median age, 29 years; range, <1 to 60 years) who underwent transplant during relapse.[330] At 3 years, OS rates were 16% (95% CI, 13%–20%).[330] Based on findings from an evidence-based review of the published literature, the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines recommend HCT for pediatric patients with ALL in CR2 after experiencing an early marrow relapse.[331]

NCCN Recommendations for *BCR::ABL1*-Negative or *BCR::ABL1*-Like ALL

Front-Line Management

The Panel recommends that pediatric and AYA patients with *BCR::ABL1*-negative or *BCR::ABL1*-like ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are initially grouped according to risk criteria (see *Risk Stratification Definitions, Initial Risk Group Stratification* in the algorithm), and induction therapy consists of multiagent chemotherapy. Patients who achieve MRD-negative CR after induction will continue risk-stratified therapy. Blinatumomab may be incorporated into frontline therapy as a post-remission approach based on data from ECOG1910.[275] Patients with MRD-positive CR after induction may undergo intensified consolidation therapy, also with the option to include blinatumomab. If MRD remains persistent, other options include blinatumomab or tisagenlecleucel (category 2B recommendation). The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. In all circumstances, HCT may be considered as part of consolidation or maintenance therapy. However, the role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood (persistent B-cell aplasia) and

negative NGS MRD have been associated with durable clinical responses without subsequent HCT.[260,313] In the global registration trial, estimated 3-year RFS rates were 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT.[313] Patients with less than CR after induction should be treated as having refractory disease.

R/R Management

For pediatric and AYA patients with *BCR::ABL1*-negative or *BCR::ABL1*-like ALL experiencing early or late first relapse, the Panel recommends initial treatment with systemic therapy. If patients experience CR (CR2) with MRD negativity, the options are to receive blinatumomab or continue on systemic therapy and receive maintenance therapy or HCT if feasible based on the risk of subsequent relapse. If patients experience CR2 with MRD positivity, or are experiencing first relapse after a prior HCT, in addition to chemotherapy, blinatumomab, tisagenlecleucel, or InO may be considered prior to either a first or second HCT. In instances of both CR2 with MRD negativity or positivity, the recommendation for blinatumomab applies to patients with bone marrow relapse, with or without extramedullary relapse.[250,276,303] If patients experience less than a CR (ie, multiple relapse), treatment options include chemotherapy, blinatumomab, tisagenlecleucel, or InO ± mini-hyper-CVD, and they may receive HCT as consolidation therapy if their disease subsequently responds to therapy. Long-term remissions have also been reported after tisagenlecleucel treatment without subsequent HCT; thus, the role of HCT following tisagenlecleucel is unclear.[186] If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care.

Management of *BCR::ABL1*-Positive B-ALL

BCR::ABL1-positive ALL is relatively rare in pediatric patients, and the development of TKIs has improved previously poor treatment outcomes.[84] The management of *BCR::ABL1*-positive B-ALL as outlined in this discussion is based on a number of clinical trials referenced in the algorithm, which are summarized below.

Front-Line Management of Ph-Positive ALL

COG AALL0031 and AALL0622

In a multicenter study (COG AALL0031), children and adolescents with *BCR::ABL1*-positive ALL (n = 92; aged 1–21 years) were treated with an intensive chemotherapy regimen combined with imatinib (340 mg/m^2/day; given during postremission induction therapy and maintenance).[178] Among the cohort (n = 44) who received continuous imatinib exposure (280 consecutive days before maintenance initiation), the 3-year EFS rate was 80.5% (95% CI, 64.5%–89.8%). This outcome compared favorably with that of a historical population of patients with *BCR::ABL1*-positive ALL (n = 120) treated on a POG protocol, which showed a 3-year EFS rate of only 35% (P < .0001).[178] Moreover, the 3-year EFS rates were similar among the groups of patients who received chemotherapy combined with continuous imatinib (88%; n = 25) or allogeneic HCT from a related donor (57%; n = 21) or unrelated donor (URD) (72%; n = 11). No major toxicities were found to be associated with the addition of imatinib to the intensive chemotherapy regimen.[178] Subsequent follow-up after 5 years confirmed these outcomes.[179] In a phase II single-arm trial (COG AALL0622) of children and young adults with *BCR::ABL1*-positive ALL (n = 60; aged 1–30 years), imatinib was replaced with dasatinib on induction day 15 and combined with the same chemotherapy used in COG AALL0031.[180] The 5-year OS and EFS rates (± SD) were 86% ± 5% and 60% ± 7%, respectively, and outcomes were similar to those observed in COG AALL0031.[180]

EsPhALL

The European intergroup study of post-induction treatment of *BCR::ABL1*-chromosome positive ALL (EsPhALL) reported results of the randomized open-label trial designed to evaluate the safety and long-term efficacy of discontinuous post-induction imatinib plus chemotherapy with the BFM backbone intensive treatment versus chemotherapy alone.[177] The study enrolled 108 patients with good-risk disease and 70 patients with poor-risk disease aged 1 year to 18 years. Patients in the good-risk group were randomized 1:1 and patients in the poor-risk group were all assigned to receive chemotherapy plus imatinib. There was a trend towards improved 4-year DFS for those in the good-risk group who received imatinib plus chemotherapy versus those who received chemotherapy alone (72.9% vs. 61.7%; *P* = .24). In the as-treated analysis, patients in the good-risk group who received imatinib with chemotherapy had a 4-year EFS of 75.2% versus 55.9% in those who did not receive imatinib (*P* = .06). The incidence of serious adverse events was not statically different between the two groups (*P* = .64).[177] Enrollment in this trial was stopped in 2009 following results of the COG AALL0031 study that demonstrated a benefit of continuous imatinib. The EsPhALL study was amended into a single-arm study to add continuous imatinib on induction day 15, with 97% of patients achieving first CR.[176] However, the 5-year EFS and OS rates (57% and 71.8%, respectively) were similar in cohorts that received discontinuous post-induction imatinib and continuous imatinib plus chemotherapy with the BFM backbone intensive treatment.[176,177] Additionally, a phase II trial evaluated the safety and efficacy of adding continuous dasatinib at day 15 to the intensive BFM regimen in pediatric patients with newly diagnosed *BCR::ABL1*-positive ALL (n = 109 enrolled; age range, 1–17 years).[332] The efficacy analysis included 104 patients, who all achieved CR; 15 of the patients received allogeneic HCT in CR1. An interim analysis showed a 3-year EFS of 66.0% (95% CI, 54.8%–75.0%) and a 3-year OS of 92.3% (95% CI, 85.2%–96.1%).[332]

St. Jude Total Therapy XV–XVII Studies

In the Total XV and XVI studies from the St. Jude Children's Research Hospital, Jeha et al sought to compare the response rates and overall clinical outcome of pediatric patients with *BCR::ABL1*-positive ALL treated in the pre-TKI era versus with the current approach of incorporating a TKI.[333] Patients with newly diagnosed B-ALL (n = 1035; age range, 1–18 years) were treated on low- and standard-/high-risk arms, including 30 patients with *BCR::ABL1*-positive ALL.[333] The TKIs imatinib or dasatinib were administered continuously through all phases of treatment starting on days 22 through 26 of remission induction therapy, and resulted in significant reductions in MRD when compared to the pre-TKI cohort that received chemotherapy alone (*P* < .001).[333] The 5-year EFS for the TKI versus pre-TKI groups was 68.6 ± 19.2% versus 31.6 ± 9.9%, respectively (*P* = .022).[333] In the Total XVII study, dasatinib will be given to patients with *BCR::ABL1*-positive ALL and patients with disease with ABL-class chimeric fusions (ie, involving *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, or *PDGFRB*) identified by RNA sequencing.[106] In this setting, dasatinib will be given on day 15 of remission induction.[106]

Blinatumomab

Treatment of adults with newly diagnosed Ph-positive ALL was evaluated in a phase 2 single-group trial using dasatinib chemotherapy-free induction followed by first-line consolidation therapy with blinatumomab.[334] Sixty-three patients, aged 24 to 84, were enrolled. At the EOI, 29% of patients achieved a molecular response, which increased to 60% after 2 cycles of blinatumomab.[334] Long-term follow-up results revealed 53-month DFS, OS, and EFS rates of 75.8%, 80.7%, and 74.6%, respectively.[335] *IKZF1*^{plus} status was associated with significantly worse outcomes. Twenty-nine patients who achieved molecular response remained on single-agent TKI and did not go on to receive chemotherapy or allogeneic HCT, and 28 of these patients remained in long-term complete hematologic response at the time of publication.

A phase II study explored the chemotherapy-free, simultaneous combination of blinatumomab and ponatinib in 60 patients ≥18 years of age with newly diagnosed Ph-positive ALL.[336] With a median follow-up of 24 months, 83% of patients achieved complete molecular response by RT-PCR and 98% achieved MRD negativity by a highly sensitive NGS-based, targeted, deep-sequencing assay. Three-year OS and EFS rates were estimated at 91% and 77%, respectively. Three patients had to discontinue blinatumomab secondary to adverse events, while 9 patients discontinued ponatinib due to adverse events (including cardiac and vascular events).

Hematopoietic Cell Transplant

A retrospective analysis by Arico et al reported significant improvement in 5-year DFS and OS for pediatric and AYA patients with *BCR::ABL1*-positive ALL in CR1 who received HCT, including matched related donor, matched URD, or mismatched related donor allogeneic HCT or autologous HCT, versus those who received chemotherapy alone without TKIs.[331,337] In the large, international, collaborative MRC UKALL XII/ECOG E2993 trial conducted in patients with previously untreated ALL, the subgroup with *BCR::ABL1*-positive disease (n = 267; median age, 40 years; range, 15–60 years) was eligible for allogeneic HCT if patients were <50 (in the ECOG E2993 trial) or 55 (in the MRC UKALL XII trial) years of age and had a matched sibling or matched URD.[338] Among the *BCR::ABL1*-positive patient cohort, post-remission treatment included matched sibling allogeneic HCT (n = 45), matched URD allogeneic HCT (n = 31), and chemotherapy alone (n = 86). The 5-year OS rate according to postremission therapy was 44%, 36%, and 19%, respectively, and the 5-year EFS rate was 41%, 36%, and 9%, respectively.[338] Both the OS and EFS outcomes for patients who underwent allogeneic HCT (related or unrelated) were significantly improved compared with those who received only chemotherapy. The incidence of transplant-related mortality was 27% with matched-sibling allogeneic HCT and 39% with matched URD HCT.

An intent-to-treat analysis of patients with a matched sibling donor versus those without a matched sibling donor showed no statistically significant difference in 5-year OS rates (34% vs. 25%, respectively).[338]

As mentioned earlier, the COG AALL0031 trial reported similar 3-year EFS rates among patients in the very-high-risk group with *BCR::ABL1*-positive ALL in CR1 who received imatinib with intensive chemotherapy followed by HCT or those who received chemotherapy with imatinib maintenance without HCT.[178,179,331]

Management of R/R *BCR::ABL1*-Positive ALL

As previously mentioned, the outcomes of pediatric patients with R/R B-ALL has been historically poor. In *BCR::ABL1*-positive ALL, several mechanisms may contribute to this including the development of resistance to TKIs.[84] Several trials referenced in the algorithm have developed regimens that are currently used to treat R/R *BCR::ABL1*-positive B-ALL and these studies are summarized below.

Chemotherapy and Tyrosine Kinase Inhibitors

In a phase I study, the efficacy and toxicity of imatinib was evaluated in pediatric patients with R/R *BCR::ABL1*-positive leukemia, including those with ALL, AML, and chronic myeloid leukemia (CML) (n = 31).[339] In this study, imatinib demonstrated a good toxicity profile and was well tolerated at doses ranging from 260 to 570 mg/m^2/day. Among patients with ALL evaluable for morphologic response (n = 10), 7 achieved an M1 (0%–5% bone marrow blast cells) and 1 achieved an M2 (>5%–25% bone marrow blast cells) bone marrow.[339] In the COG AALL0031 study, pediatric patients with *BCR::ABL1*-positive ALL who relapsed after initial treatment with imatinib and chemotherapy were able to achieve an overall CR2 rate of 67% (n = 20/30).[179] Of the patients who attained CR2, 85% (n = 17/20) remained in remission for at least 3 months.[179]

The phase II COG AALL1122 study evaluated the safety and efficacy of dasatinib combined with intensive chemotherapy (EsPhALL) in children aged >1 to <18 years with newly diagnosed *BCR::ABL1*-positive ALL.[153] Patients were considered at high risk if they had MRD of ≥0.05% following induction 1B or had detectable MRD after 3 consolidation blocks, and those deemed at high risk were allocated to HCT in CR1 (only 14% received HCT). All others were considered at standard risk and received dasatinib plus chemotherapy for 2 years. All patients who were treated achieved CR. The addition of dasatinib to chemotherapy led to a significant improvement in 3-year EFS compared to chemotherapy alone (65.5% vs. 49.2%; *P* = .032) and was found to be non-inferior to imatinib plus chemotherapy (65.5% vs. 59.1%; *P* = .027), despite relatively few patients proceeding to HCT in CR1. Febrile neutropenia and bacteremia were the most common grade 3–5 adverse events and there were no dasatinib-related deaths during the study.

The safety and efficacy of ponatinib with or without multiagent chemotherapy was retrospectively studied in 12 patients <21 years (median age, 12 years) with *BCR::ABL1*-positive ALL or *BCR::ABL1*-like ALL with mutations sensitive to ponatinib.[340] All but one patient had been treated with 1 to 3 prior TKIs. Eight patients experienced improvement in disease burden and 1 patient had stable disease. While there were no grade 4–5 adverse events, temporary discontinuation of ponatinib was required in 4 of the 12 patients due to grade 3 toxicities, including rash, pancreatitis, pleural/pericardial effusions, posterior reversible encephalopathy syndrome (PRES), and elevated bilirubin.

Venetoclax-Based Regimens

As mentioned previously, in a phase I open-label study, venetoclax combined with dexamethasone, vincristine, and pegaspargase revealed an ORR of 56% in patients <25 years of age with R/R ALL.[300] For a summary, refer to *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL*.

Blinatumomab

An open-label, single-arm, multicenter, phase II study evaluated the efficacy and safety of blinatumomab in adult patients (aged ≥18 years) with R/R *BCR::ABL1*-positive ALL who had progressed after imatinib and at least one second- or third-generation TKI (n = 45).[341] During the first two cycles of blinatumomab, 36% achieved CR or CRh, and 88% of those with response achieved a complete MRD response.[341] In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-cell ALL (*BCR::ABL1*-negative and *BCR::ABL1*-positive) and clinical studies described earlier include patients with R/R *BCR::ABL1*-positive and *BCR::ABL1*-negative ALL.[184,271-273] Several adult studies have tested the combination of blinatumomab and a TKI.[341,342] For discussion of these studies, see *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL*.

CAR T Cells

Clinical studies described earlier include patients with R/R *BCR::ABL1*-positive and *BCR::ABL1*-negative ALL.[186,312,343,344] For discussion of these studies, see *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL*.

Inotuzumab Ozogamicin

Clinical studies described earlier include patients with R/R *BCR::ABL1*-positive and *BCR::ABL1*-negative ALL.[322,323,345] For discussion of these studies, see *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL*.

Hematopoietic Cell Transplant

As mentioned previously, the ASTCT guidelines recommend HCT for pediatric patients with ALL in CR2 after experiencing an early marrow

relapse.[331] Treatment options are extremely limited for patients with *BCR::ABL1*-positive ALL who experience relapse after receiving consolidation with allogeneic HCT. Some studies have reported on the feasibility of inducing a second molecular CR with TKIs including imatinib and dasatinib in those who have experienced an early relapse after first allogeneic HCT, which allowed for a second allogeneic HCT.[346-348]

NCCN Recommendations for *BCR::ABL1*-Positive ALL

Front-Line Management

The Panel recommends that pediatric and AYA patients with *BCR::ABL1*-positive ALL be treated in a clinical trial that incorporates TKIs when possible. In the absence of an appropriate clinical trial, patients are treated with chemotherapy and a TKI. After a response assessment, patients at standard risk (ie, low MRD) continue consolidation chemotherapy and maintenance therapy with a TKI. Blinatumomab may be incorporated into frontline therapy as a post-remission approach based on data from ECOG1910.[275] As an alternative for maintenance, HCT may be considered. In patients at high risk (ie, less than CR after induction therapy or MRD+ at EOC), additional options include blinatumomab plus a TKI or tisagenlecleucel (category 2B recommendation). The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. In these patients, consolidation with HCT is recommended and post-transplant TKI should be considered. As noted previously, the role of allogeneic HCT following tisagenlecleucel is unclear (see *NCCN Recommendations for BCR::ABL1-Negative or BCR::ABL1-Like ALL, Front-Line Management*). Of note, HCT is not routinely indicated for *BCR::ABL1*-positive ALL in CR1 provided that the patient achieves MRD negativity (<0.01%) post-consolidation and is being treated on an intensive pediatric regimen plus TKI.

R/R Management

The NCCN Panel recommendations for pediatric and AYA patients with R/R *BCR::ABL1*-positive ALL are similar to what has been summarized for R/R *BCR::ABL1*-negative or *BCR::ABL1*-like ALL. If feasible, *BCR::ABL1* kinase domain mutation analysis (eg, T315I) should be performed and an appropriate TKI should be added to the regimen. Dasatinib, imatinib, or ponatinib can be utilized in this setting, with ponatinib being a category 2B recommendation.

Management of T-ALL

T-ALL is biologically distinct from B-ALL, but similar to B-ALL, MRD is a key prognostic determinant.[44] A major theme in current T-ALL treatment approaches is early intensification with multiagent chemotherapy followed by intensive consolidation therapy. Based on trials referenced in the algorithm, the management of *de novo* T-ALL is summarized below.

Front-Line Management of T-ALL

COG AALL0434

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-ALL with disease that has not responded to or that has relapsed after at least two chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-ALL who received nelarabine (n = 47) and those who did not (n = 47).[150] No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral sensory neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the R/R setting.[150]

Results from the efficacy phase of this study evaluated data from 1562 patients with newly diagnosed T-ALL.[349] Patients were randomized to receive Capizzi-MTX or HD-MTX with leucovorin rescue. Patients with intermediate- and high-risk T-ALL received prophylactic or therapeutic cranial irradiation and were also randomized into arms with or without nelarabine (650 mg/m^2/day). The 4-year DFS rate for patients with T-ALL in the nelarabine arm (n = 323) versus those who did not receive nelarabine (n = 336) was 88.2% ± 2.4% and 82.1% ± 2.7%, respectively (*P* = .029). Patients treated with Capizzi-MTX plus nelarabine had the most superior 5-year DFS of 91%. The addition of nelarabine led to significantly fewer isolated and combined CNS relapses (1.3% ± 0.63% vs. 6.9% ± 1.4%, respectively, *P* = .0001).

Another report from the COG AALL0434 study investigated the impact of two different approaches to MTX intensification on pediatric T-ALL outcomes.[119] All patients without CNS3 disease or testicular leukemia were randomized to receive an augmented BFM chemotherapy regimen with either Capizzi-MTX (n = 519) or HD-MTX (n = 512) during the 8-week IM phase.[119] The estimated 5-year DFS and OS rates in the Capizzi-MTX group were significantly higher than observed in the HD-MTX group, at 91.5% versus 85.3%, respectively (*P* = .005) and 93.7% versus 89.4%, respectively (*P* = .04).[119] These data demonstrate that the Capizzi-MTX is superior to the HD-MTX regimen in patients with T-ALL.[119]

COG AALL1231

The randomized phase III COG AALL1231 trial evaluated the efficacy of the proteasome inhibitor bortezomib in children and young adults with newly diagnosed T-ALL/LL.[149] Patients were randomized to receive a modified BFM backbone with or without bortezomib during induction and DI. The BFM backbone was modified to intensify CNS-directed systemic therapy, as the trial also aimed to reduce the use of prophylactic cranial irradiation. For patients with T-ALL, the 4-year EFS and OS rates were similar for those who received bortezomib versus those who did not (EFS, 82.9% ± 2.4% vs. 81.5% ± 2.5%; *P* = .396; OS, 87.9% ± 2.1% vs. 88.3% ± 2.1%; *P* = .469). For T-LL, however, EFS and OS rates were significantly improved with the addition of bortezomib (EFS, 86.4% ± 4.0% vs. 76.5% ± 5.1%; *P* = .041; OS, 89.5% ± 3.6% vs. 78.3% ± 4.9%; *P* = .009). Rates of peripheral neuropathy and grade 4+ pulmonary toxicity did not differ significantly between the two arms. Comparison of patients treated on COG AALL0434 who received cranial irradiation and patients treated on COG AALL1232 who did not receive cranial irradiation revealed similar EFS and OS rates (*P* = .412 and .600, respectively).

DFCI ALL Consortium Protocols 05-001 and 11-001

In the DFCI ALL Consortium Protocol 05-001, pediatric patients (aged 1–18 years) with newly diagnosed T-ALL were treated as high risk regardless of other presenting features (n = 69).[118] The 5-year EFS and OS rates were 87% and 91%, respectively.

The DFCI ALL Consortium Protocol 11-001, as previously discussed in *Front-Line Management of BCR::ABL1-Negative or BCR::ABL1-Like ALL*, also included pediatric patients with newly diagnosed T-ALL.[140] A total of 123 patients with T-ALL were enrolled in the DFCI ALL Consortium Protocols 05-001 and 11-001 combined and the 5-year EFS and OS rates for patients with T-ALL in both studies combined were 81% (95% CI, 73%–87%) and 90% (95% CI, 83%–94%), respectively.[350] Low MRD (<10^{-4}) at EOI, assessed by PCR, correlated to superior DFS. Compared to non-ETP phenotype, ETP phenotype was associated with inability to achieve CR, but not with inferior OS.

Hematopoietic Cell Transplant

In a retrospective analysis of the ALL BFM 90 and 95 trials evaluating the impact of chemotherapy alone versus allogeneic HCT in pediatric patients with T-ALL, Schrauder et al reported a significant improvement in 5-year DFS and OS with allogeneic HCT versus chemotherapy alone in CR1.[351]

However, HCT in CR1 is not indicated in the contemporary protocols, except for certain patients as described in the HCT sections below.

Management of R/R T-ALL

Most T-ALL disease recurs within 2 years of diagnosis, and successful remission induction is a significant challenge in R/R T-ALL.[44] Based on trials referenced in the algorithm, the management of R/R T-ALL is summarized below.

Nelarabine-Based Regimens

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-ALL who have unresponsive or relapsed disease after at least two chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-ALL or T-cell non-Hodgkin lymphoma (n = 121) showed a 55% response rate among the subgroup with T-ALL with first bone marrow relapse (n = 34) and a 27% response rate in the subgroup with a second or greater bone marrow relapse (n = 36).[182] Major toxicities included grade 3 or higher neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in AYAs and adults (≥16 years of age) with R/R T-ALL or T-LL in a phase II study (n = 39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, n = 26).[352] The CR rate (including CRi) was 31%; an additional 10% of patients experienced a partial remission. The median DFS and OS were both 20 weeks and the 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only one case of grade 4 CNS toxicity (reversible) was observed.[352]

In a phase I trial, NECTAR, the efficacy and safety of nelarabine in combination with etoposide and cyclophosphamide was evaluated in children with R/R T-ALL or T-LL (n = 23).[353] Of evaluable patients with R/R T-ALL (n = 12), a 33% response rate was observed.

Bortezomib-Based Regimens

The COG AALL07P1 phase II study tested the hypothesis that adding bortezomib to reinduction chemotherapy in pediatric patients experiencing first relapse would increase CR2 rates.[286] Of the evaluable patients treated with bortezomib and chemotherapy (n = 135; B-ALL, n = 103; T-ALL, n = 22; T-LL, n = 10), overall CR2 rates were 68% ± 5% for patients with precursor B-ALL (<21 years of age), 63% ± 7% for very early relapse (<18 months from diagnosis), and 72% ± 6% for early relapse (18–36 months from diagnosis). The CR2 rate for patients with relapsed T-ALL was 68% ± 10%. COG considers any T-ALL relapse as high risk, regardless of site or timing.[245]

UKALL R3

The UKALL R3 trial investigated the outcomes of pediatric patients with relapsed ALL aged 1 to 18 years (n = 212 total patients randomized, 24 of whom had relapsed T-ALL).[249] Patients were stratified into standard-, intermediate-, or high-risk groups based on the duration of CR1, site of relapse, and immunophenotype. All patients with T-ALL with isolated bone marrow and combined relapses were considered high risk. For patients with isolated extramedullary relapse, very early (<18 months from first diagnosis), early (≥18 months from diagnosis and <6 months from completing therapy), and late (≥6 months from completing therapy) relapses were considered high risk, intermediate risk, and standard risk, respectively. In addition, patients were randomized to receive mitoxantrone or idarubicin on days 1 and 2 of induction. After three blocks of therapy, all patients in the high-risk group and patients in the intermediate-risk group with post-induction high MRD (≥10^{-4} cells) received HCT. The estimated 3-year PFS and OS rates in the mitoxantrone versus idarubicin groups in the whole cohort were 64.6% versus 35.9% (P = .0004) and 69% versus 45.2% (P = .004), respectively.

ALL-REZ BFM 90

The ALL Relapse BFM 90 (ALL-REZ BFM 90) trial was designed to improve prognosis for pediatric patients with relapsed ALL (<19 years of age; n = 525) through additional multi-chemotherapy blocks.[284] The patients were stratified into three risk groups: A (early bone marrow relapses; n = 126); B (late bone marrow relapses; n = 183); and C (isolated extramedullary relapses; n = 64). Patients with early bone marrow or T-ALL relapse (PPG; n = 152) were eligible for experimental regimens. After treatment with this regimen, 440 patients (84%) achieved CR2, 25 patients died during induction, and 60 patients (11%) did not experience a response. A majority of patients in groups A, B, and C achieved CR2 (Group A: 83%; Group B: 94%; and Group C: 100%), compared to 65% in group PPG. In addition, 117 patients received HCT in CR2. Significant differences existed between strategic groups: pEFS(A) = .17 ± .03; pEFS(B) = .43 ± .04; pEFS(C) = .54 ± .06; pEFS(PPG) = .15 ± .03; log-rank *P* < .001.[284] Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HCT.

Venetoclax-Based Regimens

As mentioned previously, in a phase I open-label study, venetoclax combined with dexamethasone, vincristine, and pegaspargase revealed an ORR of 56% in patients <25 years of age with R/R ALL.[300] For a summary, refer to *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL*.

Another study retrospectively evaluated the efficacy and safety of venetoclax combined with various chemotherapy regimens in adult patients with R/R T-ALL, including patients with ETP ALL.[354] Of evaluable patients (n = 10), 6 (60%) achieved a remission with <5% bone marrow blasts.

Daratumumab-Based Regimens

The phase II, open-label DELPHINUS study evaluated the anti-CD38 monoclonal antibody daratumumab combined with vincristine, prednisone, pegaspargase, and doxorubicin in patients with R/R T-ALL/LL.[355] Among 24 pediatric patients with T-ALL who were 1 to17 years of age, ORR (CR + CRi) was 83.3%, with 41.7% achieving MRD negativity.

Revumenib

For discussion on revumenib and the ongoing phase II AUGMENT-101 study[187], see *Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL*.

Hematopoietic Cell Transplant

HCT is the only curative treatment for R/R T-ALL, but this requires successful remission induction and the data are limited.[44] In the COG AALL01P2 study, most patients with T-ALL (n = 5 of 7) did not achieve CR2.[285] In the combined cohort of patients with high-risk relapsed ALL who were enrolled in ALLR3 or ALL-REZ BFM 2002, 10-year EFS for those with B-ALL and T-ALL were 22.6% and 26.2%, respectively.[356] Ten-year OS was 32.6% and 28.2%, respectively. Achievement of “MRD good response” (10^{-4} at EOI or 10^{-3} at EOI with MRD $<10^{-4}$ during consolidation or pre-transplant) was associated with superior DFS (57.4% vs. 22.6%; *P* < .0001) and OS (57.8% vs. 32.0%; *P* = .0004). For B-ALL and T-ALL, post-HCT DFS and OS were 42.1% and 56.8% and 51.6% and 55.4%, respectively. The cumulative incidences of post-HCT relapse for B-ALL and T-ALL were 36.9% and 17.8% (*P* = .012), respectively, while the cumulative incidences of death were 10.7% and 25.5% (*P* = .013), respectively.

NCCN Recommendations for T-ALL

Front-Line Management

The Panel recommends that pediatric and AYA patients with T-ALL be treated in a clinical trial when possible. In the absence of an appropriate

clinical trial, patients are treated with chemotherapy. Recommended chemotherapy regimen options include the COG AALL1231 regimen,[149] the COG AALL0434 regimen,[150] DFCI-ALL protocol 16-001 (NCT03020030; based on DFCI ALL protocol 11-001[140]), or the St. Jude Children's Research Hospital (SJCRH) Total Therapy XVII regimen (NCT03117751; based on the Total Therapy XVI regimen[266]). It is reasonable to transition patients treated with COG AALL1231 induction to the COG AALL0434 backbone with nelarabine post-induction. The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia.[149] After a response assessment, patients at standard or high risk continue consolidation chemotherapy. The features that define standard risk in this context are: day 29 MRD <0.01%, CNS-1, absence of testicular disease, and no steroid pretreatment. Patients at very high risk have end-consolidation MRD >0.1%. Patients at high risk in this context do not exhibit any standard- or very-high-risk factors. Patients who have very-high-risk features may continue chemotherapy or pursue alternative therapy and consider HCT as part of consolidation therapy. However, it is recommended that additional therapy be given to achieve MRD negativity prior to HCT.

R/R Management

For pediatric and AYA patients with T-ALL experiencing first relapse, the Panel recommends initial treatment with clinical trial or systemic therapy. Recommended chemotherapy regimen options include nelarabine-containing regimens (eg, nelarabine, cyclophosphamide, and etoposide),[353] bortezomib-containing regimens (eg, bortezomib, vincristine, doxorubicin, pegaspargase/calaspargase, and prednisone or dexamethasone),[286] the UKALL R3 Block 1 (dexamethasone, mitoxantrone, pegaspargase/calaspargase, and vincristine),[249] the BFM Intensification Block 1 (HD-MTX, high-dose cytarabine, dexamethasone, vincristine, pegaspargase/calaspargase, and cyclophosphamide),[284] venetoclax-containing regimens (eg, venetoclax, vincristine, pegaspargase/calaspargase, and prednisone or dexamethasone),[300,354] or daratumumab-containing regimens (eg, daratumumab, vincristine, pegaspargase/calaspargase, doxorubicin, and prednisone or dexamethasone).[357] Revumenib may be considered for R/R T-ALL with a *KMT2A* rearrangement. TKI-based regimens can be considered in the setting of an *ABL*-class translocation.

If patients experience CR2, consolidation therapy with chemotherapy should be continued with HCT. If patients experience less than CR (ie, multiple relapse), treatment options include chemotherapy, and patients may receive HCT as consolidation therapy if their disease subsequently responds to therapy. If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care.

Management of Infant ALL

Most infant patients with ALL present with aggressive features, including high WBC counts, CNS involvement, and leukemia cutis, necessitating the use of intensive chemotherapy regimens.[63] However, infant patients are especially vulnerable to treatment-related toxicities, so clinical trials are continually investigating novel strategies to reduce this.[63] Based on trials referenced in the algorithm, the management of infant ALL is summarized below.

Front-Line Management of Infant ALL

Interfant-99

In a multicenter Interfant-99 trial, 482 infant patients with ALL, aged 0 to 12 months, were risk-stratified according to peripheral blood response to a 7-day prednisone prophase, and treated with a hybrid protocol that incorporated elements of standard ALL and AML regimens.[65] Response

was defined as good, and risk as standard, if the blast count in peripheral blood at day 8 was <1000 cells/µL. A poor response was defined as a blast count ≥1000 cells/µL at day 8.[65] Patients at high risk were eligible to receive HCT at the end of the reinduction phase if a donor was available. At the EOI, 94% of 474 evaluable patients were in CR (312 patients in the standard-risk group and 133 patients in the high-risk group).[65] At a median follow-up of 38 months (range, 1–78 months), 58% of patients (n = 260) who underwent hybrid treatment were in CR and the 4-year EFS was 47%. High WBC count, age <6 months, a poor response to the prednisone prophase, and *KMT2A* rearrangements were all independently associated with inferior outcomes.[65] In addition, before the maintenance phase, a subset of patients in CR were randomly assigned to receive either standard treatment or more intensive chemotherapy with high-dose cytarabine and MTX, which did not improve outcomes.[65]

Interfant-06

In infant ALL, the immature B-cell precursors frequently co-express myeloid markers and are sensitive to cytarabine, a key drug in AML treatment.[17,358,359] Based on the hypothesis that early hematopoietic precursors with myeloid differentiation potential would elicit improved responses to chemotherapy regimens developed for AML,[63] the Interfant-06 trial investigated whether consolidation with myeloid-style chemotherapy was superior to lymphoid-style chemotherapy in infant patients with ALL (n = 651).[17] In the study, three risk groups were defined: low risk (*KMT2A* germline; n = 167); high risk (*KMT2A* rearranged and >6 months with WBC count ≥300 x 10^9/L or poor prednisone response; n = 164); and medium risk (all others with *KMT2A*-rearranged; n = 320). Patients in the medium- and high-risk groups were randomly assigned to receive a lymphoid consolidation course (low-dose cytarabine, 6-MP, and cyclophosphamide [IB]) or experimental myeloid courses (cytarabine, daunorubicin, and etoposide [ADE]; and mitoxantrone, cytarabine, and etoposide [MAE]). The 6-year EFS and OS probabilities of all patients were 46.1% and 58.2%, respectively.[17] The 6-year probability of DFS was comparable for the randomized arms (ADE + MAE 39.3% vs. IB 36.8%; log-rank *P* = .47).[17]

In a study that investigated the value of MRD in infants with *KMT2A*-rearranged ALL treated on the Interfant-06 protocol, EOI and EOC MRD levels were predictive of outcomes, as previously discussed in *NCCN Recommendations for MRD Assessment*.[247] Analysis of MRD at EOI showed that infants with high MRD at EOI may benefit from myeloid type consolidation over lymphoid type consolidation (6-year DFS 45.9% vs. 23.2%), while infants with low MRD at EOI may benefit more from lymphoid style consolidation (6-year DFS 78.2% vs. 45.0%).

A prospective, single-arm, phase II study evaluated the safety and efficacy of adding blinatumomab to the Interfant-06 backbone.[360] In this study, newly diagnosed patients <1 year of age with *KMT2A*-rearranged ALL treated according to the Interfant-06 protocol and with a M1/M2 marrow at EOI received one cycle of blinatumomab 15 µg/m^2/day following induction. Patients were classified into high-risk (age <6 months at diagnosis with WBC count ≥300 x 10^9/L and/or poor prednisone response) and medium-risk (all others) groups. MRD-negative CR was achieved in 54% of patients (n = 15/28) at day 15 and day 29 of blinatumomab continuous infusion and 89% of patients (n = 25/28) had achieved MRD negative or not quantifiable (<0.05%) status at day 29. With a median follow-up of 11 months, all patients in the medium-risk group who continued chemotherapy achieved MRD-negative status during further treatment. MRD-negative CR at the end of blinatumomab treatment was achieved more frequently in the medium-risk group compared to the high-risk group (68% vs. 22%; *P* = .0418) and in the setting of low MRD at EOI (<0.05%) compared with high MRD at EOI (76% vs. 18%; *P* = .0056).[360] Longer follow-up data revealed that with a median follow-up of 26.3 months, 53% of patients achieved MRD negativity by PCR and another 40% achieved

MRD <5 x10^{-4}.[18] Two-year DFS and OS were improved compared to Interfant-06, at 81.6% versus 49.4% and 93.3% versus 65.8%, respectively. Adverse events in the blinatumomab arm included fever, infection, and hypertension.

COG AALL0631

Based on data showing aberrant activation of FLT3 pathway in infant ALL with *KMT2A* rearrangements,[361-363] the COG AALL0631 trial was designed to evaluate whether the addition of a FLT3 TKI, lestaurtinib, to post-induction chemotherapy would increase treatment efficacy in infants with newly diagnosed ALL.[63,364] Initial induction consisted of 3 weeks of therapy based on a COG P9407 backbone (Cohort 1).[364,365] Differences between the revised COG P9407 induction and the AALL0631 induction included use of low-dose cytarabine instead of cyclophosphamide, decreased daunorubicin dose, and substitution of native L-asparaginase with pegaspargase.[364] Due to excessive induction toxicity, the study was amended to include a modified 5-week Interfant-99 based induction and enhanced supportive care guidelines (Cohort 2).[364] Induction mortality and sterile site infections were significantly lower for patients in Cohort 2, and higher CR rates were observed at the end-induction intensification for Cohort 2 (week 9, n = 94/100 [94%]) versus Cohort 1 (week 7, n = 17/25 [68%]; *P* = .0012).[364] The addition of lestaurtinib did not demonstrate a benefit in outcomes.[63]

MLL-10

In this trial from the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), patients <1 year of age with ALL were stratified into 3 risk categories: low-risk (germline *KMT2A*); intermediate-risk (other *KMT2A* rearrangement), and high-risk (*KMT2A* rearrangement and age <180 days or CNS-3 disease, defined as WBC count of at least 5 leukocytes/µL in the cerebral spinal fluid [CSF] with the presence of blasts).[366] Patients in the low-risk group received chemotherapy based on the Japan Infant Leukemia Study Group MLL96/MLL98 regimens.[367] Patients with *KMT2A* rearrangements received a modified COG AALL0631 regimen, intensified with the addition of high-dose cytarabine early intensification. HCT was an option only for those in the high-risk group. The 3-year EFS and OS rates were 93.3% and 100%, 94.4% and 94.7%, and 56.6% and 83.9% for the low-, intermediate-, and high-risk groups, respectively, meeting the studies primary end point for 3-year EFS for patients with *KMT2A* rearrangements. Patients with *KMT2A* rearrangements with MRD positivity had significantly worse 3-year and 5-year EFS rates compared with those who achieved MRD negativity, at 78.4% for those achieving MRD negativity at time point 1 and time point 2, compared to 11.1% for those with MRD-positive or -negative disease at time point 2 and MRD-positive disease at time point 3 (*P* < .001).

Hematopoietic Cell Transplant

The benefit derived from using HCT in infant leukemia is unclear.[63] Several retrospective studies suggest no clinical advantage or a benefit at low EFS rates.[368] In the Interfant-99 study, only a subgroup of infant patients with *KMT2A*-rearranged ALL and additional poor prognostic factors (age <6 months, poor response to steroids at day 8, high WBC count) appeared to benefit from HCT in CR1 over chemotherapy alone.[175]

Management of R/R Infant ALL

Infant patients with R/R ALL have poor outcomes and few studies have focused on this specific group.[369,370] Studies summarized previously for B-ALL and T-ALL include some infant patients, and those management strategies apply in this context.

NCCN Recommendations for Infant ALL

Front-Line Management

The Panel recommends that infant patients with ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial,

patients are treated with Interfant-based chemotherapy. To ensure appropriate consolidation, it is important to assess the *KMT2A* status of the disease. If the patient is standard risk (ie, *KMT2A* not rearranged), after a response assessment, the patient may be treated with Interfant-based consolidation. Blinatumomab may be incorporated into frontline therapy as a post-remission approach based on data from ECOG1910.[275] Alternatively, patients who achieved MRD negativity after induction will continue risk-stratified chemotherapy similar to what has been described for *BCR::ABL1*-negative or *BCR::ABL1*-like ALL. Patients with MRD positivity after induction may undergo intensified consolidation therapy. For patients with MRD positivity ≥5 x 10^{-4} at the EOI therapy, myeloid type consolidation therapy (eg, ADE/MAE) can be considered.[247] In all circumstances, HCT may be considered as part of consolidation or maintenance therapy.

Patients with *KMT2A* rearrangement are treated with an intensive Interfant-based consolidation chemotherapy with or without blinatumomab.[18] If the patient is at high risk (ie, aged <3 months with any WBC, aged <6 months with WBC ≥300,000, or with persistent MRD positivity after intensive consolidation therapy), maintenance therapy is recommended or HCT may be considered. If a donor is available, it is preferred that a non-TBI–based prep regimen is used and the patient is at least 6 months of age at the time of transplant.[366] If the patient is at intermediate risk (ie, does not have any high-risk features), maintenance chemotherapy is recommended.

R/R Management

The NCCN Panel recommendations for infant patients with R/R ALL are similar to what has been summarized for R/R *BCR::ABL1*-negative or *BCR::ABL1*-like ALL.

Evaluation and Treatment of Extramedullary Disease

Control of CNS disease is a key part of pediatric ALL therapy[120] and CNS leukemia at diagnosis is associated with significantly decreased EFS rates.[121,126,371] CNS leukemia is defined by a WBC count of at least 5 leukocytes/µL in the CSF with the presence of lymphoblasts.[128] The classification of CNS status includes the following: CNS-1, which refers to no lymphoblasts in the CSF regardless of WBC count; CNS-2, defined as a WBC count <5 leukocytes/µL in the CSF with the presence of blasts; and CNS-3, defined as a WBC count of at least 5 leukocytes/µL with the presence of blasts, or clinical symptoms including facial nerve palsy, brain or eye involvement, CNS hemorrhage, or hypothalamic syndrome.

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥5 WBC/µL in CSF with blasts, then the Steinherz-Bleyer algorithm can be used to determine the CNS classification (if the WBC/red blood cell [RBC] ratio in the CSF is at least 2-fold greater than the WBC/RBC ratio in the blood, then the classification would be CNS-3; if not, the classification would be CNS-2). Although the presence of CNS-3 involvement at diagnosis is uncommon (approximately 3%–7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.[128]

Factors associated with an increased risk for CNS relapse in children include T-cell immunophenotype, high WBC counts at presentation, *BCR::ABL1*-positive disease, t(4;11) translocation, and presence of leukemic cells in the CSF.[136] CNS-directed therapy may include IT chemotherapy (eg, MTX, cytarabine, corticosteroids), cranial irradiation, and/or systemic chemotherapy (eg, HD-MTX, cytarabine, asparaginase).[121,128]

Although prophylactic cranial irradiation is an effective treatment modality for CNS leukemia, its use has been reduced or eliminated because it is

associated with serious adverse events, such as neurocognitive dysfunctions, secondary malignancies, and other long-term complications.[30,120,136] With the increasing use of effective IT chemotherapy and high-dose systemic chemotherapy regimens, studies have examined the feasibility of eliminating cranial irradiation as part of CNS prophylaxis. In studies of children with ALL who only received IT and/or intensive systemic chemotherapy for CNS prophylaxis, the 5-year cumulative incidence of isolated CNS relapse or any CNS relapse was 3% to 4% and 4% to 5%, respectively.[121,129]

Data from the St. Jude Total Therapy XV study showed dramatic improvements in survival outcomes for the AYA population with the omission of cranial irradiation.[121,372] In this study, patients were primarily risk-stratified based on treatment response; patients were treated according to risk-adjusted intensive chemotherapy, with the incorporation of MRD evaluation during induction (day 19) to determine the need for additional doses of asparaginase.[121,372] The 5-year EFS rate for the AYA population (aged 15–18 years; n = 45) was 86% (95% CI, 72%–94%), which was not significantly different from the 87% EFS rate (95% CI, 84%–90%; *P* = .61) observed for the younger patients (n = 448). The 5-year OS rates for the AYA patients and younger patients were 88% and 94%, respectively (*P* = .13).[121,372] The favorable EFS and OS outcomes in AYA patients in this study were attributed in part to the use of intensive dexamethasone, vincristine, and asparaginase, in addition to early IT therapy (ie, triple IT chemotherapy with MTX, hydrocortisone, and cytarabine) for CNS-directed therapy. In addition, the use of prophylactic cranial irradiation was safely omitted in this study; the 5-year cumulative incidence of isolated CNS relapse and any CNS relapse was 3% and 4%, respectively, for the entire study population (n = 498).[121] Moreover, all 11 patients with isolated CNS relapse were children <12 years of age. This study showed that, with intensive risk-adjusted therapy and effective CNS-directed IT regimens, AYA patients can obtain long-term EFS without the need for cranial irradiation or routine allogeneic HCT.[121,372]

NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement

CNS involvement should be evaluated with lumbar puncture at timing in accordance with the specific treatment protocol used for each patient. Pediatric-inspired treatment regimens typically include lumbar puncture at diagnostic workup. The Panel recommends that lumbar puncture, if performed, be conducted concomitantly with initial IT therapy. Throughout the course of ALL therapy, starting from induction, to consolidation, to the maintenance phases of treatment, all patients should receive adequate CNS prophylaxis with IT therapy and/or systemic therapy that incorporates MTX.

In general, the use of cranial irradiation for pediatric patients with ALL and CNS-3 involvement at diagnosis varies according to the treatment protocol. If cranial irradiation is done, the recommended dose is 18 Gy (at 1.5–1.8 Gy/fraction). The timing of cranial irradiation is less clear for patients with T-ALL, though it is recommended that a specific treatment protocol is followed in its entirety. TBI is recommended for select patients at high risk of receiving HCT. In patients who require cranial irradiation and TBI, cranial irradiation should be given as a boost before or after TBI (see Conditioning Regimen in *Principles of Hematopoietic Cell Transplant* in the algorithm). The entire brain and posterior half of the globe should be included in the radiation field. The inferior border should include C2. Notably, areas of the brain targeted by the radiation field in the treatment of pediatric patients with ALL are different from those targeted for brain metastases of solid tumors.

Adequate systemic therapy should also be given in the treatment of patients with isolated CNS relapse. Although the timing is dependent on the treatment protocol, cranial irradiation at a dose of 18 Gy is

recommended. All patients receiving cranial irradiation should be monitored for neurocognitive deficits and academic delays, neuroendocrine deficits, secondary malignancies, cataracts, and other late effects. For additional information, the COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.[373]

Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the EOI therapy should be considered for radiation to both testes in the scrotal sac, with timing depending on the treatment protocol. The total testicular dose should be 24 Gy (in 2.0 Gy/fraction).

Response Assessment and Surveillance

Response Criteria

Response in Bone Marrow and Peripheral Blood

A CR requires the absence of circulating blasts and absence of extramedullary disease (no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, CNS involvement, or other sites of disease). A bone marrow assessment should show trilineage hematopoiesis and fewer than 5% blasts (M1) or <1% blasts by flow or molecular testing. For a CR, absolute neutrophil counts (ANCs) should be >1000/µL and platelet counts should be >100,000/µL. In addition, no recurrence should be observed for at least 4 weeks.

A patient is considered to have a CRi if criteria for CR are met except the ANC remains <1000/µL or the platelet count remains <100,000/µL. In general, ORR is the sum of CR and CRi values. Of note, MRD assessment is not included in morphologic assessment and should be obtained.

Refractory disease is defined as the inability to achieve a CR at the EOI therapy. Progressive disease (PD) is defined as an increase in the absolute number of circulating blasts (in peripheral blood) or bone marrow blasts by at least 25%, or the development of extramedullary disease. Relapsed disease is defined as the reappearance of blasts in the blood or bone marrow (>5%; ≥M2); or >1% with previous/supportive molecular findings; or in any extramedullary site after achievement of a CR.

Response in CNS Disease

Remission of CNS disease is defined as achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at diagnosis. CNS relapse is defined as development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, CNS hemorrhage, hypothalamic syndrome) without an alternative explanation. CNS relapse is also considered in development of CNS-2 status on two consecutive lumbar punctures (between 2–4 weeks apart) with confirmation by immunophenotyping or other molecular testing methods.

Surveillance

After completion of the ALL treatment regimen (including maintenance therapy), the Panel recommends surveillance at regular intervals to assess disease status. During the first year after completion of therapy, every 1 to 4 months, patients should undergo a complete physical examination (including a testicular examination as applicable) and blood tests (CBC with differential). Liver function tests should be performed until normal values are achieved. During the second year after completion of therapy, a physical examination (including a testicular examination as applicable) and blood tests (CBC with differential) should be performed every 2 to 6 months. During the third year (and beyond) after completion of therapy, physical examination (including a testicular examination as applicable) and blood tests (CBC with differential) can be performed every 6 to 12 months or as clinically indicated.

An assessment of bone marrow aspirate and CSF for suspected relapse should be performed as clinically indicated; if a bone marrow aspirate is

performed, flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular tests, and MRD assessments should be carried out. If relapse is suspected, a full workup should be considered. For *BCR::ABL1*-positive ALL, periodic quantification of the *BCR::ABL1* transcript should be determined.

To monitor for late effects related to cumulative anthracycline exposure, an echocardiogram should be performed with frequency based on cumulative anthracycline dose or sooner, as clinically indicated. In addition, given the increased risk of neurotoxicity associated with ALL treatment in survivors, neuropsychological testing as clinically indicated is recommended. Patients with a history of pediatric ALL are also at risk for developing obesity[374]; therefore, monitor for healthy weight and encourage healthy lifestyle choices. As previously discussed in *NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement,* the COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.[373] These guidelines serve as a resource for clinicians and family members/caretakers, and have the goal of providing screening and management recommendations for late effects (those that may impact growth, cognitive function, emotional concerns, reproductive health, risks for secondary malignancies, and other important health issues) that may arise during the lifetime of an AYA cancer survivor as a result of the therapeutic agents used during the course of antitumor treatment.

Supportive Care for Pediatric Patients with ALL

Given the highly complex and intensive treatment protocols used in the management of ALL, supportive care issues are important considerations to ensure that patients derive the most benefit from ALL therapy. Although differences may exist between institutional standards and practices, supportive care measures for patients with ALL generally include the use of antiemetics for prevention of nausea and vomiting, blood product transfusions for severe cytopenias, nutritional support for prevention of weight loss, gastroenterology support, pain management, prevention and management of infectious complications, and prophylaxis for TLS. In addition, both short- and long-term consequences of potential toxicities associated with specific agents used in ALL regimens should be considered, such as with steroids (eg, risks for hyperglycemia or peptic ulcerations in the acute setting; risks for avascular necrosis with long-term use) and asparaginase (eg, risks for hypersensitivity reactions, hyperglycemia, coagulopathy, hepatotoxicity, and/or pancreatitis). Supportive care measures should be tailored to meet the individual needs of each patient based on factors such as age, performance status, extent of cytopenias before and during therapy, risks for infectious complications, disease status, and the specific agents used in the ALL treatment regimen.

NCCN Recommendations for Supportive Care

For comprehensive supportive care recommendations made by the Pediatric ALL Panel, see the *Principles of Supportive Care* section in the algorithm.

Infection Control

Patients with ALL undergoing intensive chemotherapy or allogeneic HCT are highly susceptible to infections. Immunosuppression caused by the underlying disease and therapeutic regimens can predispose patients to common bacterial and viral infections, and to various opportunistic infections (eg, candidiasis, invasive mold infections, *Pneumocystis jirovecii*, CMV reactivation and infection), particularly during periods of prolonged neutropenia. During induction, all patients with fever (as defined by the Infectious Diseases Society of America[375] or institutional standards) should be evaluated by a medical provider and treated promptly with broad-spectrum antibiotics with activity against gram-positive and gram-negative bacteria (including *Pseudomonas*), regardless of neutrophil

count. Following completion of induction, antibiotics may not be indicated for fever based on clinical status.

Patients with ALL should take appropriate antibacterial and antifungal prophylaxis throughout therapy[376,377] and also be closely monitored for any signs or symptoms of infections. All patients with ALL are at high risk for *Pneumocystis jirovecii* (*Pneumocystis carinii*) and should take prophylaxis throughout anti-leukemic therapy. Trimethoprim/sulfamethoxazole (TMP/SMX) is the preferred therapy for *Pneumocystis jirovecii* prophylaxis.[378] TMP/SMX may be held for a short period of time if blood counts are low, given risk of drug-induced myelosuppression with this agent; however, holding TMP/SMX for prolonged periods or permanently discontinuing TMP/SMX should be avoided. TMP/SMX may be held when HD-MTX is administered and re-started when MTX clearance is achieved per protocol or institutional guidelines. If TMP/SMX is not tolerated, atovaquone, dapsone, or pentamidine (aerosolized or IV) can be considered.

Fluoroquinolone prophylaxis should be considered in patients receiving anthracyclines during induction therapy for newly diagnosed ALL or therapy for relapsed ALL who are anticipated to have neutropenia.[376,377,379] However, fluoroquinolones can be associated with significant toxicities and may not be appropriate for all patients. Alternative antibiotics per institutional standard or monitoring without antibiotics may be considered.[380,381]

Antifungal prophylaxis should be considered during induction, especially in patients receiving anthracyclines. However, some antifungal agents (azoles) have potential interactions with vincristine and should be used with caution.[382-386] G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) are not generally recommended but may be used at the discretion of the health care provider in situations of prolonged neutropenia or serious/life-threatening situations in the context of neutropenia. Similarly, granulocyte transfusions are not generally recommended but may be used at the discretion of the health care provider in situations of serious/life-threatening infection in the context of neutropenia. Certain populations of patients require more aggressive infection prophylaxis and monitoring (for specific details, see the Infection Control subheading in the *Principles of Supportive Care* section in the algorithm).

Consideration should be made for inactivated vaccines and live vaccines (varicella, measles, mumps, and rubella) 3 months after chemotherapy following the Centers for Disease Control and Prevention (CDC) schedule for immunocompetent individuals. For patients receiving regimens that include anti-B-cell antibodies, vaccinations should be delayed at least 6 months.[387] Consultation with Infectious Disease or Immunology may be appropriate for specific vaccination recommendations for each individual patient. The American Society of Hematology (ASH) has more specific information regarding COVID-19 vaccinations and management of pediatric ALL in patients with SARS-CoV-2.[388] For general information regarding COVID-19 vaccination in patients with cancer, see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Acute Tumor Lysis Syndrome Management

Patients with ALL may be at high risk of developing acute TLS, particularly those with highly elevated WBC counts before induction chemotherapy. TLS is characterized by metabolic abnormalities stemming from the sudden release of intracellular contents into the peripheral blood because of cellular disintegration induced by chemotherapy. If left untreated, TLS can result in profound metabolic changes leading to cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and even death. Standard prophylaxis for TLS includes hyperhydration with crystalloid IV fluids that do not contain potassium. If urine output remains low after achieving an optimal state of hydration, a loop diuretic agent (eg, furosemide) may be used to promote diuresis. Urine alkalinization is not

recommended.[389] In patients at high risk for TLS, to reduce the risk of renal complications, low-intensity initial therapy (corticosteroid monotherapy for 3–7 days) may be used. Allopurinol should be started prior to initiation of chemotherapy for patients with low WBC counts (eg, <100 x 10^9/L) and LDH <2 x upper limit of normal (ULN), and low tumor burden. Rasburicase is indicated prophylactically for patients with high WBC counts (eg, >100 x 10^9/L), LDH >2 x ULN, high tumor burden, or those presenting with renal dysfunction, elevated uric acid (eg, >8 mg/dL), or inability to tolerate hydration.

Methotrexate Toxicity Management

High doses of MTX can result in toxic plasma MTX concentrations in patients with significant renal dysfunction, large effusions/ascites, and delayed MTX clearance (plasma MTX concentrations >2 SDs of the mean MTX excretion curve specific for the dose of MTX administered). Toxic plasma MTX concentrations in patients may also be observed due to other interacting medications (eg, penicillins, PPIs, nonsteroidal anti-inflammatory drugs [NSAIDs], amphotericin).

In the event a patient receiving MTX experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended when plasma MTX concentrations are two SDs above the mean expected MTX plasma concentration as determined by MTXPK.org, or if the 36-hour plasma MTX level is >30 µM, 42-hour level is >10 µM, or 48-hour level is >5 µM. Optimal administration of glucarpidase is within 48 to 60 hours from the start of MTX infusion. Leucovorin should be dosed on pre-glucarpidase plasma MTX concentration and should be continued for at least 2 days following glucarpidase administration. However, because leucovorin is a substrate for glucarpidase, it should not be administered within 2 hours before or after glucarpidase.[390] Measurements of plasma MTX levels after glucarpidase by standard immunoassay methods do not distinguish MTX from its metabolites and may overestimate the true MTX concentration.

Children with Down syndrome and ALL often experience severe treatment-related toxicities especially associated with HD-MTX.[391] Patients who have experienced excessive systemic MTX toxicity and subsequently receive IT MTX may benefit from leucovorin rescue after IT therapy.

CNS toxicity can also occur after high-dose or IT MTX.[392] Symptoms may include seizures or stroke-like symptoms, which tend to occur 10 to 14 days from MTX exposure and typically spontaneously resolve without intervention or long-term sequalae.[392-394] An MRI may help distinguish between MTX-induced neurotoxicity and PRES. Patients who present with seizures may benefit from antiepileptics—preferably non-hepatic enzyme inducers such as levetiracetam[395] and lacosamide[396] to avoid potential interactions with chemotherapy—for the remainder of their therapy. The final choice of an antiepileptic should be made with input from a pediatric neurology specialist and consideration of all patient factors. Although the risk of recurrence of MTX-induced CNS toxicity is low, to minimize or prevent further neurotoxicity, treatment providers may consider gradual introduction of MTX or alternate IT therapy such as cytarabine following acute MTX neurotoxicity.

Management of Anthracycline-Related Cardiotoxicity

With current treatment strategies, many patients will not be exposed to a cumulative dose of anthracycline and/or radiation therapy, which places them at risk for cardiotoxicity. However, some patients may have underlying conditions or prior therapies that place them at higher risk for anthracycline-related cardiotoxicity.[397] Previous or anticipated radiation therapy focused on the chest, abdomen, spine, or TBI has the potential to impact the heart. Prior to each anthracycline dose, treatment with dexrazoxane, an iron chelator, may mitigate this.[398,399] Although a study observed that dexrazoxane may be associated with a risk of developing secondary malignancies,[400] other subsequent studies have not observed this phenomenon.[401,402]

Steroid Management

Corticosteroids such as prednisone and dexamethasone constitute a core component of nearly every ALL induction regimen and are frequently incorporated into consolidation and/or maintenance regimens.

Acute side effects of steroids may include hyperglycemia and steroid-induced diabetes mellitus. Patients should be monitored for glucose control to minimize the risk of developing infectious complications. Steroid myopathy is another potentially acute side effect of steroids and may present with proximal limb and neck flexor weakness. Respiratory muscles may also become weak in patients with more severe presentations.[403] Holding or reducing the dose of steroids per treatment protocol and/or a referral to physical therapy may be considered. Another acute side effect of steroid therapy includes peptic ulceration and dyspeptic symptoms; the use of histamine-2 receptor antagonists or PPIs should be considered during steroid therapy to reduce these risks. There may also be important drug interactions between PPIs and MTX that need to be considered prior to initiation of MTX-based therapy. Corticosteroids are also associated with mood alterations, psychosis, and other neuropsychiatric complications in pediatric patients with ALL.[404-406] In this context, anti-psychotics may be considered. If no response is observed, a 50% dose reduction may be considered, or switching from dexamethasone to prednisone, if applicable.[407] The addition of hydrocortisone has not been shown to reduce significant dexamethasone-induced neuropsychological adverse effects in pediatric patients with ALL.[408]

A potential long-term side effect associated with steroid therapy includes osteonecrosis/avascular necrosis.[409,410] Osteonecrosis most often affects weight-bearing joints, such as the hip and/or knee, and seems to have a higher incidence among adolescents (presumably because of the period of skeletal growth) than younger children or adults.[409,411-415] The treatment protocols may differ on this practice, but the Panel suggests considering not withholding corticosteroids in induction or intensification blocks. However, if severe avascular necrosis occurs during therapy, consider holding corticosteroids during maintenance therapy. If MRI findings have significantly improved or patient's symptoms have resolved in 6 months, corticosteroids may be resumed at that time. Prednisone may be preferred over dexamethasone in this context.[415] There is no evidence for vitamin D and calcium replacement in pediatric patients regarding the prevention and treatment of osteonecrosis/avascular necrosis.[416-418] Interestingly, among patients in the high-risk group on COG AALL0232, the development of osteonecrosis was associated with reduced rates of relapse ($P = .0014$) and higher 5-year EFS ($P < .0001$) and OS ($P < .0001$).[419]

Vincristine Management

Vincristine is an essential chemotherapeutic agent in many ALL regimens that is associated with dose-limiting neurotoxicity.[420] Regimens to maintain bowel movements and prevent the occurrence of constipation may need to be considered if receiving vincristine. Consider holding vincristine dose for the following: ileus or typhlitis, vocal cord paralysis, and severe neuropathic pain (grade >3) that affects activities of daily living; then restart at half of the previous dose. Once symptoms resolve, the full dose may be resumed as tolerated. For pain control, consider use of gabapentin, pregabalin, or other gamma-aminobutyric acid (GABA) analog. Some patients may require additional pain medication including opioids.

Thiopurines Management

SOS, previously called veno-occlusive disease, of the liver is an adverse effect that can be associated with 6-TG.[421] Risk factors include thiopurine exposure, *TPMT* polymorphisms, and HCT.[422] Defibrotide may be used in severe SOS.[423,424]

Skewed metabolism of 6-MP can result in preferential formation of hepatotoxic metabolites over antileukemic metabolites, leading to hepatotoxicity, GI symptoms, hypoglycemia, and inadequate myelosuppression.[425-427] Allopurinol has been shown to modify 6-MP metabolism, reducing the formation of hepatotoxic metabolites. For patients with significant GI symptoms (ie, nausea, vomiting) and/or grade 4 alanine transaminase (ALT), aspartate transaminase (AST), and/or direct bilirubin >2 mg/dL, and/or hypoglycemia, obtaining mercaptopurine metabolites may be considered. If methylated metabolites are elevated and ANC indicates that the dose of 6-MP should be increased, or for those with GI toxicity or hypoglycemia that is dose limiting, the addition of allopurinol 50 mg/m^2 with a 50% to 75% decreased dose of 6-MP may be considered.[425-427] Careful ANC monitoring should be considered with this approach, as the interaction of 6-MP and allopurinol carries a significant risk of myelosuppression.

Hyperleukocytosis Management

Hyperleukocytosis (leukostasis), in general, occurs most often in patients with a highly elevated WBC count (usually >200 × 10^9/L), T-cell immunophenotype, and *BCR::ABL1*, and in infants with *KMT2A* rearrangement.[428-430] Leukapheresis has been demonstrated to decrease complications of leukostasis in patients with ALL, but in circumstances of hyperleukocytosis without symptoms of leukostasis, leukapheresis does not provide clinical advantage over aggressive chemotherapy. Leukapheresis may also be associated with adverse outcomes.[431,432]

Antiemetics

Most chemotherapy regimens used in ALL contain agents that are at least moderately emetogenic, which may necessitate antiemetic support before initiating emetogenic chemotherapy. Antiemesis prophylaxis may include the use of agents such as serotonin receptor antagonists, corticosteroids, and/or neurokinin-1–receptor antagonists. Recommendations for antiemetic support for patients receiving chemotherapy are available in the NCCN Guidelines for Antiemesis. For patients with ALL, the routine use of corticosteroids as part of antiemetic therapy should be avoided given that steroids constitute a major component of ALL regimens.

Behavior and Psychosocial Support

Given the established risk for neurocognitive late effects associated with CNS-directed chemotherapy, neurocognitive monitoring during therapy and after completion of therapy should be considered for all patients.[433,434] Neurocognitive studies in survivors of ALL treated with chemotherapy-only regimens also highlight difficulty in areas of executive functioning, attention, fine motor skills, processing speed, and mathematics.[435] Studies in patients who have undergone treatment for childhood ALL have noted that bacteremia, sepsis, and acute MTX neurotoxicity increase the risk for neurocognitive deficits, and supportive care interventions such as repeated exposure to general anesthesia for procedures have also been associated with neurocognitive late effects.[434] Neurocognitive monitoring could occur at the completion of treatment and/or at school entry or re-entry. A baseline assessment may be considered to provide a context in which to appreciate change.[433] The Panel encourages referral for a comprehensive neuropsychological assessment if there is evidence of new concerns or change. For further recommendations for behavior and psychosocial support, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

Nutritional Support

For patients experiencing >10% weight loss, appetite stimulants, or enteral or parenteral nutritional support should be considered. The increased risk of obesity in pediatric patients with ALL[436] despite reduction in total caloric intake suggests alternative interventions, particularly those that prevent loss of muscle mass like physical activity, are needed.

Transfusions

For patients requiring transfusion support for severe or prolonged cytopenias, irradiated blood and leukodepleted products should be used when possible.

Treatment for Pain

Bone pain and vincristine-associated neuropathic pain are commonly associated with ALL. Pain management should be used for patients with cancer, regardless of disease stage. The Panel encourages consultation with pediatric pain or palliative specialists.

Leukemia Predisposition Syndromes

Patients who have leukemia predisposition syndromes have an increased risk of treatment-related toxicity and secondary malignancy, and require close surveillance; however, the specifics are unclear due to limited data and guidelines in this arena are evolving.[437-439] Therefore, it is important for the treating clinician to conduct a thorough family history in order to screen for patients who have a leukemia predisposition syndrome, although de novo mutations have been reported. If there is a concern for a leukemia predisposition syndrome, consider referral to a genetic counselor or geneticist to identify appropriate clinical testing (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate).

Asparaginase Toxicity Management

Asparaginase is also a core component of ALL regimens and should only be used in specialized centers. In this context, patients should also be closely monitored in the period during and after infusion for allergic response.[440] Three different formulations of the enzyme are in clinical use: 1) pegaspargase (only available for patients <1 month [31 days] or ≥21.5 years as of December 1, 2022)[141]; 2) calaspargase; and 3) ERW-rywn. Therapeutic drug monitoring (TDM) for asparaginase therapy using the SAA is available as a Clinical Laboratory Improvement Amendments (CLIA)-certified test allowing real-time decision-making and therapeutic adjustments.[441,442] Modifications in asparaginase dose or schedule depend on the clinical context.

Asparaginase products are associated with potentially severe hypersensitivity reactions (including anaphylaxis) due to anti-asparaginase or anti-PEG antibodies.[443-446] These reactions may be (though not always) associated with the production of neutralizing antibodies and lack of asparaginase activity.[447-449] ERW-rywn is used for patients who develop allergic reactions to *E. coli*-derived asparaginase. With IV pegaspargase and calaspargase, nonallergic infusion reactions can also occur, typically shortly into the infusion (within minutes or seconds), and the symptoms can overlap with hypersensitivity reactions. These nonallergic infusion reactions may manifest with flushing, hypotension, tachycardia, dyspnea, tachypnea, and anxiety. Slowing the infusion to ≥2 hours (but <4 hours for calaspargase), with concurrent infusion of saline and use of anti-allergy premedications given IV or PO (such as hydrocortisone, diphenhydramine, or other antihistamines [eg, cetirizine (category 2B for IV cetirizine)], acetaminophen), can reduce these reactions.[442,445,450,451]

Routine premedication has been generally avoided for fear of masking hypersensitivity reactions. However, given the difficulty in distinguishing hypersensitivity and non-allergic infusion reactions and the availability of TDM, universal premedication and TDM can be considered, which can decrease the incidence and severity of adverse events and the need to substitute pegaspargase with ERW-rywn. In patients with previous hypersensitivity reaction to pegaspargase, some studies have found desensitization protocols helpful.[452,453] However, this practice is not currently recommended in the guidelines.

Asparaginase is associated with other toxicities, including pancreatitis[454,455] (ranging from asymptomatic presentation with amylase or lipase elevation, to symptomatic presentation with vomiting or severe abdominal pain),

hepatotoxicity (eg, increased alanine or glutamine aminotransferase, hyperbilirubinemia, SOS), fatigue that substantially impairs health-related quality of life,[456] and coagulopathy (eg, thrombosis, hemorrhage). Patients without contraindications may be considered for apixaban prophylaxis with use of asparaginase.[457] For detailed recommendations regarding the management of these toxicities, see the *Principles of Supportive Care* in the algorithm.

References

1. National Cancer Institute. SEER cancer statistics review, 1975-2015: Leukemia, annual incidence rates (acute lymphocytic leukemia). 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 24, 2023.

2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38230766.

3. Esparza SD, Sakamoto KM. Topics in pediatric leukemia--acute lymphoblastic leukemia. MedGenMed 2005;7:23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16369328.

4. Jabbour EJ, Faderl S, Kantarjian HM. Adult acute lymphoblastic leukemia. Mayo Clin Proc 2005;80:1517-1527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16295033.

5. National Cancer Institute. SEER cancer statistics review, 1975-2015: Overview, median age at diagnosis. 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 24, 2023.

6. National Cancer Institute. SEER cancer statistics review, 1975-2015: Overview, age distribution of incidence cases by site. 2018. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed January 24, 2023.

7. Teachey DT, O'Connor D. How I treat newly diagnosed T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in children. Blood 2020;135:159-166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31738819.

8. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol 2019;20:e142-e154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30842058.

9. Polonen P, Mullighan CG, Teachey DT. Classification and risk stratification in T-lineage acute lymphoblastic leukemia. Blood 2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39357057.

10. Ma H, Sun H, Sun X. Survival improvement by decade of patients aged 0-14 years with acute lymphoblastic leukemia: a SEER analysis. Sci Rep 2014;4:4227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24572378.

11. Pulte D, Gondos A, Brenner H. Improvement in survival in younger patients with acute lymphoblastic leukemia from the 1980s to the early 21st century. Blood 2009;113:1408-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18974371.

12. Geyer MB, Hsu M, Devlin SM, et al. Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. Blood 2017;129:1878-1881. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28122741.

13. Pulte D, Jansen L, Gondos A, et al. Survival of adults with acute lymphoblastic leukemia in Germany and the United States. PLoS One 2014;9:e85554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24475044.

14. Sive JI, Buck G, Fielding A, et al. Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. Br J Haematol 2012;157:463-471. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22409379.

15. Wermann WK, Viardot A, Kayser S, et al. Comorbidities are frequent in older patients with de novo acute lymphoblastic leukemia (ALL) and correlate with induction mortality: Analysis of more than 1200 patients from GMALL data bases. Blood 2018;132:660-660. Available at: https://doi.org/10.1182/blood-2018-99-111954.

16. Miller KD, Fidler-Benaoudia M, Keegan TH, et al. Cancer statistics for adolescents and young adults, 2020. CA Cancer J Clin 2020;70:443-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32940362.

17. Pieters R, De Lorenzo P, Ancliffe P, et al. Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the Interfant-06 protocol: Results from an international phase III randomized study. J Clin Oncol 2019;37:2246-2256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31283407.

18. van der Sluis IM, de Lorenzo P, Kotecha RS, et al. Blinatumomab Added to Chemotherapy in Infant Lymphoblastic Leukemia. N Engl J Med 2023;388:1572-1581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37099340.

19. Stock W. Adolescents and young adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010;2010:21-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21239766.

20. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed January 24, 2023.

21. Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer 2010;116:1165-1176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20101737.

22. Karimi M, Cohan N, Zareifar S, et al. Initial presentation of childhood leukaemia with facial palsy: three case reports. BMJ Case Rep 2009;2009. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22162740.

23. Kraigher-Krainer E, Lackner H, Sovinz P, et al. Numb chin syndrome as initial manifestation in a child with acute lymphoblastic leukemia. Pediatr Blood Cancer 2008;51:426-428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18506757.

24. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Lymphoid neoplasms. Leukemia 2022;36:1720-1748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35732829.

25. Amin HM, Yang Y, Shen Y, et al. Having a higher blast percentage in circulation than bone marrow: clinical implications in myelodysplastic syndrome and acute lymphoid and myeloid leukemias. Leukemia 2005;19:1567-1572. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16049515.

26. Weinkauff R, Estey EH, Starostik P, et al. Use of peripheral blood blasts vs bone marrow blasts for diagnosis of acute leukemia. Am J Clin Pathol 1999;111:733-740. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10361507.

27. Bassan R, Maino E, Cortelazzo S. Lymphoblastic lymphoma: an updated review on biology, diagnosis, and treatment. Eur J Haematol 2016;96:447-460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26679753.

28. Cortelazzo S, Ferreri A, Hoelzer D, Ponzoni M. Lymphoblastic lymphoma. Crit Rev Oncol Hematol 2017;113:304-317. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28427520.

29. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol 2011;29:532-543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21220592.

30. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. Pediatr Clin North Am 2015;62:61-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25435112.

31. Borowitz MJ, Chan JKC, Bene MC, Arber DA. T-lymphoblastic leukaemia/lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4th). Lyon, France: IARC; 2017:209-212.

32. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med 2004;350:1535-1548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15071128.

33. Bassan R, Gatta G, Tondini C, Willemze R. Adult acute lymphoblastic leukaemia. Crit Rev Oncol Hematol 2004;50:223-261. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15182827.

34. Attarbaschi A, Mann G, Konig M, et al. Mixed lineage leukemia-rearranged childhood pro-B and CD10-negative pre-B acute lymphoblastic leukemia constitute a distinct clinical entity. Clin Cancer Res 2006;12:2988-2994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16707593.

35. Pui CH, Gaynon PS, Boyett JM, et al. Outcome of treatment in childhood acute lymphoblastic leukaemia with rearrangements of the 11q23 chromosomal region. Lancet 2002;359:1909-1915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12057554.

36. Dworzak MN, Schumich A, Printz D, et al. CD20 up-regulation in pediatric B-cell precursor acute lymphoblastic leukemia during induction treatment: setting the stage for anti-CD20 directed immunotherapy. Blood 2008;112:3982-3988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18780832.

37. Jeha S, Behm F, Pei D, et al. Prognostic significance of CD20 expression in childhood B-cell precursor acute lymphoblastic leukemia. Blood 2006;108:3302-3304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16896151.

38. Harvey RC, Wood BL, Chen I-M, et al. Identification of CRLF2 genomic lesions in patients with pediatric B-precursor acute lymphoblastic leukemia (BCP ALL) by flow cytometry or quantitative RT-PCR: A Children's Oncology Group (COG) Study. Blood 2012;120:2529-2529. Available at: http://www.bloodjournal.org/content/120/21/2529.

39. Bene MC, Castoldi G, Knapp W, et al. Proposals for the immunological classification of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). Leukemia 1995;9:1783-1786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7564526.

40. Coustan-Smith E, Mullighan CG, Onciu M, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol 2009;10:147-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19147408.

41. Inukai T, Kiyokawa N, Campana D, et al. Clinical significance of early T-cell precursor acute lymphoblastic leukaemia: results of the Tokyo Children's Cancer Study Group Study L99-15. Br J Haematol 2012;156:358-365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22128890.

42. Ma M, Wang X, Tang J, et al. Early T-cell precursor leukemia: a subtype of high risk childhood acute lymphoblastic leukemia. Front Med 2012;6:416-420. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23065427.

43. Patrick K, Wade R, Goulden N, et al. Outcome for children and young people with Early T-cell precursor acute lymphoblastic leukaemia treated on a contemporary protocol, UKALL 2003. Br J Haematol 2014;166:421-424. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24708207.

44. Raetz EA, Teachey DT. T-cell acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2016;2016:580-588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27913532.

45. Wood BL, Devidas M, Summers RJ, et al. Prognostic significance of ETP phenotype and minimal residual disease in T-ALL: a Children's Oncology Group study. Blood 2023;142:2069-2078. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37556734.

46. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35767897.

47. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35732831.

48. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin

Oncol 2011;29:551-565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21220611.

49. Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: results from the UK Medical Research Council ALL97/99 randomised trial. Lancet Oncol 2010;11:429-438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20409752.

50. Yasuda T, Tsuzuki S, Kawazu M, et al. Recurrent DUX4 fusions in B cell acute lymphoblastic leukemia of adolescents and young adults. Nat Genet 2016;48:569-574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27019113.

51. Gu Z, Churchman ML, Roberts KG, et al. PAX5-driven subtypes of B-progenitor acute lymphoblastic leukemia. Nat Genet 2019;51:296-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30643249.

52. Boer JM, Valsecchi MG, Hormann FM, et al. Favorable outcome of NUTM1-rearranged infant and pediatric B cell precursor acute lymphoblastic leukemia in a collaborative international study. Leukemia 2021;35:2978-2982. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34211097.

53. Fazio G, Bardini M, De Lorenzo P, et al. Recurrent genetic fusions redefine MLL germ line acute lymphoblastic leukemia in infants. Blood 2021;137:1980-1984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33512459.

54. Jeha S, Choi J, Roberts KG, et al. Clinical significance of novel subtypes of acute lymphoblastic leukemia in the context of minimal residual disease-directed therapy. Blood Cancer Discov 2021;2:326-337. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34250504.

55. Moorman AV. New and emerging prognostic and predictive genetic biomarkers in B-cell precursor acute lymphoblastic leukemia. Haematologica 2016;101:407-416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27033238.

56. Carroll AJ, Shago M, Mikhail FM, et al. Masked hypodiploidy: Hypodiploid acute lymphoblastic leukemia (ALL) mimicking hyperdiploid ALL in children: A report from the Children's Oncology Group. Cancer Genet 2019;238:62-68. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31425927.

57. Raimondi SC, Zhou Y, Mathew S, et al. Reassessment of the prognostic significance of hypodiploidy in pediatric patients with acute lymphoblastic leukemia. Cancer 2003;98:2715-2722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14669294.

58. Moorman AV, Chilton L, Wilkinson J, et al. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. Blood 2010;115:206-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19897583.

59. Schultz KR, Pullen DJ, Sather HN, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood 2007;109:926-935. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17003380.

60. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013;45:242-252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23334668.

61. Muhlbacher V, Zenger M, Schnittger S, et al. Acute lymphoblastic leukemia with low hypodiploid/near triploid karyotype is a specific clinical entity and exhibits a very high TP53 mutation frequency of 93%. Genes Chromosomes Cancer 2014;53:524-536. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24619868.

62. Behm FG, Raimondi SC, Frestedt JL, et al. Rearrangement of the MLL gene confers a poor prognosis in childhood acute lymphoblastic leukemia, regardless of presenting age. Blood 1996;87:2870-2877. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8639906.

63. Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood 2019;133:205-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30459160.

64. Hilden JM, Dinndorf PA, Meerbaum SO, et al. Analysis of prognostic factors of acute lymphoblastic leukemia in infants: report on CCG 1953 from the Children's Oncology Group. Blood 2006;108:441-451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16556894.

65. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. The Lancet 2007;370:240-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17658395.

66. Pui CH, Chessells JM, Camitta B, et al. Clinical heterogeneity in childhood acute lymphoblastic leukemia with 11q23 rearrangements. Leukemia 2003;17:700-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12682627.

67. Attarbaschi A, Moricke A, Harrison CJ, et al. Outcomes of childhood noninfant acute lymphoblastic leukemia with 11q23/KMT2A rearrangements in a modern therapy era: A retrospective international study. J Clin Oncol 2023;41:1404-1422. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36256911.

68. Fischer U, Forster M, Rinaldi A, et al. Genomics and drug profiling of fatal TCF3-HLF-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. Nat Genet 2015;47:1020-1029. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26214592.

69. Inukai T, Hirose K, Inaba T, et al. Hypercalcemia in childhood acute lymphoblastic leukemia: frequent implication of parathyroid hormone-related peptide and E2A-HLF from translocation 17;19. Leukemia 2007;21:288-296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17183364.

70. Felice MS, Gallego MS, Alonso CN, et al. Prognostic impact of t(1;19)/ TCF3-PBX1 in childhood acute lymphoblastic leukemia in the context of Berlin-Frankfurt-Munster-based protocols. Leuk Lymphoma 2011;52:1215-1221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21534874.

71. Heerema NA, Carroll AJ, Devidas M, et al. Intrachromosomal amplification of chromosome 21 is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk children's oncology group studies: a report from the children's oncology group. J Clin Oncol 2013;31:3397-3402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23940221.

72. Moorman AV, Robinson H, Schwab C, et al. Risk-directed treatment intensification significantly reduces the risk of relapse among children and adolescents with acute lymphoblastic leukemia and intrachromosomal amplification of chromosome 21: a comparison of the MRC ALL97/99 and UKALL2003 trials. J Clin Oncol 2013;31:3389-3396. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23940220.

73. Moorman AV, Richards SM, Robinson HM, et al. Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). Blood 2007;109:2327-2330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17095619.

74. Arico M, Valsecchi MG, Camitta B, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. N Engl J Med 2000;342:998-1006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10749961.

75. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 2006;354:166-178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16407512.

76. Caye A, Beldjord K, Mass-Malo K, et al. Breakpoint-specific multiplex polymerase chain reaction allows the detection of IKZF1 intragenic deletions and minimal residual disease monitoring in B-cell precursor acute lymphoblastic leukemia. Haematologica 2013;98:597-601. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23065506.

77. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature 2008;453:110-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18408710.

78. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360:470-480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19129520.

79. Boer JM, van der Veer A, Rizopoulos D, et al. Prognostic value of rare IKZF1 deletion in childhood B-cell precursor acute lymphoblastic leukemia: an international collaborative study. Leukemia 2016;30:32-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26202931.

80. Stanulla M, Dagdan E, Zaliova M, et al. IKZF1(plus) defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. J Clin Oncol 2018;36:1240-1249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29498923.

81. Mangum DS, Meyer JA, Mason CC, et al. Association of combined focal 22q11.22 deletion and IKZF1 alterations with outcomes in childhood acute lymphoblastic leukemia. JAMA Oncol 2021;7:1521-1528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34410295.

82. Clappier E, Auclerc MF, Rapion J, et al. An intragenic ERG deletion is a marker of an oncogenic subtype of B-cell precursor acute lymphoblastic leukemia with a favorable outcome despite frequent IKZF1 deletions. Leukemia 2014;28:70-77. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24064621.

83. Zaliova M, Zimmermannova O, Dorge P, et al. ERG deletion is associated with CD2 and attenuates the negative impact of IKZF1 deletion in childhood acute lymphoblastic leukemia. Leukemia 2014;28:182-185. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24072102.

84. Bernt KM, Hunger SP. Current concepts in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. Front Oncol 2014;4:54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24724051.

85. Mullighan CG. The molecular genetic makeup of acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2012;2012:389-396. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23233609.

86. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol 2009;10:125-134. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19138562.

87. Roberts KG, Gu Z, Payne-Turner D, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. J Clin Oncol 2017;35:394-401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27870571.

88. van der Veer A, Waanders E, Pieters R, et al. Independent prognostic value of BCR-ABL1-like signature and IKZF1 deletion, but not high CRLF2 expression, in children with B-cell precursor ALL. Blood 2013;122:2622-2629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23974192.

89. Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood 2010;115:5312-5321. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20139093.

90. Reshmi SC, Harvey RC, Roberts KG, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. Blood 2017;129:3352-3361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28408464.

91. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med

2014;371:1005-1015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25207766.

92. Roberts KG, Yang YL, Payne-Turner D, et al. Oncogenic role and therapeutic targeting of ABL-class and JAK-STAT activating kinase alterations in Ph-like ALL. Blood Adv 2017;1:1657-1671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29296813.

93. Aifantis I, Raetz E, Buonamici S. Molecular pathogenesis of T-cell leukaemia and lymphoma. Nat Rev Immunol 2008;8:380-390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18421304.

94. Hernandez Tejada FN, Galvez Silva JR, Zweidler-McKay PA. The challenge of targeting notch in hematologic malignancies. Front Pediatr 2014;2:54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24959528.

95. O'Neil J, Grim J, Strack P, et al. FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. J Exp Med 2007;204:1813-1824. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17646409.

96. Weng AP, Ferrando AA, Lee W, et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 2004;306:269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15472075.

97. Asnafi V, Buzyn A, Le Noir S, et al. NOTCH1/FBXW7 mutation identifies a large subgroup with favorable outcome in adult T-cell acute lymphoblastic leukemia (T-ALL): a Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) study. Blood 2009;113:3918-3924. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19109228.

98. Breit S, Stanulla M, Flohr T, et al. Activating NOTCH1 mutations predict favorable early treatment response and long-term outcome in childhood precursor T-cell lymphoblastic leukemia. Blood 2006;108:1151-1157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16614245.

99. Clappier E, Collette S, Grardel N, et al. NOTCH1 and FBXW7 mutations have a favorable impact on early response to treatment, but not on outcome, in children with T-cell acute lymphoblastic leukemia (T-ALL) treated on EORTC trials 58881 and 58951. Leukemia 2010;24:2023-2031. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20861920.

100. Trinquand A, Tanguy-Schmidt A, Ben Abdelali R, et al. Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification of adult T-cell acute lymphoblastic leukemia: a Group for Research in Adult Acute Lymphoblastic Leukemia study. J Clin Oncol 2013;31:4333-4342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24166518.

101. Jenkinson S, Kirkwood AA, Goulden N, et al. Impact of PTEN abnormalities on outcome in pediatric patients with T-cell acute lymphoblastic leukemia treated on the MRC UKALL2003 trial. Leukemia 2016;30:39-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26220040.

102. Zuurbier L, Homminga I, Calvert V, et al. NOTCH1 and/or FBXW7 mutations predict for initial good prednisone response but not for improved outcome in pediatric T-cell acute lymphoblastic leukemia patients treated on DCOG or COALL protocols. Leukemia 2010;24:2014-2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20861909.

103. Polonen P, Di Giacomo D, Seffernick AE, et al. The genomic basis of childhood T-lineage acute lymphoblastic leukaemia. Nature 2024;632:1082-1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39143224.

104. Roberts KG, Reshmi SC, Harvey RC, et al. Genomic and outcome analyses of Ph-like ALL in NCI standard-risk patients: a report from the Children's Oncology Group. Blood 2018;132:815-824. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29997224.

105. Harvey RC, Kang H, Roberts KG, et al. Development and validation of a highly sensitive and specific gene expression classifier to prospectively screen and identify B-precursor acute lymphoblastic leukemia (ALL) patients with a Philadelphia chromosome-like ("Ph-like"

or “BCR-ABL1-like”) signature for therapeutic targeting and clinical intervention. Blood 2013;122:826. Available at: http://www.bloodjournal.org/content/122/21/826.

106. Inaba H, Azzato EM, Mullighan CG. Integration of next-generation sequencing to treat acute lymphoblastic leukemia with targetable lesions: the St. Jude Children's Research Hospital approach. Front Pediatr 2017;5:258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29255701.

107. Mulder RL, Font-Gonzalez A, Green DM, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2021;22:e57-e67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33539754.

108. Mulder RL, Font-Gonzalez A, Hudson MM, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2021;22:e45-e56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33539753.

109. Pui CH, Nichols KE, Yang JJ. Somatic and germline genomics in paediatric acute lymphoblastic leukaemia. Nat Rev Clin Oncol 2019;16:227-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30546053.

110. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355:165-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10675114.

111. Hunger SP, Sklar J, Link MP. Acute lymphoblastic leukemia occurring as a second malignant neoplasm in childhood: report of three cases and review of the literature. J Clin Oncol 1992;10:156-163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1309379.

112. Smith M, Arthur D, Camitta B, et al. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol 1996;14:18-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8558195.

113. Vrooman LM, Blonquist TM, Harris MH, et al. Refining risk classification in childhood B acute lymphoblastic leukemia: results of DFCI ALL Consortium Protocol 05-001. Blood Adv 2018;2:1449-1458. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29941458.

114. Gadner H, Masera G, Schrappe M, et al. The Eighth International Childhood Acute Lymphoblastic Leukemia Workshop ('Ponte di legno meeting') report: Vienna, Austria, April 27-28, 2005. Leukemia 2006;20:9-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16281070.

115. Hunger SP, Loh ML, Whitlock JA, et al. Children's Oncology Group's 2013 blueprint for research: acute lymphoblastic leukemia. Pediatr Blood Cancer 2013;60:957-963. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23255467.

116. Sutcliffe MJ, Shuster JJ, Sather HN, et al. High concordance from independent studies by the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) associating favorable prognosis with combined trisomies 4, 10, and 17 in children with NCI Standard-Risk B-precursor Acute Lymphoblastic Leukemia: a Children's Oncology Group (COG) initiative. Leukemia 2005;19:734-740. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15789069.

117. Romana SP, Mauchauffe M, Le Coniat M, et al. The t(12;21) of acute lymphoblastic leukemia results in a tel-AML1 gene fusion. Blood 1995;85:3662-3670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7780150.

118. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. Lancet

Oncol 2015;16:1677-1690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26549586.

119. Winter SS, Dunsmore KP, Devidas M, et al. Improved survival for children and young adults with T-lineage acute lymphoblastic leukemia: Results from the Children's Oncology Group AALL0434 Methotrexate Randomization. J Clin Oncol 2018;36:2926-2934. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30138085.

120. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet 2013;381:1943-1955. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23523389.

121. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009;360:2730-2741. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19553647.

122. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. Leukemia 2010;24:371-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20010620.

123. Silverman LB, Declerck L, Gelber RD, et al. Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981-1995). Leukemia 2000;14:2247-2256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11187916.

124. Silverman LB, Stevenson KE, O'Brien JE, et al. Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985-2000). Leukemia 2010;24:320-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20016537.

125. Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia 2010;24:265-284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20010625.

126. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. German-Austrian-Swiss ALL-BFM Study Group. Blood 2000;95:3310-3322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10828010.

127. Kluk MJ, Lindsley RC, Aster JC, et al. Validation and implementation of a custom next-generation sequencing clinical assay for hematologic malignancies. J Mol Diagn 2016;18:507-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27339098.

128. Seibel NL. Treatment of acute lymphoblastic leukemia in children and adolescents: peaks and pitfalls. Hematology Am Soc Hematol Educ Program 2008:374-380. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19074113.

129. Kamps WA, Bokkerink JP, Hakvoort-Cammel FG, et al. BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: results of DCLSG protocol ALL-8 (1991-1996). Leukemia 2002;16:1099-1111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12040440.

130. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 2008;111:4477-4489. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18285545.

131. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. Blood 2008;111:2548-2555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18039957.

132. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood

2008;112:1646-1654. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18502832.

133. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 1995;85:2025-2037. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7718875.

134. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood 2003;101:3809-3817. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12531809.

135. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol 2005;129:734-745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15952999.

136. Pui CH. Central nervous system disease in acute lymphoblastic leukemia: prophylaxis and treatment. Hematology Am Soc Hematol Educ Program 2006:142-146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17124053.

137. Moricke A, Zimmermann M, Valsecchi MG, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. Blood 2016;127:2101-2112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26888258.

138. Teuffel O, Kuster SP, Hunger SP, et al. Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. Leukemia 2011;25:1232-1238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21527934.

139. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. Blood 2002;99:1986-1994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11877270.

140. Vrooman LM, Blonquist TM, Stevenson KE, et al. Efficacy and toxicity of pegaspargase and calaspargase pegol in childhood acute lymphoblastic leukemia: Results of DFCI 11-001. J Clin Oncol 2021;39:3496-3505. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34228505.

141. Sandley M, Angus J. Asparaginase therapy in patients with acute lymphoblastic leukemia: expert opinion on use and toxicity management. Leuk Lymphoma 2023;64:776-787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36781296.

142. Maese L, Loh ML, Choi MR, et al. Recombinant erwinia asparaginase (JZP458) in acute lymphoblastic leukemia: results from the phase 2/3 AALL1931 study. Blood 2023;141:704-712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36108304.

143. FDA approves a new dosing regimen for asparaginase erwinia chrysanthemi (recombinant). 2022. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-new-dosing-regimen-asparaginase-erwinia-chrysanthemi-recombinant. Accessed August 4, 2023.

144. A study to investigate blinatumomab in combination with chemotherapy in patients with newly diagnosed B-lymphoblastic leukemia. Available at: https://clinicaltrials.gov/study/NCT03914625. Accessed January 29, 2024.

145. Angiolillo AL, Schore RJ, Kairalla JA, et al. Excellent outcomes with reduced frequency of vincristine and dexamethasone pulses in standard-risk B-lymphoblastic leukemia: Results from Children's Oncology Group AALL0932. J Clin Oncol 2021;39:1437-1447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33411585.

146. Inotuzumab ozogamicin and post-induction chemotherapy in treating patients with high-risk B-all, mixed phenotype acute leukemia, and B-LLy. Available at: https://www.clinicaltrials.gov/study/NCT03959085. Accessed January 29, 2024.

147. Burke MJ, Salzer WL, Devidas M, et al. Replacing cyclophosphamide/cytarabine/mercaptopurine with cyclophosphamide/etoposide during consolidation/delayed intensification does not improve outcome for pediatric B-cell acute lymphoblastic leukemia: a report from the COG. Haematologica 2019;104:986-992. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30545921.

148. Tasian SK, Assad A, Hunter DS, et al. A phase 2 study of ruxolitinib with chemotherapy in children with Philadelphia chromosome-like acute lymphoblastic leukemia (INCB18424-269/AALL1521): Dose-finding results from the Part 1 safety phase. Blood 2018;132:555-555. Available at: https://doi.org/10.1182/blood-2018-99-110221.

149. Teachey DT, Devidas M, Wood BL, et al. Children's Oncology Group trial AALL1231: A phase III clinical trial testing bortezomib in newly diagnosed T-cell acute lymphoblastic leukemia and lymphoma. J Clin Oncol 2022;40:2106-2118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35271306.

150. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434. Pediatr Blood Cancer 2015;62:1176-1183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25755211.

151. Imatinib mesylate and combination chemotherapy in treating patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia. Available at: https://clinicaltrials.gov/study/NCT03007147. Accessed January 29, 2024.

152. Azacitidine and combination chemotherapy in treating infants with acute lymphoblastic leukemia and KMT2A gene rearrangement. Available at: https://www.clinicaltrials.gov/study/NCT02828358. Accessed January 29, 2024.

153. Hunger SP, Tran TH, Saha V, et al. Dasatinib with intensive chemotherapy in de novo paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (CA180-372/COG AALL1122): a single-arm, multicentre, phase 2 trial. Lancet Haematol 2023;10:e510-e520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37407142.

154. Chrzanowska M, Kolecki P, Duczmal-Cichocka B, Fiet J. Metabolites of mercaptopurine in red blood cells: a relationship between 6-thioguanine nucleotides and 6-methylmercaptopurine metabolite concentrations in children with lymphoblastic leukemia. Eur J Pharm Sci 1999;8:329-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10425383.

155. Lennard L, Lilleyman JS. Variable mercaptopurine metabolism and treatment outcome in childhood lymphoblastic leukemia. J Clin Oncol 1989;7:1816-1823. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2585022.

156. Hawwa AF, Collier PS, Millership JS, et al. Population pharmacokinetic and pharmacogenetic analysis of 6-mercaptopurine in paediatric patients with acute lymphoblastic leukaemia. Br J Clin Pharmacol 2008;66:826-837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18823306.

157. McLeod HL, Coulthard S, Thomas AE, et al. Analysis of thiopurine methyltransferase variant alleles in childhood acute lymphoblastic leukaemia. Br J Haematol 1999;105:696-700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10354134.

158. McLeod HL, Relling MV, Crom WR, et al. Disposition of antineoplastic agents in the very young child. Br J Cancer Suppl 1992;18:S23-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1503923.

159. Collie-Duguid ES, Pritchard SC, Powrie RH, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and

Asian populations. Pharmacogenetics 1999;9:37-42. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10208641.

160. McLeod HL, Lin JS, Scott EP, et al. Thiopurine methyltransferase activity in American white subjects and black subjects. Clin Pharmacol Ther 1994;55:15-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8299312.

161. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. Am J Hum Genet 1980;32:651-662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7191632.

162. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30447069.

163. Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. J Clin Oncol 2012;30:2094-2101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22564992.

164. Guolla L, Breitbart S, Foroutan F, et al. Impact of vincristine-steroid pulses during maintenance for B-cell pediatric ALL: a systematic review and meta-analysis Blood 2023;141:2944-2954. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36821772.

165. Gossai NP, Devidas M, Chen Z, et al. Central nervous system status is prognostic in T-cell acute lymphoblastic leukemia: a Children's Oncology Group report. Blood 2023;141:1802-1811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36603187.

166. Winick N, Devidas M, Chen S, et al. Impact of initial CSF findings on outcome among patients with National Cancer Institute standard- and high-risk B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. J Clin Oncol 2017;35:2527-2534. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28535084.

167. Richards S, Pui CH, Gayon P, Childhood Acute Lymphoblastic Leukemia Collaborative G. Systematic review and meta-analysis of randomized trials of central nervous system directed therapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2013;60:185-195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22693038.

168. Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. Lancet 2005;366:635-642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16112299.

169. Leung W, Campana D, Yang J, et al. High success rate of hematopoietic cell transplantation regardless of donor source in children with very high-risk leukemia. Blood 2011;118:223-230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21613256.

170. Eapen M, Rubinstein P, Zhang MJ, et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet 2007;369:1947-1954. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17560447.

171. Peters C, Dalle JH, Locatelli F, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: A multinational, randomized, noninferiority phase III study. J Clin Oncol 2021;39:295-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33332189.

172. Davies SM, Ramsay NK, Klein JP, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol 2000;18:340-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10637248.

173. Bunin N, Aplenc R, Kamani N, et al. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant 2003;32:543-548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12953124.

174. Dreyer ZE, Dinndorf PA, Camitta B, et al. Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: a report from the Children's Oncology Group. J Clin Oncol 2011;29:214-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21135279.

175. Mann G, Attarbaschi A, Schrappe M, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. Blood 2010;116:2644-2650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20592248.

176. Biondi A, Gandemer V, De Lorenzo P, et al. Imatinib treatment of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial. Lancet Haematol 2018;5:e641-e652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30501871.

177. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol 2012;13:936-945. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22898679.

178. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-5181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19805687.

179. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014;28:1467-1471. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24441288.

180. Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: Results of Children's Oncology Group Trial AALL0622. J Clin Oncol 2018;36:2306-2314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29812996.

181. Mullighan CG, Zhang J, Harvey RC, et al. JAK mutations in high-risk childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 2009;106:9414-9418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19470474.

182. Berg SL, Blaney SM, Devidas M, et al. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. J Clin Oncol 2005;23:3376-3382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15908649.

183. Hoelzer D. Novel antibody-based therapies for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2011;2011:243-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22160041.

184. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016;34:4381-4389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27998223.

185. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011;29:2493-2498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21576633.

186. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378:439-448. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29385370.

187. Issa GC, Aldoss I, Thirman MJ, et al. Menin Inhibition With Revumenib for KMT2A-Rearranged Relapsed or Refractory Acute Leukemia (AUGMENT-101). J Clin Oncol 2024:JCO2400826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39121437.

188. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol 2003;21:774-780. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12610173.

189. Ramanujachar R, Richards S, Hann I, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer 2007;48:254-261. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16421910.

190. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2008;111:1827-1833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18048644.

191. Thiebaut A, Vernant JP, Degos L, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation. A follow-up report of the French protocol LALA 87. Hematol Oncol Clin North Am 2000;14:1353-1366, x. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11147227.

192. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004;101:2788-2801. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15481055.

193. Vey N, Thomas X, Picard C, et al. Allogeneic stem cell transplantation improves the outcome of adults with t(1;19)/E2A-PBX1 and t(4;11)/MLL-AF4 positive B-cell acute lymphoblastic leukemia: results of the prospective multicenter LALA-94 study. Leukemia 2006;20:2155-2161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17039234.

194. Zhang MJ, Hoelzer D, Horowitz MM, et al. Long-term follow-up of adults with acute lymphoblastic leukemia in first remission treated with chemotherapy or bone marrow transplantation. The Acute Lymphoblastic Leukemia Working Committee. Ann Intern Med 1995;123:428-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7639442.

195. Nachman J. Clinical characteristics, biologic features and outcome for young adult patients with acute lymphoblastic leukaemia. Br J Haematol 2005;130:166-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16029445.

196. Aguiar RC, Sohal J, van Rhee F, et al. TEL-AML1 fusion in acute lymphoblastic leukaemia of adults. M.R.C. Adult Leukaemia Working Party. Br J Haematol 1996;95:673-677. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8982044.

197. Secker-Walker LM, Craig JM, Hawkins JM, Hoffbrand AV. Philadelphia positive acute lymphoblastic leukemia in adults: age distribution, BCR breakpoint and prognostic significance. Leukemia 1991;5:196-199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2013979.

198. Neumann M, Heesch S, Gokbuget N, et al. Clinical and molecular characterization of early T-cell precursor leukemia: a high-risk subgroup in adult T-ALL with a high frequency of FLT3 mutations. Blood Cancer J 2012;2:e55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22829239.

199. Pieters R, Kaspers GJ, Klumper E, Veerman AJ. Clinical relevance of in vitro drug resistance testing in childhood acute lymphoblastic leukemia: the state of the art. Med Pediatr Oncol 1994;22:299-308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8127253.

200. Raetz EA, Devidas M, Carroll AJ, et al. Cytogenetic and early-response characteristics of adolescents and young adults with acute lymphoblastic leukemia (ALL): A Children's Oncology Group (COG) study. Journal of Clinical Oncology 2010;28:9509. Available at: https://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.9509.

201. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. Cancer 2006;107:1645-1655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16906507.

202. Fern LA, Whelan JS. Recruitment of adolescents and young adults to cancer clinical trials--international comparisons, barriers, and implications. Semin Oncol 2010;37:e1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20494693.

203. Schmiegelow K, Heyman M, Gustafsson G, et al. The degree of myelosuppression during maintenance therapy of adolescents with B-lineage intermediate risk acute lymphoblastic leukemia predicts risk of relapse. Leukemia 2010;24:715-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20130603.

204. Martin S, Ulrich C, Munsell M, et al. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist 2007;12:816-824. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17673613.

205. Pui CH, Kane JR, Crist WM. Biology and treatment of infant leukemias. Leukemia 1995;9:762-769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7769837.

206. Margolin JF, Poplack DG. Acute Lymphoblastic Leukemia. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology (ed Third edition). Philadelphia: Lippincott-Raven; 1997:409-462.

207. Heerema NA, Arthur DC, Sather H, et al. Cytogenetic features of infants less than 12 months of age at diagnosis of acute lymphoblastic leukemia: impact of the 11q23 breakpoint on outcome: a report of the Childrens Cancer Group. Blood 1994;83:2274-2284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8161794.

208. Whitlock JA. Down syndrome and acute lymphoblastic leukaemia. Br J Haematol 2006;135:595-602. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17054672.

209. Hertzberg L, Vendramini E, Ganmore I, et al. Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. Blood 2010;115:1006-1017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19965641.

210. Mullighan CG, Collins-Underwood JR, Phillips LA, et al. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet 2009;41:1243-1246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19838194.

211. Malinge S, Izraeli S, Crispino JD. Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome. Blood 2009;113:2619-2628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19139078.

212. Izraeli S, Vora A, Zwaan CM, Whitlock J. How I treat ALL in Down's syndrome: pathobiology and management. Blood 2014;123:35-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24235135.

213. Bassal M, La MK, Whitlock JA, et al. Lymphoblast biology and outcome among children with Down syndrome and ALL treated on CCG-1952. Pediatr Blood Cancer 2005;44:21-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15368546.

214. Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the

ALL-REZ BFM Study Group. J Clin Oncol 2009;27:377-384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19064980.

215. Cave H, van der Werff ten Bosch J, Suciu S, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. European Organization for Research and Treatment of Cancer--Childhood Leukemia Cooperative Group. N Engl J Med 1998;339:591-598. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9718378.

216. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood 2008;111:5477-5485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18388178.

217. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 2010;115:3206-3214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20154213.

218. Eckert C, Hagedorn N, Sramkova L, et al. Monitoring minimal residual disease in children with high-risk relapses of acute lymphoblastic leukemia: prognostic relevance of early and late assessment. Leukemia 2015;29:1648-1655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25748682.

219. Eckert C, von Stackelberg A, Seeger K, et al. Minimal residual disease after induction is the strongest predictor of prognosis in intermediate risk relapsed acute lymphoblastic leukaemia - long-term results of trial ALL-REZ BFM P95/96. Eur J Cancer 2013;49:1346-1355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23265714.

220. Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood 2011;118:2077-2084. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21719599.

221. Van der Velden VH, Corral L, Valsecchi MG, et al. Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol. Leukemia 2009;23:1073-1079. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19212338.

222. Wood BL, Winter SS, Dunsmore KP, et al. T-lymphoblastic leukemia (T-ALL) shows excellent outcome, lack of significance of the early thymic precursor (ETP) immunophenotype, and validation of the prognostic value of end-induction minimal residual disease (MRD) in Children's Oncology Group (COG) Study AALL0434. Blood 2014;124:1-1. Available at: http://www.bloodjournal.org/content/124/21/1.

223. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: A meta-analysis. JAMA Oncol 2017;3:e170580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28494052.

224. Carlson CS, Emerson RO, Sherwood AM, et al. Using synthetic templates to design an unbiased multiplex PCR assay. Nat Commun 2013;4:2680. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24157944.

225. Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2013;27:635-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22945774.

226. Faham M, Zheng J, Moorhead M, et al. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. Blood 2012;120:5173-5180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23074282.

227. Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. Haematologica 2012;97:1582-1593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22581001.

228. Ladetto M, Bruggemann M, Monitillo L, et al. Next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. Leukemia 2014;28:1299-1307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24342950.

229. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. Blood 2010;115:4657-4663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20304809.

230. Wood B, Wu D, Crossley B, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. Blood 2018;131:1350-1359. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29284596.

231. Cherian S, Soma LA. How I diagnose minimal/measurable residual disease in B lymphoblastic leukemia/lymphoma by flow cytometry. Am J Clin Pathol 2021;155:38-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33236071.

232. Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010;2010:7-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21239764.

233. Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia 2010;24:521-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20033054.

234. Neale GA, Coustan-Smith E, Stow P, et al. Comparative analysis of flow cytometry and polymerase chain reaction for the detection of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2004;18:934-938. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15029212.

235. Wu D, Emerson RO, Sherwood A, et al. Detection of minimal residual disease in B lymphoblastic leukemia by high-throughput sequencing of IGH. Clin Cancer Res 2014;20:4540-4548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24970842.

236. Wu D, Sherwood A, Fromm JR, et al. High-throughput sequencing detects minimal residual disease in acute T lymphoblastic leukemia. Sci Transl Med 2012;4:134ra163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22593176.

237. Kerst G, Kreyenberg H, Roth C, et al. Concurrent detection of minimal residual disease (MRD) in childhood acute lymphoblastic leukaemia by flow cytometry and real-time PCR. Br J Haematol 2005;128:774-782. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15755280.

238. Coustan-Smith E, Behm FG, Sanchez J, et al. Immunological detection of minimal residual disease in children with acute lymphoblastic leukaemia. Lancet 1998;351:550-554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9492773.

239. Coustan-Smith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in childhood acute lymphoblastic leukemia. Blood 2000;96:2691-2696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11023499.

240. Coustan-Smith E, Sancho J, Behm FG, et al. Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia. Blood 2002;100:52-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12070008.

241. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. Blood 2015;126:964-971. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26124497.

242. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised

controlled trial. Lancet Oncol 2014;15:809-818. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24924991.

243. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013;14:199-209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23395119.

244. Campbell M, Kiss C, Zimmermann M, et al. Childhood acute lymphoblastic leukemia: Results of the randomized Acute Lymphoblastic Leukemia Intercontinental-Berlin-Frankfurt-Munster 2009 trial. J Clin Oncol 2023;41:3499-3511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37141547.

245. O'Connor D, Enshaei A, Bartram J, et al. Genotype-specific minimal residual disease interpretation improves stratification in pediatric acute lymphoblastic leukemia. J Clin Oncol 2018;36:34-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29131699.

246. Moorman AV, Antony G, Wade R, et al. Time to cure for childhood and young adult acute lymphoblastic leukemia is independent of early risk factors: Long-term follow-up of the UKALL2003 trial. J Clin Oncol 2022;40:4228-4239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35714315.

247. Stutterheim J, van der Sluis IM, de Lorenzo P, et al. Clinical implications of minimal residual disease detection in infants with KMT2A-rearranged acute lymphoblastic leukemia treated on the Interfant-06 Protocol. J Clin Oncol 2021;39:652-662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33405950.

248. Eckert C, Henze G, Seeger K, et al. Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group. J Clin Oncol 2013;31:2736-2742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23775972.

249. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. Lancet 2010;376:2009-2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21131038.

250. Hogan LE, Brown PA, Ji L, et al. Children's Oncology Group AALL1331: Phase III trial of blinatumomab in children, adolescents, and young adults with low-risk B-Cell ALL in first relapse. J Clin Oncol 2023;41:4118-4129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37257143.

251. Coustan-Smith E, Sandlund JT, Perkins SL, et al. Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children's oncology group. J Clin Oncol 2009;27:3533-3539. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19546402.

252. Hayashi RJ, Winter SS, Dunsmore KP, et al. Successful outcomes of newly diagnosed T lymphoblastic lymphoma: Results from Children's Oncology Group AALL0434. J Clin Oncol 2020;38:3062-3070. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32552472.

253. Hayashi RJ, Hermiston ML, Wood BL, et al. MRD at the end of induction and EFS in T-cell lymphoblastic lymphoma: Children's Oncology Group trial AALL1231. Blood 2024;143:2053-2058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38457359.

254. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol 2010;28:648-654. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19841326.

255. Coustan-Smith E, Gajjar A, Hijiya N, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia after first relapse. Leukemia 2004;18:499-504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14981525.

256. Paganin M, Fabbri G, Conter V, et al. Postinduction minimal residual disease monitoring by polymerase chain reaction in children with

acute lymphoblastic leukemia. J Clin Oncol 2014;32:3553-3558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25287825.

257. Paganin M, Zecca M, Fabbri G, et al. Minimal residual disease is an important predictive factor of outcome in children with relapsed 'high-risk' acute lymphoblastic leukemia. Leukemia 2008;22:2193-2200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18754029.

258. Basso G, Veltroni M, Valsecchi MG, et al. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. J Clin Oncol 2009;27:5168-5174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19805690.

259. Panzer-Grumayer ER, Schneider M, Panzer S, et al. Rapid molecular response during early induction chemotherapy predicts a good outcome in childhood acute lymphoblastic leukemia. Blood 2000;95:790-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10648387.

260. Pulsipher MA, Han X, Maude SL, et al. Next-generation sequencing of minimal residual disease for predicting relapse after tisagenlecleucel in children and young adults with acute lymphoblastic leukemia. Blood Cancer Discov 2022;3:66-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35019853.

261. Maloney KW, Devidas M, Wang C, et al. Outcome in children with standard-risk B-cell acute lymphoblastic leukemia: Results of Children's Oncology Group Trial AALL0331. J Clin Oncol 2020;38:602-612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31825704.

262. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: A report from Children's Oncology Group Study AALL0232. J Clin Oncol 2016;34:2380-2388. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27114587.

263. Salzer WL, Burke MJ, Devidas M, et al. Toxicity associated with intensive postinduction therapy incorporating clofarabine in the very high-risk stratum of patients with newly diagnosed high-risk B-lymphoblastic leukemia: A report from the Children's Oncology Group study AALL1131. Cancer 2018;124:1150-1159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29266189.

264. Salzer WL, Burke MJ, Devidas M, et al. Impact of Intrathecal Triple Therapy Versus Intrathecal Methotrexate on Disease-Free Survival for High-Risk B-Lymphoblastic Leukemia: Children's Oncology Group Study AALL1131. J Clin Oncol 2020;38:2628-2638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32496902.

265. Tasian SK, Hunter DS, Chen IML, et al. A phase 2 study of ruxolitinib with chemotherapy in children with Philadelphia chromosome-like acute lymphoblastic leukemia (AALL1521/INCB18424-269): biologic characteristics and minimal residual disease response of patients with non-CRLF2-rearranged JAK pathway alterations. Blood 2022;140:6117-6118. Available at: https://doi.org/10.1182/blood-2022-164699.

266. Jeha S, Pei D, Choi J, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total Therapy Study 16. J Clin Oncol 2019;37:3377-3391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31657981.

267. Dreier T, Lorenczewski G, Brandl C, et al. Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. Int J Cancer 2002;100:690-697. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12209608.

268. Hoffmann P, Hofmeister R, Brischwein K, et al. Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct. Int J Cancer 2005;115:98-104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15688411.

269. Topp MS, Gokbuget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood 2012;120:5185-5187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23024237.

270. Gokbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131:1522-1531. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29358182.

271. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med 2017;376:836-847. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28249141.

272. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16:57-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25524800.

273. Topp MS, Gokbuget N, Zugmaier G, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol 2014;32:4134-4140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25385737.

274. Jabbour E, Short NJ, Jain N, et al. Hyper-CVAD and sequential blinatumomab for newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: a single-arm, single-centre, phase 2 trial. Lancet Haematol 2022;9:e878-e885. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36279879.

275. Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. N Engl J Med 2024;391:320-333. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39047240.

276. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: A randomized clinical trial. JAMA 2021;325:843-854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33651091.

277. FDA approves blinatumomab as consolidation for CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. 2024. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-blinatumomab-consolidation-cd19-positive-philadelphia-chromosome-negative-b-cell. Accessed July 7, 2024.

278. McNeer JL, Devidas M, Dai Y, et al. Hematopoietic stem-cell transplantation does not improve the poor outcome of children with hypodiploid acute lymphoblastic leukemia: A report from Children's Oncology Group. J Clin Oncol 2019;37:780-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30742559.

279. Mullighan CG, Jeha S, Pei D, et al. Outcome of children with hypodiploid ALL treated with risk-directed therapy based on MRD levels. Blood 2015;126:2896-2899. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26527677.

280. Nachman JB, Heerema NA, Sather H, et al. Outcome of treatment in children with hypodiploid acute lymphoblastic leukemia. Blood 2007;110:1112-1115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17473063.

281. Pui CH, Rebora P, Schrappe M, et al. Outcome of children with hypodiploid acute lymphoblastic leukemia: A retrospective multinational study. J Clin Oncol 2019;37:770-779. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30657737.

282. Parker C, Krishnan S, Hamadeh L, et al. Outcomes of patients with childhood B-cell precursor acute lymphoblastic leukaemia with late bone marrow relapses: long-term follow-up of the ALLR3 open-label randomised trial. Lancet Haematol 2019;6:e204-e216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30826273.

283. Sun W, Malvar J, Sposto R, et al. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: a therapeutic advances in childhood leukemia & lymphoma study. Leukemia 2018;32:2316-2325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29728694.

284. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol 2010;28:2339-2347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20385996.

285. Raetz EA, Borowitz MJ, Devidas M, et al. Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study[corrected]. J Clin Oncol 2008;26:3971-3978. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18711187.

286. Horton TM, Whitlock JA, Lu X, et al. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. Br J Haematol 2019;186:274-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30957229.

287. Messinger Y, Gaynon P, Raetz E, et al. Phase I study of bortezomib combined with chemotherapy in children with relapsed childhood acute lymphoblastic leukemia (ALL): a report from the therapeutic advances in childhood leukemia (TACL) consortium. Pediatr Blood Cancer 2010;55:254-259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20582937.

288. Messinger YH, Gaynon PS, Sposto R, et al. Bortezomib with chemotherapy is highly active in advanced B-precursor acute lymphoblastic leukemia: Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) Study. Blood 2012;120:285-290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22653976.

289. Horton TM, Lu X, O'Brien MM, et al. Bortezomib reinduction therapy to improve response rates in pediatric ALL in first relapse: A Children's Oncology Group (COG) study (AALL07P1). Journal of Clinical Oncology 2013;31:Abstract #10003. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2013.31.15_suppl.10003.

290. Jeha S, Gandhi V, Chan KW, et al. Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemia. Blood 2004;103:784-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14551141.

291. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006;24:1917-1923. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16622268.

292. Hijiya N, Thomson B, Isakoff MS, et al. Phase 2 trial of clofarabine in combination with etoposide and cyclophosphamide in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. Blood 2011;118:6043-6049. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21967976.

293. Miano M, Pistorio A, Putti MC, et al. Clofarabine, cyclophosphamide and etoposide for the treatment of relapsed or resistant acute leukemia in pediatric patients. Leuk Lymphoma 2012;53:1693-1698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22303898.

294. Frey NV, Luger SM. How I treat adults with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. Blood 2015;126:589-596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25966988.

295. Montillo M, Tedeschi A, Centurioni R, Leoni P. Treatment of relapsed adult acute lymphoblastic leukemia with fludarabine and cytosine arabinoside followed by granulocyte colony-stimulating factor (FLAG-GCSF). Leuk Lymphoma 1997;25:579-583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9250830.

296. Specchia G, Pastore D, Carluccio P, et al. FLAG-IDA in the treatment of refractory/relapsed adult acute lymphoblastic leukemia. Ann Hematol 2005;84:792-795. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16047203.

297. Yavuz S, Paydas S, Disel U, Sahin B. IDA-FLAG regimen for the therapy of primary refractory and relapse acute leukemia: a single-center experience. Am J Ther 2006;13:389-393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16988532.

298. Gabriel MA, O'Brien TA, Tapp H, et al. Fludarabine, idarubicin and high dose cytarabine (FLAG-IDA) followed by allogeneic transplantation: A successful strategy for remission re-induction in high risk pediatric patients with relapsed, refractory and secondary acute leukemias. Blood 2006;108:3145. Available at: http://www.bloodjournal.org/content/108/11/3145.

299. Harris RE, Sather HN, Feig SA. High-dose cytosine arabinoside and L-asparaginase in refractory acute lymphoblastic leukemia: the Children's Cancer Group experience. Med Pediatr Oncol 1998;30:233-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9473758.

300. Place AE, Karol SE, Forlenza CJ, et al. Pediatric patients with relapsed/refractory acute lymphoblastic leukemia harboring heterogeneous genomic profiles respond to venetoclax in combination with chemotherapy. Blood 2020;136:37-38. Available at: https://doi.org/10.1182/blood-2020-137376.

301. Topp MS, Goekbuget N, Zugmaier G, et al. Anti-CD19 BiTE blinatumomab induces high complete remission rate in adult patients with relapsed B-precursor ALL: Updated results of an ongoing phase II trial. Blood 2011;118:252-252. Available at: http://www.bloodjournal.org/content/118/21/252.

302. Topp MS, Goekbuget N, Stein AS, et al. Confirmatory open-label, single-arm, multicenter phase 2 study of the BiTE antibody blinatumomab in patients (pts) with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL). Journal of Clinical Oncology 2014;32:7005-7005. Available at: https://doi.org/10.1200/jco.2014.32.15_suppl.7005.

303. Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and youngaAdults with first relapse of B-cell acute lymphoblastic leukemia: A randomized clinical trial. JAMA 2021;325:833-842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33651090.

304. Locatelli F, Eckert C, Hrusak O, et al. Blinatumomab overcomes poor prognostic impact of measurable residual disease in pediatric high-risk first relapse B-cell precursor acute lymphoblastic leukemia. Pediatr Blood Cancer 2022;69:e29715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35482538.

305. Portell CA, Wenzell CM, Advani AS. Clinical and pharmacologic aspects of blinatumomab in the treatment of B-cell acute lymphoblastic leukemia. Clin Pharmacol 2013;5:5-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23671399.

306. Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. Sci Transl Med 2013;5:177ra138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23515080.

307. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med 2013;368:1509-1518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23527958.

308. Grupp SA, Maude SL, Rives S, et al. Updated analysis of the efficacy and safety of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory (r/r) acute lymphoblastic leukemia. Blood 2018;132:895-895. Available at: https://doi.org/10.1182/blood-2018-99-112599.

309. Elsallab M, Ellithi M, Hempel S, et al. Long-term response to autologous anti-CD19 chimeric antigen receptor T cells in relapsed or refractory B cell acute lymphoblastic leukemia: a systematic review and meta-analysis. Cancer Gene Ther 2023;30:845-854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36750666.

310. June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med 2018;379:64-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29972754.

311. Hollyman D, Stefanski J, Przybylowski M, et al. Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. J Immunother 2009;32:169-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19238016.

312. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-1517. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25317870.

313. Laetsch TW, Maude SL, Rives S, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. J Clin Oncol 2023;41:1664-1669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36399695.

314. A VS, Jaschke K, Jousseaume E, et al. Tisagenlecleucel vs. historical standard of care in children and young adult patients with relapsed/refractory B-cell precursor acute lymphoblastic leukemia. Leukemia 2023;37:2346-2355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37880478.

315. Myers RM, Li Y, Barz Leahy A, et al. Humanized CD19-targeted chimeric antigen receptor (CAR) t cells in CAR-naive and CAR-exposed children and young adults with relapsed or refractory acute lymphoblastic leukemia. J Clin Oncol 2021;39:3044-3055. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34156874.

316. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321-3330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27207799.

317. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28925994.

318. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30592986.

319. Mahadeo KM, Khazal SJ, Abdel-Azim H, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol 2019;16:45-63. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30082906.

320. Leahy AB, Newman H, Li Y, et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: a post-hoc analysis of pooled data from five clinical trials. Lancet Haematol 2021;8:e711-e722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34560014.

321. Wang T, Tang Y, Cai J, et al. Coadministration of CD19- and CD22-directed chimeric antigen receptor T-cell therapy in childhood B-cell acute lymphoblastic leukemia: A single-arm, multicenter, phase II trial. J Clin Oncol 2023;41:1670-1683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36346962.

322. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol 2012;13:403-411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22357140.

323. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375:740-753. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27292104.

324. Jabbour EJ, Sasaki K, Ravandi F, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-HCVD) with or without blinatumomab versus standard intensive chemotherapy (HCVAD) as frontline therapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: A propensity score analysis. Cancer 2019;125:2579-2586. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30985931.

325. O'Brien MM, Ji L, Shah NN, et al. Phase II trial of inotuzumab ozogamicin in children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia: Children's Oncology Group Protocol AALL1621. J Clin Oncol 2022;40:956-967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35007127.

326. Pennesi E, Michels N, Brivio E, et al. Inotuzumab ozogamicin as single agent in pediatric patients with relapsed and refractory acute lymphoblastic leukemia: results from a phase II trial. Leukemia 2022;36:1516-1524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35468945.

327. Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol 2017;4:e387-e398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28687420.

328. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer 2019;125:2474-2487. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30920645.

329. Kebriaei P, Cutler C, de Lima M, et al. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant 2018;53:449-456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29330398.

330. Duval M, Klein JP, He W, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. J Clin Oncol 2010;28:3730-3738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20625136.

331. Oliansky DM, Camitta B, Gaynon P, et al. Role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. Biol Blood Marrow Transplant 2012;18:505-522. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22209888.

332. Hunger SP, Saha V, Devidas M, et al. CA180-372: An international collaborative phase 2 trial of dasatinib and chemotherapy in pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Blood 2017;130:98-98. Available at: https://doi.org/10.1182/blood.V130.Suppl_1.98.98.

333. Jeha S, Coustan-Smith E, Pei D, et al. Impact of tyrosine kinase inhibitors on minimal residual disease and outcome in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer 2014;120:1514-1519. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24501014.

334. Foà R, Bassan R, Vitale A, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. N Engl J Med 2020;383:1613-1623. Available at: https://pubmed.ncbi.nlm.nih.gov/33085860/.

335. Foà R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. J Clin Oncol 2024;42:881-885. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38127722.

336. Kantarjian H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. J Clin Oncol 2024:JCO2400272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39028925.

337. Arico M, Schrappe M, Hunger SP, et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. J Clin Oncol 2010;28:4755-4761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20876426.

338. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood

2009;113:4489-4496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19244158.

339. Champagne MA, Capdeville R, Krailo M, et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood 2004;104:2655-2660. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15231574.

340. Rossoff J, Huynh V, Rau RE, et al. Experience with ponatinib in paediatric patients with leukaemia. Br J Haematol 2020;189:363-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31975387.

341. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: Results from a phase II, single-arm, multicenter study. J Clin Oncol 2017;35:1795-1802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28355115.

342. Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. Clin Lymphoma Myeloma Leuk 2017;17:897-901. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28927784.

343. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6:224ra225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24553386.

344. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 2018;378:449-459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29385376.

345. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia 2019;33:884-892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30267011.

346. Giebel S, Czyz A, Ottmann O, et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A position statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Cancer 2016;122:2941-2951. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27309127.

347. Ishida Y, Terasako K, Oshima K, et al. Dasatinib followed by second allogeneic hematopoietic stem cell transplantation for relapse of Philadelphia chromosome-positive acute lymphoblastic leukemia after the first transplantation. Int J Hematol 2010;92:542-546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20824399.

348. Millot F, Cividin M, Brizard F, et al. Successful second allogeneic stem cell transplantation in second remission induced by dasatinib in a child with Philadelphia chromosome positive acute lymphoblastic leukemia. Pediatr Blood Cancer 2009;52:891-892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19202569.

349. Dunsmore KP, Winter SS, Devidas M, et al. Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia. J Clin Oncol 2020;38:3282-3293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32813610.

350. Burns MA, Place AE, Stevenson KE, et al. Identification of prognostic factors in childhood T-cell acute lymphoblastic leukemia: Results from DFCI ALL Consortium Protocols 05-001 and 11-001. Pediatr Blood Cancer 2021;68:e28719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33026184.

351. Schrauder A, Reiter A, Gadner H, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results

from ALL-BFM 90 and 95. J Clin Oncol 2006;24:5742-5749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17179108.

352. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. Blood 2007;109:5136-5142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17344466.

353. Whitlock JA, Malvar J, Dalla-Pozza L, et al. Nelarabine, etoposide, and cyclophosphamide in relapsed pediatric T-acute lymphoblastic leukemia and T-lymphoblastic lymphoma (study T2008-002 NECTAR). Pediatr Blood Cancer 2022;69:e29901. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35989458.

354. Richard-Carpentier G, Jabbour E, Short NJ, et al. Clinical experience with venetoclax combined with chemotherapy for relapsed or refractory T-cell acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk 2020;20:212-218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32035785.

355. Bhatla T, Hogan LM, Teachey DT, et al. Daratumumab in pediatric relapsed/refractory acute lymphoblastic leukemia or lymphoblastic lymphoma: DELPHINUS study. Blood 2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39158071.

356. Eckert C, Parker C, Moorman AV, et al. Risk factors and outcomes in children with high-risk B-cell precursor and T-cell relapsed acute lymphoblastic leukaemia: combined analysis of ALLR3 and ALL-REZ BFM 2002 clinical trials. Eur J Cancer 2021;151:175-189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34010787.

357. Hogan LE, Bhatla T, Teachey DT, et al. Efficacy and safety of daratumumab (DARA) in pediatric and young adult patients (pts) with relapsed/refractory T-cell acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL): Results from the phase 2 DELPHINUS study. Journal of Clinical Oncology 2022;40:10001-10001. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.10001.

358. Ramakers-van Woerden NL, Beverloo HB, Veerman AJ, et al. In vitro drug-resistance profile in infant acute lymphoblastic leukemia in relation to age, MLL rearrangements and immunophenotype. Leukemia 2004;18:521-529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14712291.

359. Stam RW, den Boer ML, Meijerink JP, et al. Differential mRNA expression of Ara-C-metabolizing enzymes explains Ara-C sensitivity in MLL gene-rearranged infant acute lymphoblastic leukemia. Blood 2003;101:1270-1276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12406912.

360. Van Der Sluis IM, De Lorenzo P, Kotecha RS, et al. A phase 2 study to test the feasibility, safety and efficacy of the addition of blinatumomab to the Interfant06 backbone in infants with newly diagnosed KMT2A-rearranged acute lymphoblastic leukemia. A collaborative study of the Interfant Network. Blood 2021;138:361-361. Available at: https://doi.org/10.1182/blood-2021-144843.

361. Armstrong SA, Staunton JE, Silverman LB, et al. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet 2002;30:41-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11731795.

362. Kang H, Wilson CS, Harvey RC, et al. Gene expression profiles predictive of outcome and age in infant acute lymphoblastic leukemia: a Children's Oncology Group study. Blood 2012;119:1872-1881. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22210879.

363. Stam RW, den Boer ML, Schneider P, et al. Targeting FLT3 in primary MLL-gene-rearranged infant acute lymphoblastic leukemia. Blood 2005;106:2484-2490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15956279.

364. Salzer WL, Jones TL, Devidas M, et al. Decreased induction morbidity and mortality following modification to induction therapy in infants with acute lymphoblastic leukemia enrolled on AALL0631: a report from the Children's Oncology Group. Pediatr Blood Cancer

2015;62:414-418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25407157.

365. Salzer WL, Jones TL, Devidas M, et al. Modifications to induction therapy decrease risk of early death in infants with acute lymphoblastic leukemia treated on Children's Oncology Group P9407. Pediatr Blood Cancer 2012;59:834-839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22488662.

366. Tomizawa D, Miyamura T, Imamura T, et al. A risk-stratified therapy for infants with acute lymphoblastic leukemia: a report from the JPLSG MLL-10 trial. Blood 2020;136:1813-1823. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32845001.

367. Nagayama J, Tomizawa D, Koh K, et al. Infants with acute lymphoblastic leukemia and a germline MLL gene are highly curable with use of chemotherapy alone: results from the Japan Infant Leukemia Study Group. Blood 2006;107:4663-4665. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16478880.

368. Sison EA, Brown P. Does hematopoietic stem cell transplantation benefit infants with acute leukemia? Hematology Am Soc Hematol Educ Program 2013;2013:601-604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24319238.

369. Driessen EM, de Lorenzo P, Campbell M, et al. Outcome of relapsed infant acute lymphoblastic leukemia treated on the interfant-99 protocol. Leukemia 2016;30:1184-1187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26369984.

370. Tomizawa D, Koh K, Hirayama M, et al. Outcome of recurrent or refractory acute lymphoblastic leukemia in infants with MLL gene rearrangements: A report from the Japan Infant Leukemia Study Group. Pediatr Blood Cancer 2009;52:808-813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19229974.

371. Burger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. J Clin Oncol 2003;21:184-188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12525508.

372. Pui CH, Pei D, Campana D, et al. Improved prognosis for older adolescents with acute lymphoblastic leukemia. J Clin Oncol 2011;29:386-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21172890.

373. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. 2018. Available at: http://survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf . Accessed January 24, 2023.

374. Browne EK, Zhou Y, Chemaitilly W, et al. Changes in body mass index, height, and weight in children during and after therapy for acute lymphoblastic leukemia. Cancer 2018;124:4248-4259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30358906.

375. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol 2018;36:1443-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29461916.

376. Alexander S, Fisher BT, Gaur AH, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: A randomized clinical trial. JAMA 2018;320:995-1004. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30208456.

377. Sulis ML, Blonquist TM, Stevenson KE, et al. Effectiveness of antibacterial prophylaxis during induction chemotherapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2018;65:e26952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29319209.

378. Maertens J, Cesaro S, Maschmeyer G, et al. ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J

Antimicrob Chemother 2016;71:2397-2404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27550992.

379. Wolf J, Tang L, Flynn PM, et al. Levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. Clin Infect Dis 2017;65:1790-1798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29020310.

380. Lehrnbecher T, Fisher BT, Phillips B, et al. Guideline for antibacterial prophylaxis administration in pediatric cancer and hematopoietic stem cell transplantation. Clin Infect Dis 2020;71:226-236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31676904.

381. Egan G, Robinson PD, Martinez JPD, et al. Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: A systematic review of randomized trials. Cancer Med 2019;8:4536-4546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31274245.

382. Nikanjam M, Sun A, Albers M, et al. Vincristine-associated neuropathy with antifungal usage: A Kaiser Northern California Experience. J Pediatr Hematol Oncol 2018;40:e273-e277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29771861.

383. Yang L, Yu L, Chen X, et al. Clinical analysis of adverse drug reactions between vincristine and triazoles in children with acute lymphoblastic leukemia. Med Sci Monit 2015;21:1656-1661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26050202.

384. van Schie RM, Bruggemann RJ, Hoogerbrugge PM, te Loo DM. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother 2011;66:1853-1856. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21652620.

385. Bruggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis 2009;48:1441-1458. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19361301.

386. Moriyama B, Henning SA, Leung J, et al. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. Mycoses 2012;55:290-297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22126626.

387. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24421306.

388. American Society of Hematology COVID-19 Resources: COVID-19 and Pediatric ALL. 2021. Available at: https://www.hematology.org/covid-19/covid-19-and-pediatric-all. Accessed January 30, 2023.

389. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-2778. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18509186.

390. Ramsey LB, Balis FM, O'Brien MM, et al. Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018;23:52-61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29079637.

391. Kroll M, Kaupat-Bleckmann K, Morickel A, et al. Methotrexate-associated toxicity in children with Down syndrome and acute lymphoblastic leukemia during consolidation therapy with high dose methotrexate according to ALL-BFM treatment regimen. Haematologica 2020;105:1013-1020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31371414.

392. Howard SC, McCormick J, Pui CH, et al. Preventing and managing toxicities of high-dose methotrexate. Oncologist 2016;21:1471-1482. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27496039.

393. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic

leukemia. J Clin Oncol 2014;32:949-959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24550419.

394. Rubnitz JE, Relling MV, Harrison PL, et al. Transient encephalopathy following high-dose methotrexate treatment in childhood acute lymphoblastic leukemia. Leukemia 1998;12:1176-1181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9697870.

395. Wheless JW. Levetiracetam in the treatment of childhood epilepsy. Neuropsychiatr Dis Treat 2007;3:409-421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19300570.

396. Buck ML, Goodkin HP. Use of lacosamide in children with refractory epilepsy. J Pediatr Pharmacol Ther 2012;17:211-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23258963.

397. Harake D, Franco VI, Henkel JM, et al. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. Future Cardiol 2012;8:647-670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22871201.

398. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med 2004;351:145-153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15247354.

399. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol 2010;11:950-961. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20850381.

400. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol 2007;25:493-500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17290056.

401. Barry EV, Vrooman LM, Dahlberg SE, et al. Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. J Clin Oncol 2008;26:1106-1111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18309945.

402. Vrooman LM, Neuberg DS, Stevenson KE, et al. The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. Eur J Cancer 2011;47:1373-1379. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21514146.

403. Batchelor TT, Taylor LP, Thaler HT, et al. Steroid myopathy in cancer patients. Neurology 1997;48:1234-1238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9153449.

404. Hochhauser CJ, Lewis M, Kamen BA, Cole PD. Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia. Support Care Cancer 2005;13:967-974. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16189647.

405. Warris LT, van den Heuvel-Eibrink MM, den Hoed MA, et al. Does dexamethasone induce more neuropsychological side effects than prednisone in pediatric acute lymphoblastic leukemia? A systematic review. Pediatr Blood Cancer 2014;61:1313-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24532490.

406. Bhasin S, Brown J, Dorste A, et al. Measuring neurobehavioral side effects of corticosteroids in pediatric acute lymphoblastic leukemia: A scoping review. Pediatr Blood Cancer 2024;71:e30881. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38263506.

407. Warris LT, van den Heuvel-Eibrink MM, Aarsen FK, et al. Hydrocortisone as an intervention for dexamethasone-induced adverse effects in pediatric patients with acute lymphoblastic leukemia: Results of a double-blind, randomized controlled trial. J Clin Oncol 2016;34:2287-2293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27161966.

408. van Hulst AM, van den Akker ELT, Verwaaijen EJ, et al. Hydrocortisone to reduce dexamethasone-induced neurobehavioral side-effects in children with acute lymphoblastic leukaemia-results of a double-blind, randomised controlled trial with cross-over design. Eur J Cancer 2023;187:124-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37149961.

409. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. Blood 2011;117:2340-2347; quiz 2556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21148812.

410. Patel B, Richards SM, Rowe JM, et al. High incidence of avascular necrosis in adolescents with acute lymphoblastic leukaemia: a UKALL XII analysis. Leukemia 2008;22:308-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17989709.

411. Mattano LA, Jr., Devidas M, Nachman JB, et al. Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncol 2012;13:906-915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22901620.

412. Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 2000;18:3262-3272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10986059.

413. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. J Clin Oncol 2011;29:4143-4150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21947829.

414. Vora A. Management of osteonecrosis in children and young adults with acute lymphoblastic leukaemia. Br J Haematol 2011;155:549-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22077340.

415. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol 2013;31:1202-1210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23358966.

416. Kaste SC, Qi A, Smith K, et al. Calcium and cholecalciferol supplementation provides no added benefit to nutritional counseling to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer 2014;61:885-893. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24395288.

417. Leblicq C, Laverdiere C, Decarie JC, et al. Effectiveness of pamidronate as treatment of symptomatic osteonecrosis occurring in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer 2013;60:741-747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23002054.

418. Mostoufi-Moab S, Halton J. Bone morbidity in childhood leukemia: epidemiology, mechanisms, diagnosis, and treatment. Curr Osteoporos Rep 2014;12:300-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24986711.

419. Mattano LA, Jr., Devidas M, Loh ML, et al. Development of osteonecrosis and improved survival in B-ALL: results of Children's Oncology Group Trial AALL0232. Leukemia 2024;38:258-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38062123.

420. Mora E, Smith EM, Donohoe C, Hertz DL. Vincristine-induced peripheral neuropathy in pediatric cancer patients. Am J Cancer Res 2016;6:2416-2430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27904761.

421. McAtee CL, Schneller N, Brackett J, et al. Treatment-related sinusoidal obstruction syndrome in children with de novo acute lymphoblastic leukemia during intensification. Cancer Chemother

Pharmacol 2017;80:1261-1264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29051993.

422. Stanulla M, Schaeffeler E, Moricke A, et al. Hepatic sinusoidal obstruction syndrome and short-term application of 6-thioguanine in pediatric acute lymphoblastic leukemia. Leukemia 2021;35:2650-2657. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33714975.

423. Kernan NA, Richardson PG, Smith AR, et al. Defibrotide for the treatment of hepatic veno-occlusive disease/sinusoidal obstruction syndrome following nontransplant-associated chemotherapy: Final results from a post hoc analysis of data from an expanded-access program. Pediatr Blood Cancer 2018;65:e27269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29873895.

424. Richardson P, Aggarwal S, Topaloglu O, et al. Systematic review of defibrotide studies in the treatment of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS). Bone Marrow Transplant 2019;54:1951-1962. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30804485.

425. Cohen G, Cooper S, Sison EA, et al. Allopurinol use during pediatric acute lymphoblastic leukemia maintenance therapy safely corrects skewed 6-mercaptopurine metabolism, improving inadequate myelosuppression and reducing gastrointestinal toxicity. Pediatr Blood Cancer 2020;67:e28360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32909665.

426. Brackett J, Schafer ES, Leung DH, Bernhardt MB. Use of allopurinol in children with acute lymphoblastic leukemia to reduce skewed thiopurine metabolism. Pediatr Blood Cancer 2014;61:1114-1117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24376133.

427. Miller MB, Brackett J, Schafer ES, Rau RE. Prevention of mercaptopurine-induced hypoglycemia using allopurinol to reduce methylated thiopurine metabolites. Pediatr Blood Cancer 2019;66:e27577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30548777.

428. Inaba H, Fan Y, Pounds S, et al. Clinical and biologic features and treatment outcome of children with newly diagnosed acute myeloid leukemia and hyperleukocytosis. Cancer 2008;113:522-529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18484648.

429. Porcu P, Cripe LD, Ng EW, et al. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. Leuk Lymphoma 2000;39:1-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10975379.

430. Sung L, Aplenc R, Alonzo TA, et al. Predictors and short-term outcomes of hyperleukocytosis in children with acute myeloid leukemia: a report from the Children's Oncology Group. Haematologica 2012;97:1770-1773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22801969.

431. Abla O, Angelini P, Di Giuseppe G, et al. Early complications of hyperleukocytosis and leukapheresis in childhood acute leukemias. J Pediatr Hematol Oncol 2016;38:111-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26794706.

432. Nguyen R, Jeha S, Zhou Y, et al. The role of leukapheresis in the current management of hyperleukocytosis in newly diagnosed childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2016;63:1546-1551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27187265.

433. Annett RD, Patel SK, Phipps S. Monitoring and assessment of neuropsychological outcomes as a standard of care in pediatric oncology. Pediatr Blood Cancer 2015;62 Suppl 5:S460-513. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26700917.

434. Jacola LM, Partanen M, Lemiere J, et al. Assessment and monitoring of neurocognitive function in pediatric cancer. J Clin Oncol 2021;39:1696-1704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33886364.

435. van der Plas E, Modi AJ, Li CK, et al. Cognitive impairment in survivors of pediatric acute lymphoblastic leukemia treated with

chemotherapy only. J Clin Oncol 2021;39:1705-1717. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33886368.

436. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood 2014;124:3932-3938. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25349177.

437. Brodeur GM, Nichols KE, Plon SE, et al. Pediatric cancer predisposition and surveillance: An overview, and a tribute to Alfred G. Knudson Jr. Clin Cancer Res 2017;23:e1-e5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28572261.

438. Kohlmann W, Schiffman JD. Discussing and managing hematologic germ line variants. Blood 2016;128:2497-2503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27881370.

439. Porter CC, Druley TE, Erez A, et al. Recommendations for surveillance for children with leukemia-predisposing conditions. Clin Cancer Res 2017;23:e14-e22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28572263.

440. Hijiya N, van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leuk Lymphoma 2016;57:748-757. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26457414.

441. Bleyer A, Asselin BL, Koontz SE, Hunger SP. Clinical application of asparaginase activity levels following treatment with pegaspargase. Pediatr Blood Cancer 2015;62:1102-1105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25393506.

442. Cooper SL, Young DJ, Bowen CJ, et al. Universal premedication and therapeutic drug monitoring for asparaginase-based therapy prevents infusion-associated acute adverse events and drug substitutions. Pediatr Blood Cancer 2019;66:e27797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31099154.

443. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma 2015;56:2273-2280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25586605.

444. Liu Y, Smith CA, Panetta JC, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. J Clin Oncol 2019;37:2051-2061. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31188727.

445. Burke MJ, Rheingold SR. Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. Leuk Lymphoma 2017;58:540-551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27546298.

446. Salzer W, Bostrom B, Messinger Y, et al. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. Leuk Lymphoma 2018;59:1797-1806. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29045165.

447. Wang B, Relling MV, Storm MC, et al. Evaluation of immunologic crossreaction of antiasparaginase antibodies in acute lymphoblastic leukemia (ALL) and lymphoma patients. Leukemia 2003;17:1583-1588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12886246.

448. Willer A, Gerss J, Konig T, et al. Anti-Escherichia coli asparaginase antibody levels determine the activity of second-line treatment with pegylated E coli asparaginase: a retrospective analysis within the ALL-BFM trials. Blood 2011;118:5774-5782. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21940824.

449. Zalewska-Szewczyk B, Gach A, Wyka K, et al. The cross-reactivity of anti-asparaginase antibodies against different L-asparaginase preparations. Clin Exp Med 2009;9:113-116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19184328.

450. Holmes JP, Peguero JA, Garland RC, et al. Intravenous cetirizine vs intravenous diphenhydramine for the prevention of hypersensitivity infusion reactions: Results of an exploratory phase 2 study. J Infus Nurs

2021;44:315-322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34555839.

451. Blaiss MS, Bernstein JA, Kessler A, et al. The role of cetirizine in the changing landscape of iv antihistamines: A narrative review. Adv Ther 2022;39:178-192. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34862952.

452. August KJ, Farooki S, Fulbright JM, et al. Desensitization to pegaspargase in children with acute lymphoblastic leukemia and lymphoblastic lymphoma. Pediatr Blood Cancer 2020;67:e28021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31571395.

453. Verma A, Chen K, Bender C, et al. PEGylated E. coli asparaginase desensitization: an effective and feasible option for pediatric patients with acute lymphoblastic leukemia who have developed hypersensitivity to pegaspargase in the absence of asparaginase Erwinia chrysanthemi availability. Pediatr Hematol Oncol 2019;36:277-286. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31296092.

454. Kearney SL, Dahlberg SE, Levy DE, et al. Clinical course and outcome in children with acute lymphoblastic leukemia and asparaginase-associated pancreatitis. Pediatr Blood Cancer 2009;53:162-167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19405141.

455. Wolthers BO, Frandsen TL, Baruchel A, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study. Lancet Oncol 2017;18:1238-1248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28736188.

456. Welch JJG, Flamand Y, Stevenson KE, et al. Impairment of health-related quality of life for children with acute lymphoblastic leukemia over the first year of therapy: A report from the DFCI ALL Consortium. Pediatr Blood Cancer 2023;70:e30560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37461125.

457. O'Brien SH, Rodriguez V, Lew G, et al. Apixaban versus no anticoagulation for the prevention of venous thromboembolism in children with newly diagnosed acute lymphoblastic leukaemia or lymphoma (PREVAPIX-ALL): a phase 3, open-label, randomised, controlled trial. Lancet Haematol 2024;11:e27-e37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37980924.