National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Acute Lymphoblastic Leukemia

Version 2.2023 — March 10, 2023

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NCCN Guidelines Version 2.2023
Pediatric Acute Lymphoblastic Leukemia

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***Hiroto Inaba, MD, PhD/ Chair € ‡**
St. Jude Children's Research Hospital/
The University of Tennessee
Health Science Center

***David Teachey, MD/ Vice-Chair € ‡**
Abramson Cancer Center
at the University of Pennsylvania -
Children's Hospital of Philadelphia

Colleen Annesley, MD €
Fred Hutchinson Cancer Center

Sandeep Batra, MD €
Indiana University
Melvin and Bren Simon
Comprehensive Cancer Center

Jill Beck, MD €
Fred & Pamela Buffett Cancer Center

Jong Chung, MD €
UC Davis Comprehensive Cancer Center

Susan Colace, MD, MSCI €
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Stacy Cooper, MD ‡
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Kevin Curran, MD ξ
Memorial Sloan Kettering Cancer Center

Mari Dallas, MD ‡ €
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Satiro De Oliveira, MD €
UCLA Jonsson Comprehensive Cancer Center

Kara Kelly, MD €
Roswell Park Comprehensive Cancer Center

Carrie Kitko, MD ξ €
Vanderbilt-Ingram Cancer Center

Mira Kohorst, MD €
Mayo Clinic Cancer Center

Norman Lacayo, MD €
Stanford Cancer Institute

Cathy Lee-Miller, MD €
University of Wisconsin
Carbone Cancer Center

Kathleen Ludwig, MD €
UT Southwestern Simmons
Comprehensive Cancer Center

Luke Maese, DO €
Huntsman Cancer Institute
at the University of Utah

Kris Mahadeo, MD, MPH ξ €
The University of Texas
MD Anderson Cancer Center

Kelly Maloney, MD €
University of Colorado Cancer Center

Valentina Nardi, MD ≠
Massachusetts General Hospital Cancer Center

Jenna Rossoff, MD ‡ €
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University
Ann & Robert H. Lurie Children's
Hospital of Chicago

Laura Schuettpelz, MD, PhD €
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Bijal Shah, MD €
Moffitt Cancer Center

Shilpa Shahani, MD €
City of Hope National Medical Center

Lewis Silverman, MD €
Dana-Farber/Brigham and Women's
Cancer Center

Jessica Sun, MD ‡ €
Duke Cancer Institute

Aman Wadhwa, MD €
O'Neal Comprehensive Cancer Center at UAB

Victor Wong, MD €
UC San Diego Moores Cancer Center -
Rady Children's Hospital of San Diego

Gregory Yanik, MD €
University of Michigan Rogel Cancer Center

NCCN
Deborah Freedman-Cass, PhD
Megan Lyons, MS
Katie Stehman, PA-C

ξ Bone marrow transplantation
‡ Hematology/Hematology oncology
≠ Pathology
€ Pediatric oncology
* Discussion Section Writing Committee

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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 2.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2023 include:

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

Updates in Version 1.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2022 include:

PEDALL-1A
- Footnote b modified: ~~Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities includes hypodiploidy, hyperdiploidy, and commonly occurring translocations: t(9;22)(q34.1;q11.2)[BCR-ABL1]; t(v;11q23.3)[KMT2A rearranged]; t(12;21)(p13.2;q22.1)[ETV6-RUNX1]; 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);(moved below) t(1;19)(q23;p13.3)[TCF3-PBX1]; t(5;14)(q31.1;q32.3)[IL3-IGH]; B-cell lymphoblastic leukemia/lymphoma, not otherwise specified; B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like; B-lymphoblastic leukemia/lymphoma with iAMP21; and early T-cell precursor (ETP) lymphoblastic leukemia. Additional FISH probes that may be useful include: centromeric probes for chromosomes 4, 10, and 17 to detect hyperdiploidy; CDKN2A at 9p21.3 to detect deletions; probes to detect cryptic t(X;14)(p22;q32)/t(Y;14)(p11;q32) IGH-CRLF2 rearrangements; 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 ABL1, ABL2, and PDGFRB rearrangements; probes to detect BCR::ABL1 and KMT2Ar rearrangements in patients with high-risk disease; and probes to detect cryptic JAK2 and FGFR1 rearrangements.~~ *B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) subtypes include those not otherwise specified (NOS), with high hyperdiploidy, hypodiploidy, and 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]; and t(17;19)(q22;p13.3)[TCF3::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.*
- Footnote c added: T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) subtypes include T-ALL/T-LBL, NOS and early T-cell precursor (ETP) lymphoblastic leukemia/lymphoma.
- Footnote d added: 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 *KMT2Ar* 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.
- Footnote j modified: The following immunophenotypic findings are particularly notable: CD10 negativity correlates with KMT2A rearrangement (KMT2Ar); ETP T-ALL (typically lacking expression of CD5, CD8, and CD1a and 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 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.

PEDALL-4
- Footnote bb added: To confirm adherence to oral chemotherapy during maintenance therapy, clinicians can take a detailed history, perform pill counts, and/or measure metabolites. (Also on PEDALL-5)

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2022 include:

PEDALL-6

- Footnote ee added: The panel believes it is reasonable to consider the addition of bortezomib to Berlin-Frankfurt-Münster (BFM) backbone chemotherapy in patients with pediatric T-LBL, because it was shown to improve event-free survival (EFS)/overall survival (OS) in T-LBL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).

PEDALL-8

- Monitoring for late effects, 1st bullet modified: Echocardiogram ~~as clinically indicated (related to cumulative anthracycline dose)~~ *(frequency based on cumulative anthracycline dose or sooner, as clinically indicated).*

PEDALL-A 1 of 2

- Risk groups
  - Favorable-risk features, Genetics:
    - ◊ 1st bullet, 1st sub-bullet modified: *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
    - ◊ 3rd bullet added: *DUX4r*
    - ◊ 4th bullet added: *NUTM1r*
  - Risk group added: Intermediate-risk features
    - ◊ Genetics, bullet added: *MEF2Dr, ZNF384r, PAX5alt, PAX5 P80R, ETV6::RUNX1*-like

PEDALL-A 2 of 2

- Footnote b added: 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.
- 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 mutations and Li-Fraumeni syndrome.
- Footnote d modified: There are other results that are not less than 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.
- Footnote f added: *IKZF1* deletions with deletions in *CDKN2A, CDKN2B, 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. *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. 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 1.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2022 include:

- Footnote removed: Emerging evidence suggests new subtypes: DUX4r, NUTM1r, ZNF384r, MEF2Dr, PAX5alt, PAX5 P80R, and ETV6/RUNX1-like. DUX4r and NUTM1r are associated with favorable outcomes. KZF1 deletions with deletions in CDKN2A, CDKN2B, 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 worse outcomes. However, in cases of DUX4r, IKZF1 alterations do not confer poor prognosis. ZNF384r, MEF2Dr, PAX5alt, PAX5 P80R, and ETV6/RUNX1-like are considered intermediate risk. Further confirmatory studies are necessary. 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, et al. Association of Combined Focal 22q11.22 Deletion and IKZF1 Alterations With Outcomes in Childhood Acute Lymphoblastic Leukemia. JAMA Oncol. 2021 1;7(10):1521-1528.
- Footnote removed: Emerging evidence suggests DUX4r ALL is favorable. Additionally in cases of DUX4r, IKZF1 alterations do not confer poor prognosis.

PEDALL-B 2 of 10

- The following bullets and sub-bullets have been added to the right column:
  - Patients should be vaccinated for varicella, measles, mumps, and rubella three 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. It may be appropriate to refer to Infectious Disease or Immunology for guidance regarding specific vaccinations for each individual patient. For general information regarding COVID-19 vaccinations in patients with cancer and for management of concurrent COVID-19 and cancer, see:
    - ◊ https://www.nccn.org/covid-19
    - ◊ 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 SARSCoV-2, see:
    - ◊ https://www.hematology.org/covid-19/covid-19-and-pediatric-all

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- Acute Tumor Lysis Syndrome
  - 5th bullet modified: Consider prophylactic rasburicase in patients with high white blood cell (WBC) count *(eg, >100 x10^9/L) or LDH (eg, >2 x ULN)* prior to starting therapy even if uric acid <8 mg/dL.

PEDALL-B 4 of 10

- Methotrexate (MTX) Toxicity Management
  - Bullet removed: Consider use of glucarpidase in patients with significant renal dysfunction and toxic plasma MTX concentrations with delayed MTX clearance (plasma MTX concentrations >2 standard deviations of the mean MTX excretion curve specific for the dose of MTX administered). Leucovorin remains a component in the treatment of MTX toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within 2 hours prior to or following glucarpidase.

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2022 include:

- 2nd bullet added: 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 on preglucarpidase 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 two 2 hours prior to or following glucarpidase.
- 3rd bullet added: 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.

PEDALL-B 5 of 10

• Steroid Management, Bone fractures:
- 1st sub-bullet modified: *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.

PEDALL-B 7 of 10

• Asparaginase Toxicity Management
- 2nd bullet modified: There are ~~four~~ *three* formulations of asparaginase in clinical use: 1) pegaspargase, 2) calaspargase, ~~3) asparaginase Erwinia chrysanthemi (ERW)~~, and ~~4)~~ *3)* asparaginase Erwinia chrysanthemi (recombinant)- rywn (ERW-rywn).
- 5th bullet added: For pegaspargase and calaspargase, dose capping at 3,750 units/dose (1 vial) can be considered in cases of baseline obesity.
- 6th bullet added: For ERW-rywn, a phase 2/3 study supports a new IM dosing schedule of 25 mg/m^2 Monday/Wednesday, 50 mg/m^2 Friday based on positive risk:benefit ratio.

PEDALL-B 8 of 10

• Hypersensitivity, Allergy, Anaphylaxis
- 1st bullet modified: 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 or~~ ERW-rywn is indicated for patients with hypersensitivity to E. coli asparaginase products.
- 4th bullet modified: 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 with ~~ERW or~~ ERW-rywn.

• Non-CNS Thromboembolism
- 3rd bullet added: Line-associated thromboses are also fairly common in treatment. Anticoagulation therapy can be safely administered during treatment.

PEDALL-B 9 of 10

• Hepatotoxicity (elevation in bilirubin, AST, ALT)
- Bullet modified: If elevated bilirubin and/or transaminitis *per protocol-specific criteria*, consider holding asparaginase until improvement, then resume with very close monitoring.

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2022 include:

PEDALL-B 10 of 10
- References added:
  - 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.
  - 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. 2022; Online ahead of print.
  - 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.
  - 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.

PEDALL-C
- Evaluation and treatment of extramedullary involvement
  - 3rd bullet, 3rd sub-bullet modified: 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/red blood cell (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.
  - 10th bullet, 1st sub-bullet added: See COG Long-Term Follow-up Guidelines: http://www.survivorshipguidelines.org/

PEDALL-D
- Down syndrome considerations
  - 2nd bullet added: An intermediate dose of MTX (eg, 500 mg/m2) can be used instead of high-dose MTX.

PEDALL-E 3 of 3
- Footnote c modified: Adverse genetic risk features include BCR::ABL1 fusion/t(9;22); TCF3::PBX1 fusion/t(1;19); ~~rearranged *MLL*~~ *KMT2Ar*; hypodiploidy; intrachromosomal amplification of chromosome 21 (iAMP21); or MEF2D fusion.

PEDALL-F 2 of 12
- Regimens for Infant ALL
  - Modified: Interfant regimens ± *blinatumomab*

PEDALL-F 3 of 12
- Footnote h modified: For patients who develop hypersensitivity to E. coli-derived asparaginase, ~~ERW or~~ ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course. (Also on PEDALL-F 4 of 12, PEDALL-F 5 of 12, and PEDALL-F 6 of 12)

PEDALL-F 4 of 12
- Ph-Like B-ALL
  - Total therapy XVII regimen + dasatinib or Total therapy XVII regimen ± ruxolitinib, induction:
    - ◊ 2nd bullet modified: For mutations associated with JAK-STAT pathway activation: Total Therapy XVII regimen ~~+~~ ± ruxolitinib

Continued

Updates in Version 1.2023 of the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia from Version 1.2022 include:

- **PEDALL-F 7 of 12**
- Ph-negative ALL
  - Other recommended regimens, 7th bullet modified: Inotuzumab ozogamicin *± mini-hyper-CVD*

PEDALL-F 10 of 12
- Tisagenlecleucel
  - 10th bullet added: Next-generation sequencing (NGS) can be used for MRD monitoring.

PEDALL-F 11 of 12
- Reference added: 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.

PEDALL-F 12 of 12
- Reference added: 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.

PEDALL-G 1 of 3
- Footnote b added: The recommendations for dose reductions may differ based on the treatment regimen. (Also on PEDALL-G 2 of 3)

PEDALL-I 1 of 2
- Minimal Residual Disease
  - 9th bullet added: Infants with high MRD after the EOI may benefit from AML-like consolidation.

PEDALL-I 2 of 2
- Reference added: 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 Feb;39:652-662.

PEDALL-J 2 of 5
- B-ALL first relapse, Medullary (isolated or combined), ≥36 months from initial diagnosis, subsequent therapy, modified:
  - If MRD ≥~~0.01~~ *0.1%* within 4–8 weeks of re-induction, or any subsequent relapse
- Footnote e added: The recommendations may differ based on the treatment regimen.

PEDALL-J 3 of 5
- Impact of Pre-HCT MRD Status
  - 2nd bullet added: The absence of detectable MRD by NGS before and after HCT may be associated with favorable outcomes.

PEDALL-J 5 of 5
- Reference added: 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.

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,i] upon hematopathology review of bone marrow aspirate and biopsy materials, 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[j]**
- **Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal residual disease (MRD) analysis[k] (see PEDALL-I)**

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 *BCR::ABL1* in 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[l]**

Additional optional tests include:

- **Additional assessment (eg, microarray comparative genomic hybridization [CGH]) in cases of aneuploidy or failed karyotype**
- **Assessment of various potentially actionable or prognostic mutations (see Genetic Risk Groups [PEDALL-A])**

CLASSIFICATION

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

→ **See Workup (PEDALL-2)**

See Footnotes on PEDALL-1A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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-lymphoblastic leukemia/lymphoma (B-ALL/LBL) 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*]; and t(17;19)(q22;p13.3)[*TCF3*::*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.

[c] T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) subtypes include T-ALL/T-LBL, 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 2016 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.

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

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

[h] If there are sufficient numbers of circulating lymphoblasts (at least 1,000 per microliter as a general guideline) and clinical situation precludes bone marrow aspirate and biopsy, then peripheral blood can be substituted for bone marrow.

[i] 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 failure to treat a patient when there are <20% marrow lymphoblasts has an adverse effect on outcome. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017.

[j] The following immunophenotypic findings are particularly notable: CD10 negativity correlates with *KMT2A* rearrangement (*KMT2A*r); ETP T-ALL (typically lacking expression of CD5, CD8, and CD1a and 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* 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.

[k] By either flow cytometric analysis or by identification of clonal immunoglobulin or T-cell receptor gene rearrangements.

[l] 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), next-generation sequencing (NGS)-based assays, 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.

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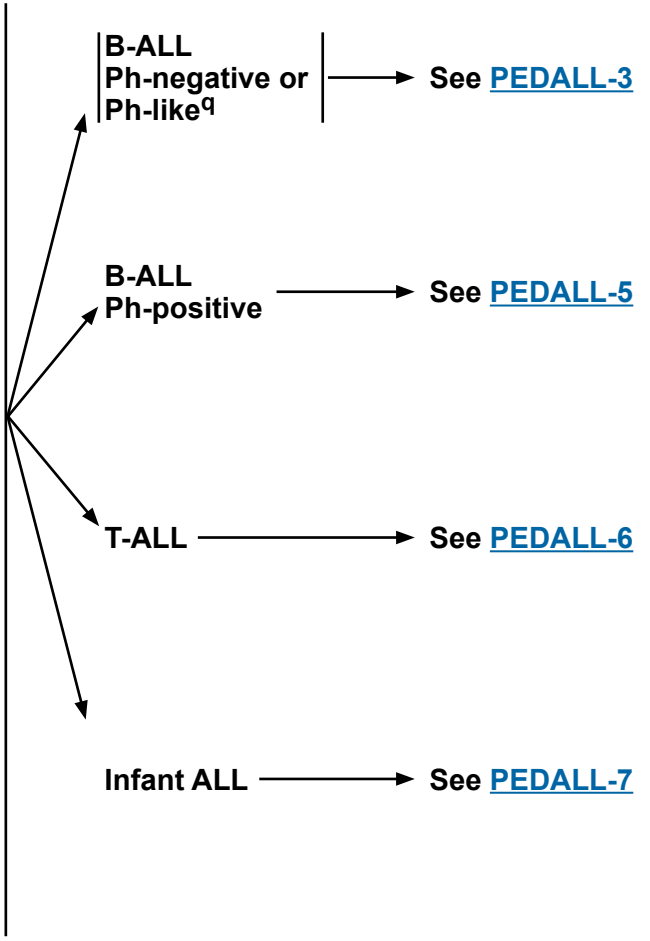
WORKUP[m]

- 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, K, Ca, Phos (See Tumor Lysis Syndrome in Principles of Supportive Care [PEDALL-B])
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Pregnancy testing, fertility counseling, and preservation as indicated
- CT/MRI of head with contrast, if neurologic symptoms
- Chest x-ray to rule out mediastinal mass
- Whole body PET/CT if lymphoblastic lymphoma suspected
- Lumbar puncture (LP)[n,o] with IT chemotherapy
  - See Evaluation and Treatment of Extramedullary Involvement (PEDALL-C)
- 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* (see Pharmacogenomics [PEDALL-G])
- 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 hypodiploid ALL where germline *TP53* mutations are common and testing should be considered.
  - Other germline mutations associated with ALL risk have been reported.[p] A complete family history can help identify risk for a cancer predisposition syndrome, although de novo mutations have been reported.
  - 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, and Pancreatic)



[m] The following list represents minimal recommendations; other testing may be warranted according to clinical symptoms and discretion of the clinician.

[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-C).

[o] Timing of LP should be consistent with the chosen treatment regimen. Pediatric-inspired regimens typically include LP and prophylactic intrathecal (IT) chemotherapy at the time of diagnostic workup. The panel recommends that LP be done concurrently with initial IT therapy.

[p] Germline mutations in genes often somatically mutated in ALL, particularly *PAX5, ETV6, IKZF1,* and *SH2B3,* have been shown to confer predisposition to developing B-ALL. Pui CH, et al. Nat Rev Clin Oncol 2019;16:227-240.

[q] Ph-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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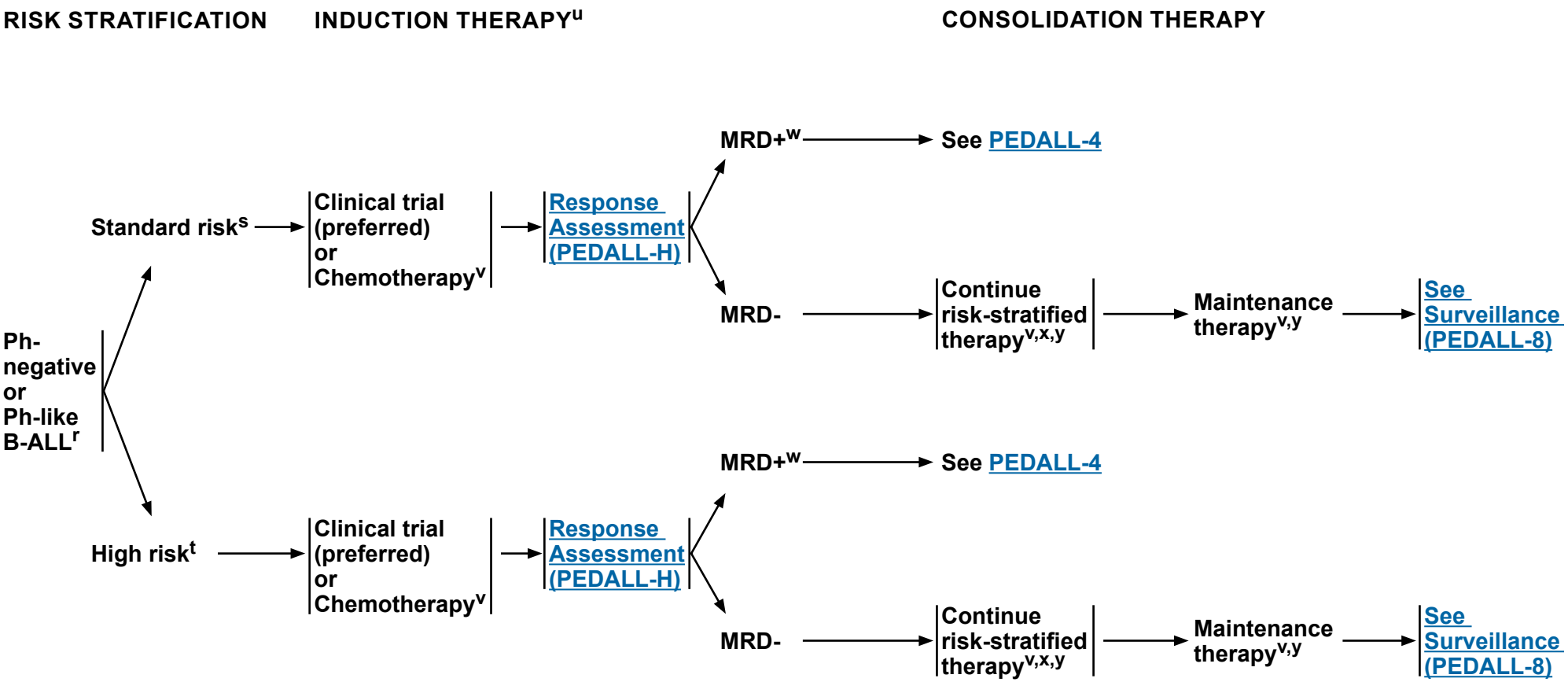

[r] For patients with Down syndrome, see Special Considerations for Vulnerable Populations (PEDALL-D).
[s] Standard risk criteria are consistent with NCI: WBC count <50,000/mm^3, ≥1 y to <10 y. For further details, see the Risk Stratification Definitions (PEDALL-E).
[t] High-risk criteria are consistent with NCI: White blood cell (WBC) count ≥50,000/mm^3, <1 y or ≥10 y. For further details, see the Risk Stratification Definitions (PEDALL-E).
[u] See Principles of Supportive Care (PEDALL-B).
[v] See Principles of Systemic Therapy (PEDALL-F).
[w] 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-I).
[x] See Risk Stratification Definitions for Post-Induction Therapy (PEDALL-E, 2 of 3).
[y] For Ph-like patients, tyrosine kinase inhibitors (TKIs) may be considered. For more information, see Principles of Systemic Therapy (PEDALL-F).

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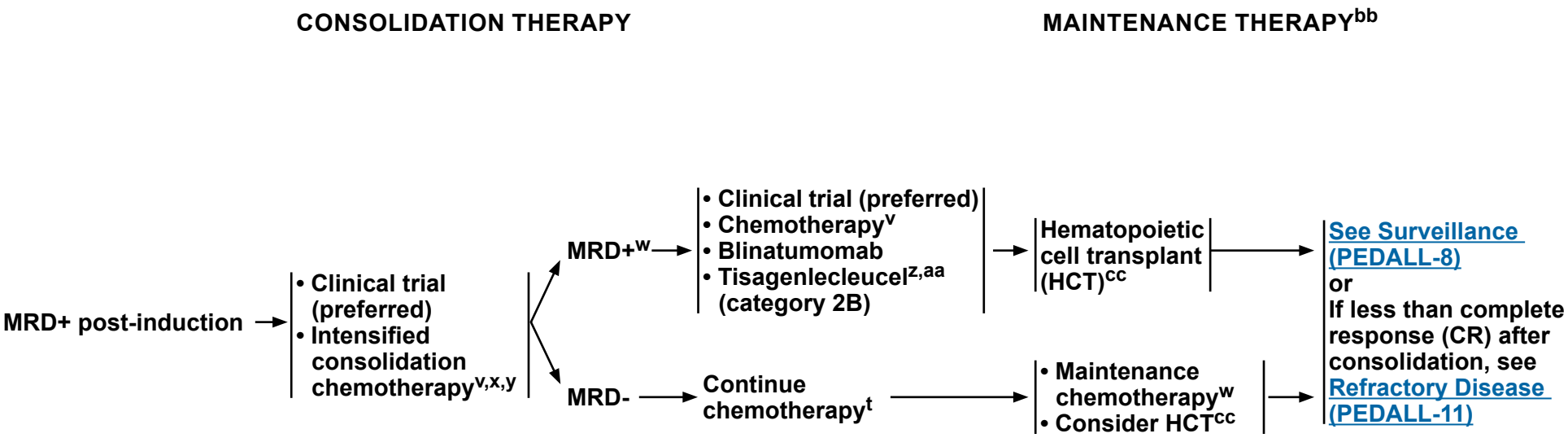

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[z] The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. See Tisagenlecleucel section in the Principles of Systemic Therapy (PEDALL-F [10 of 12]).
[aa] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent HCT. In the global registration trial, relapse-free survival was 59% at 12 months, with only 9% of patients proceeding to HCT (Maude SL, et al. N Engl J Med 2018;378:439-448). See Principles of Hematopoietic Cell Transplant (PEDALL-J).
[bb] To confirm adherence to oral chemotherapy during maintenance therapy, clinicians can take a detailed history, perform pill counts, and/or measure metabolites.
[cc] See Principles of Hematopoietic Cell Transplant (PEDALL-J).

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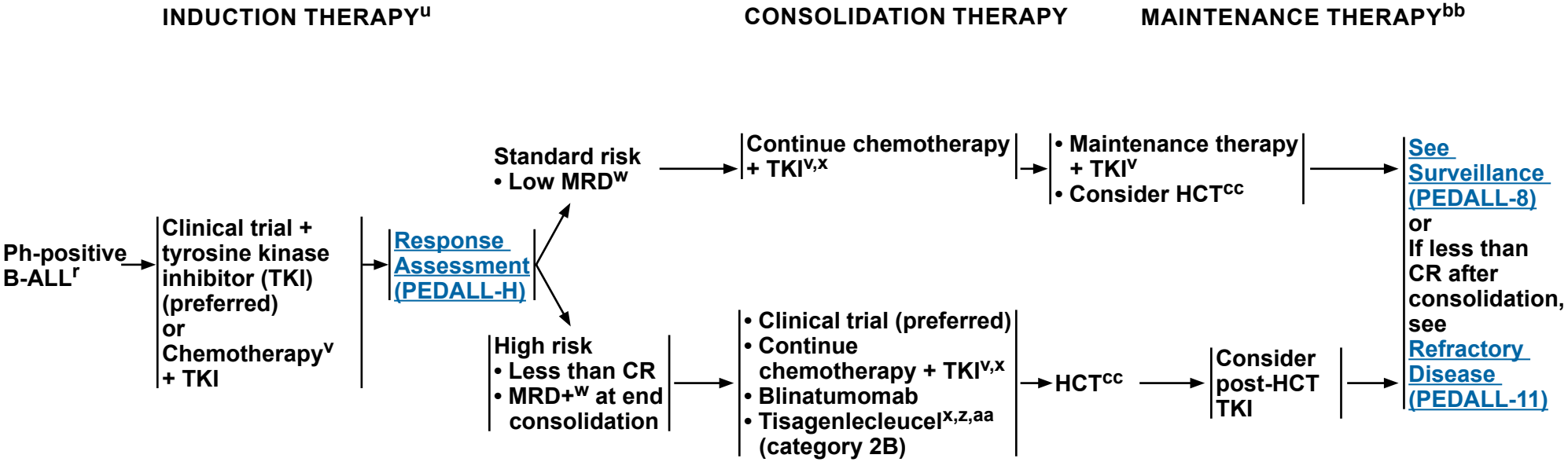

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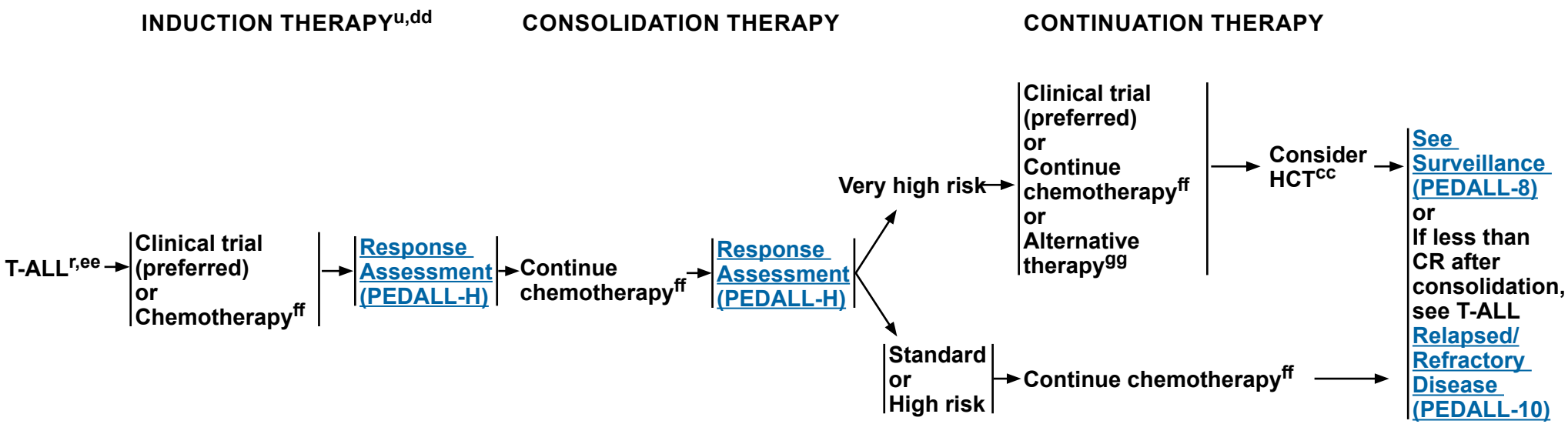

T-ALL Post-Induction Risk Group Definitions:

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

[r] For patients with Down syndrome, see Special Considerations for Vulnerable Populations (PEDALL-D).
[u] See Principles of Supportive Care (PEDALL-B).
[w] 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-I).
[cc] See Principles of Hematopoietic Cell Transplant (PEDALL-J).
[dd] 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-I).
[ee] The panel believes it is reasonable to consider the addition of bortezomib to Berlin-Frankfurt-Münster (BFM) backbone chemotherapy in patients with pediatric T-LBL, because it was shown to improve event-free survival (EFS)/overall survival (OS) in T-LBL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[ff] See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-F, 2 of 12).
[gg] See regimens for T-ALL on Principles of Systemic Therapy (PEDALL-F, 9 of 12).
[hh] The specific definition of steroid pretreatment differs by protocol. Refer to regimen-specific definition of steroid pretreatment.

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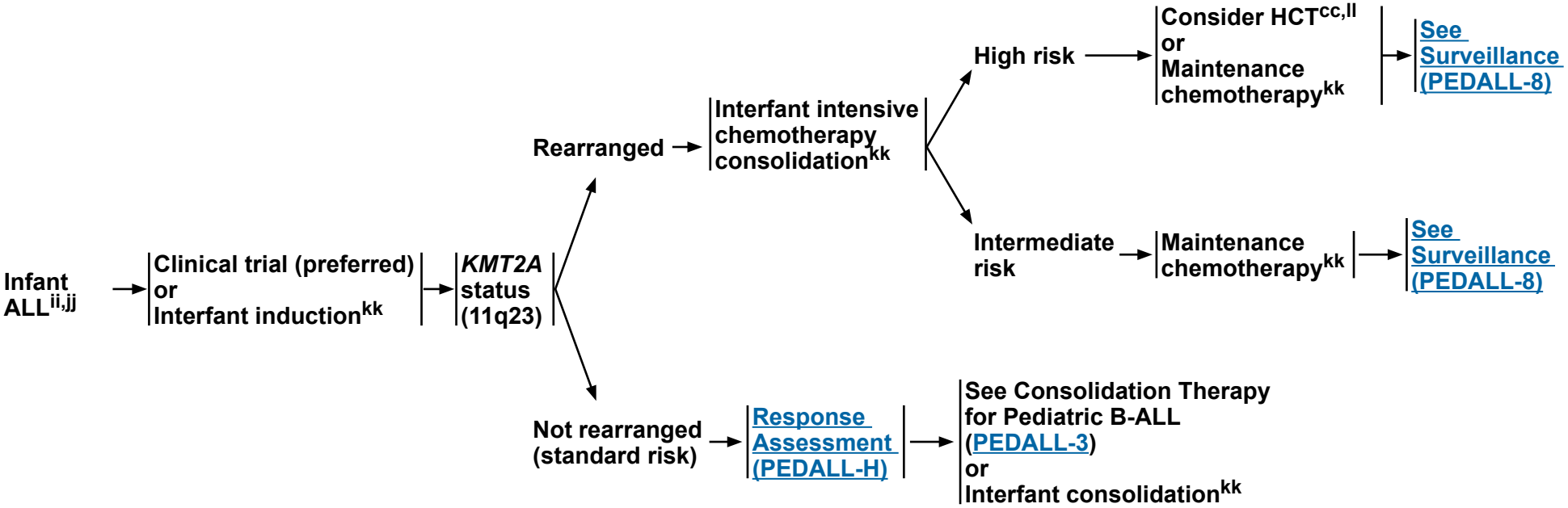

Infant Risk Group Definitions:

Risk Group	Features[w]
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

[u] See Principles of Supportive Care (PEDALL-B).
[w] 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-I).
[cc] See Principles of Hematopoietic Cell Transplant (PEDALL-J).
[ii] See Special Considerations for Vulnerable Populations (PEDALL-D).
[jj] Reproduced with permission: Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood 2019;133:205-214.
[kk] See Principles of Systemic Therapy for Infant ALL (PEDALL-F, 2 of 12).
[ll] If donor available, prefer non-total body irradiation (TBI)-based prep regimen and age ≥6 mo at time of HCT.

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SURVEILLANCE[mm]

- **Year 1 (every 1–2 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 (Ph+ ALL)**
- **See Response Assessment (PEDALL-H) 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 Survivorship recommendations in the NCCN Guidelines for Survivorship.**
- **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)

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

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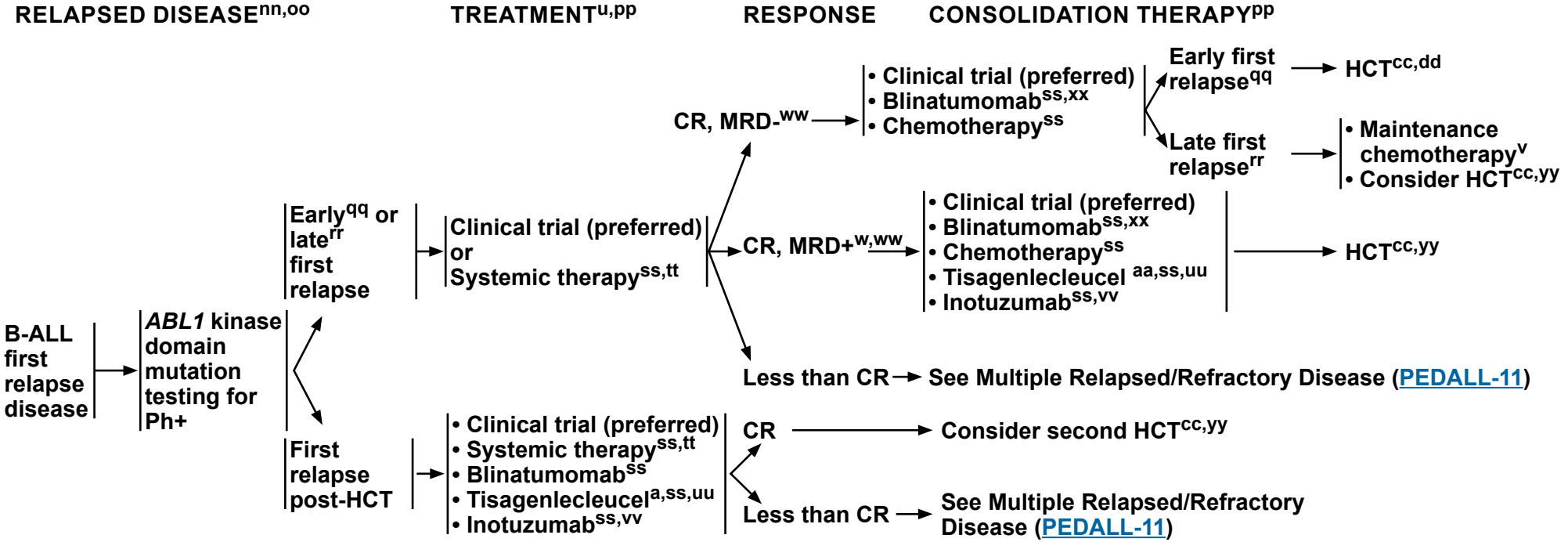

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[nn] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.
[oo] See NCCN Guidelines for Palliative Care.
[pp] For Ph+ALL add TKI to the treatment; see Regimens for Relapsed/Refractory Ph-positive ALL (PEDALL-F, 8 of 12).
[qq] 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.
[rr] 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.
[ss] See Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-F, 7 of 12).
[tt] If patients relapse >3 months from initial diagnosis, consider treatment with the same induction regimen; see Principles of Systemic Therapy (PEDALL-F).
[uu] See Tisagenlecleucel in the Principles of Systemic Therapy (PEDALL-F, 10 of 12).
[vv] Inotuzumab ozogamicin is not FDA approved for children and is associated with hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease (VOD), and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.
[ww] See Minimal Residual Disease (PEDALL-I).
[xx] This recommendation for blinatumomab pertains only to patients with early first relapse (Locatelli F, et al. JAMA 2021;325:843-854; Brown PA, et al. JAMA 2021;325:833-842).
[yy] 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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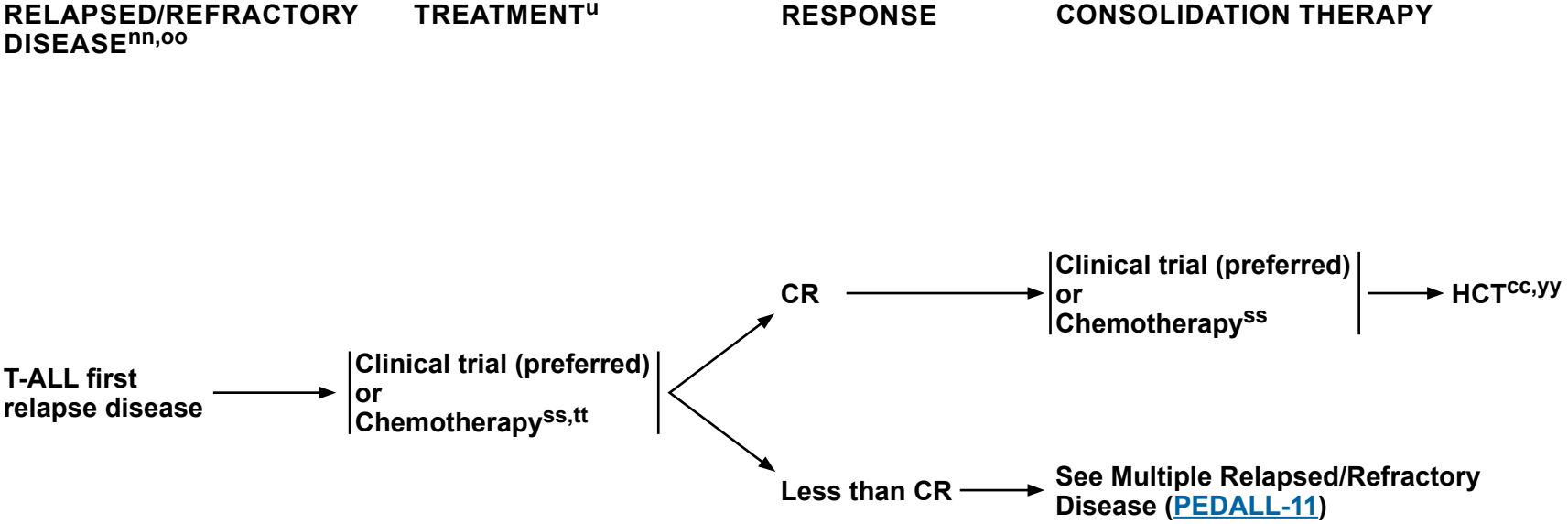

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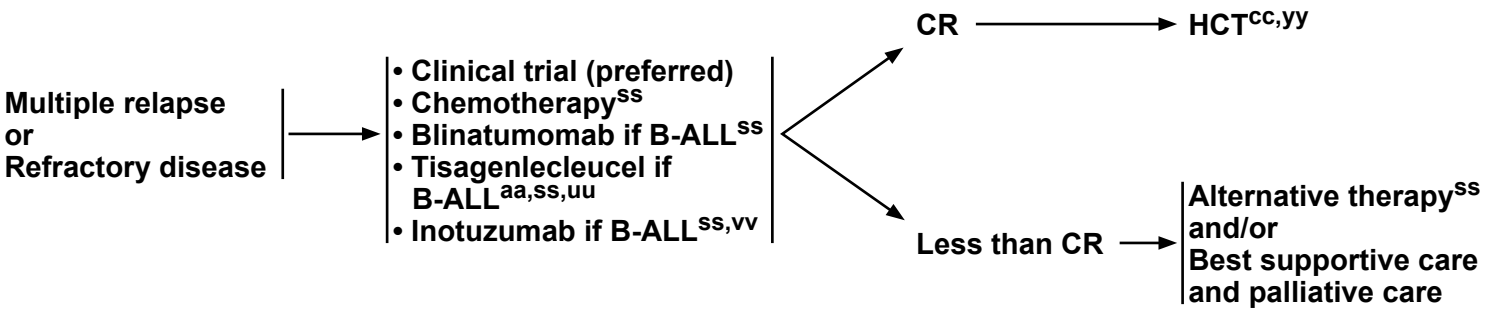
MULTIPLE RELAPSE/REFRACTORY DISEASE[nn,oo]



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[vv] Inotuzumab ozogamicin is not FDA approved for children and is associated with hepatotoxicity, including fatal and life-threatening hepatic VOD, and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.

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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
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 (Ph-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* fusion • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1*[f]	

See footnotes on PEDALL-A 2 of 2

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FOOTNOTES

[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 mutations and Li-Fraumeni syndrome.

[d] There are other results that are not less than 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, 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.

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PRINCIPLES OF SUPPORTIVE CARE

Infection Control

- Prior to the start of induction chemotherapy for newly diagnosed patients, viral serologies (ie, HSV IgG, CMV IgG, 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 high-risk populations (infants and trisomy 21, see Special Considerations for Vulnerable Populations [PEDALL-D]), 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 re-started 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.[4-6] Consider micafungin or other echinocandin antifungal drugs during induction and potentially during other high-intensity phases. Prophylaxis with liposomal amphotericin is also allowed.
- 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][7] or institutional standards) should be evaluated by a medical provider and treated immediately with broad-spectrum antibiotics, regardless of absolute neutrophil count.
  - 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.
  - Antibiotics should be administered as soon as possible and within one hour of presentation with fever, neutropenia, or sepsis. Recommend stress dose steroids for patients with sepsis.
  - Both aerobic and anaerobic blood cultures of appropriate volume (based on child's age and weight) should be collected simultaneously from each lumen of an existing central venous catheter.
  - 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 respiratory tract infections.

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- Fever and neutropenia (continued)
  - 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 bacteria [AFB]) or viral PCR tests (eg, enterovirus, herpes simplex virus [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, 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 an anti-pseudomonal agent 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, obtain one set of repeat blood cultures and 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.
  - Filgrastim (granulocyte colony-stimulating factor [G-CSF]), pegfilgrastim, 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 serious/life-threatening infection in the context of neutropenia.
  - Additional diagnostic investigation, such as radiographic evaluation of lungs and sinuses, 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.
- 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.[8]
  - It may be appropriate to refer to Infectious Disease or Immunology for guidance regarding specific vaccinations for each individual patient.
- For general information regarding COVID-19 vaccinations in patients with cancer and for management of concurrent COVID-19 and cancer, see:
  - https://www.nccn.org/covid-19
  - 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 SARS-CoV-2, see:
  - https://www.hematology.org/covid-19/covid-19-and-pediatric-all

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Acute Tumor Lysis Syndrome (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, K, Ca, Phos, 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.
  - Start allopurinol on admission if uric acid <8 mg/dL and no evidence of renal dysfunction – oral is preferred route if tolerated.
- If uric acid >8 mg/dL and/or patient has renal dysfunction or LDH >2 x upper limit of normal (ULN), rasburicase is strongly recommended if available. Use of rasburicase in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency may be associated with methemoglobinemia or hemolysis.
- Consider prophylactic rasburicase in patients with high white blood cell (WBC) count (eg, >100 x10^9/L) or LDH (eg, >2 x ULN) prior to starting therapy even if uric acid <8 mg/dL.
- 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: treat 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: 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 per square deciliter.
- 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.

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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 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.[9]
- 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.
- MTX neurotoxicity
  - Can occur following high-dose or IT MTX, more frequently in children >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 Biotene mouthwash (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 infection with viral (HSV) or fungal (Candida), pain management with topical anesthetics, and use of oral or IV analgesics.

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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[10]).
  - 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 hydrocortisone (10 mg/m^2/day) with dexamethasone.[11]
    - 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, or PPIs. Histamine-2 antagonists (eg, famotidine) may be used, although they may contribute to myelosuppression.
    - 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 greater than 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. Avoid calcium channel blockers if possible due to increased risk of hemorrhage. Typically occurs in setting of hypertension in first months of treatment.
    - 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.
- 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.

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PRINCIPLES OF SUPPORTIVE CARE

Vincristine Management

- Consider starting a bowel regimen to avoid constipation if receiving vincristine. If bowel regimen 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.

Thiopurines Management - See Pharmacogenomics (PEDALL-G)

- Veno-occlusive disease (VOD) of the liver (sinusoidal obstruction syndrome) 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 VOD 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 VOD, which presents with disproportionate thrombocytopenia and evidence of chronic portal hypertension.

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.[16,17]
  - In cases where leukapheresis is indicated for symptomatic leukostasis, leukapheresis should be discontinued once symptoms resolve and blast cell 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.

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PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management

Antiemetics (See 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 should be considered for all patients, given established risk for neurocognitive late effects associated with IT chemotherapy.
- 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, 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.

Asparaginase Toxicity Management
- 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]
- Pegaspargase is a common component of therapy for children, adolescents, and young adults with ALL. These agents can be given intramuscularly (IM) or IV; the IV route is increasingly being used. 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 and calaspargase, dose capping at 3,750 units/dose (1 vial) can be considered in cases of baseline obesity.
- For ERW-rywn, a phase 2/3 study supports a new IM dosing schedule of 25 mg/m^2 Monday/Wednesday, 50 mg/m^2 Friday based on positive risk:benefit ratio.[18]

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

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PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management

Hypersensitivity, Allergy, and Anaphylaxis[19-22]

- 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 is the standard formulation currently in use and is usually given intravenously. With IV pegaspargase, 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-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, infusing normal saline concurrently, and using anti-allergy premedication (such as hydrocortisone, diphenhydramine, and acetaminophen) can reduce the risk of these reactions.
- 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 less than one week, allowing 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.
- 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 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.[23,24]

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.[25,26]

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.

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PRINCIPLES OF SUPPORTIVE CARE
Asparaginase Toxicity Management

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.**

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References

PRINCIPLES OF SUPPORTIVE CARE
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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). 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 patient 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-cell ALL. It is recommended that a specific treatment protocol be followed in its entirety.
- TBI is given for select high-risk patients 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-J 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 NCCN Guidelines for Survivorship.
  - 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.

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SPECIAL CONSIDERATIONS FOR VULNERABLE POPULATIONS[1,2,3]

Patients with Down syndrome and B-ALL/LLy 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 vulnerable populations is recommended. During treatment of these vulnerable 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 less than 400 mg/dL.
- Aggressive management of 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 not responding 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.

Infant Considerations

- Respiratory syncytial virus (RSV) prophylaxis with palivizumab IM monthly should be considered before the onset of and continued through 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, and/or antiviral therapy based on clinical evaluation.

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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 (see PEDALL-5) • Steroid pre-treatment	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 standard risk (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 high-risk (HR)/very-high-risk (VHR) adverse biologic features	• T-ALL • iAMP21 • *BCR::ABL1* is considered HR feature (see 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-E (2 of 3) for Post-Induction Risk Stratification Definitions

[a] For T-cell ALL risk stratification, see PEDALL-6. For infant risk stratification, see PEDALL-7.
[b] See Evaluation and Treatment of Extramedullary Involvement (PEDALL-C) 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 Rapid Heme Panel (targeted fusion sequencing panel), "Initial Risk Group" is assigned.

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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%		• 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] • Any cytogenetics • EOI bone marrow MRD (positive or negative)

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

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

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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 low risk (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-cell ALL risk stratification, see PEDALL-6. For infant risk stratification, see PEDALL-7.
[b] See Evaluation and Treatment of Extramedullary Involvement (PEDALL-C) 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).

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PRINCIPLES OF SYSTEMATIC THERAPY[a,b]

Regimens for Ph-Negative B-ALL

Regimen Components and Risk Stratification Applications on PEDALL-F (3 of 12)

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

Regimens for Ph-Like B-ALL

Regimen Components and Risk Stratification Applications on PEDALL-F (4 of 12)

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

Regimens for Ph-Positive B-ALL

Regimen Components and Risk Stratification Applications on PEDALL-F (5 of 12)

Preferred	Other Recommended Regimens
• Clinical trial	• Standard arm of COG AALL1631[c] (based on COG AALL1122/EsPhALL regimen): imatinib or dasatinib[c]; combined with an HR 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[c]

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

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

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

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

Regimens for T-ALL[d,e,f]

Regimen Components and Risk Stratification Applications on PEDALL-F (6 of 12)

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

Regimens for Infant ALL

Regimen Components and Risk Stratification Applications on PEDALL-F (6 of 12)

Preferred	Other Recommended Regimens
• Clinical trial	• Interfant regimens ± blinatumomab[14-16,17]

[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-G) for recommended dosing alterations for 6-MP and 6-TG.
[c] Ongoing clinical trials from multi-institutional or cooperative group studies.
[d] 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 fail induction (not in CR after induction therapy).
[e] CNS-directed therapy with IT chemotherapy is recommended during all phases of therapy in all patients.
[f] Cranial radiation should be strongly considered for CNS-3 patients and is reasonable for other patients with high-risk T-ALL.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,g,h]

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

Ph-Negative ALL	Induction	Consolidation
COG AALL0932 regimen[1,18] (SR)	SR arm: dexamethasone, vincristine, pegaspargase; 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; IT therapy: MTX
COG AALL1131 regimen[2,3,4,19] (HR)	HR arm: prednisone or dexamethasone, vincristine, pegaspargase, daunorubicin; IT therapy: cytarabine then MTX	HR arm: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase; IT therapy: MTX
DFCI ALL Protocol 11-001 regimen[5,6]	Prednisone, vincristine, pegaspargase, doxorubicin, IT cytarabine, then IT triple therapy (ITT)[a]	SR arm: high-dose MTX, vincristine, pegaspargase, mercaptopurine,[b] dexamethasone; IT therapy: MTX or ITT[a]
		HR/VHR[i] arms: high-dose MTX, vincristine, pegaspargase, mercaptopurine,[b] dexamethasone, doxorubicin, dexrazoxane; IT therapy: MTX or ITT[a]
Total Therapy XVI regimen[20]	Prednisone, vincristine, daunorubicin, pegaspargase, cyclophosphamide, cytarabine, mercaptopurine (6-MP),[b] age-adjusted 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 (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-G) for recommended dosing alterations for 6-MP and 6-TG.
[g] 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.
[h] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.
[i] VHR arm also includes cyclophosphamide, cytarabine, and etoposide.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,g,h]

Ph-like B-ALL	Induction	Consolidation
COG AALL1131 regimen + dasatinib[c,2,4,7]	Vincristine, dexamethasone or prednisone, daunorubicin, pegaspargase; IT therapy: cytarabine then MTX	For *CRLF2*- with *ABL* class kinase fusion: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase, + dasatinib; IT therapy: MTX
COG AALL1521 regimen ± ruxolitinib[c,21]		For *CRLF2*+ or *CRLF2*- with *JAK2* fusions, *EPOR* rearrangements, *SH2B3* alterations, *IL7R* insertions/deletions: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase, + ruxolitinib; IT therapy: MTX
DFCI-ALL Protocol 16-001 regimen + dasatinib[c,5,6]	For *ABL* class kinase fusion: DFCI-ALL Protocol 16-001 VHR arm: dexamethasone, vincristine, pegaspargase, 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, doxorubicin + dasatinib; IT therapy: MTX
Total Therapy XVII regimen + dasatinib[8] **or Total Therapy XVII regimen ± ruxolitinib**[c,8]	• For *ABL* class kinase fusion: Total Therapy XVII regimen + dasatinib[20] • For mutations associated with JAK-STAT pathway activation: Total Therapy XVII regimen ± ruxolitinib	• For *ABL* class kinase fusion: Total Therapy XVII regimen (either LR or SR/HR arm) + dasatinib[7] • 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 (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-G) for recommended dosing alterations for 6-MP and 6-TG.
[c] Ongoing clinical trials from multi-institutional or cooperative group studies.
[g] 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.
[h] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.

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Continued
References

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,g,h]

Ph-positive ALL	Induction	Consolidation
Standard arm of COG AALL1631[c] (based on COG AALL1122/EsPhALL regimen)	EsPhALL backbone (cyclophosphamide, mercaptopurine, cytarabine, MTX) + imatinib[9]/ dasatinib[c]	• Dexamethasone, vincristine, MTX, ifosfamide, cytarabine, pegaspargase, 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, 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, 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[c] + dasatinib	Total XVII regimen: prednisone, vincristine, daunorubicin, pegaspargase, 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, 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-G) for recommended dosing alterations for 6-MP and 6-TG.
[c] Ongoing clinical trials from multi-institutional or cooperative group studies.
[g] 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.
[h] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.

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References

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,g,h]

T-ALL	Induction	Consolidation
COG AALL1231 regimen[c,j]	Dexamethasone, vincristine, pegaspargase, daunorubicin;[j] IT therapy[a]	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase, vincristine[j]; IT therapy[a]
COG AALL0434 regimen[13]	Prednisone, vincristine, pegaspargase, daunorubicin; IT therapy: Age-adjusted cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase, vincristine, nelarabine; IT therapy: MTX
DFCI ALL 16-001[c] **based on DFCI-ALL Protocol 11-001**	Dexamethasone, vincristine, pegaspargase, 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[c]	Prednisone, vincristine, pegaspargase, cyclophosphamide, daunorubicin, mercaptopurine,[b] cytarabine;[k] ITT[a]	High-dose MTX, mercaptopurine,[b] pegaspargase; ITT[a]

Infant ALL	Induction	Consolidation[l,m]
Interfant regimens[14-16]	Prednisone, dexamethasone, vincristine, cytarabine, daunorubicin, pegaspargase, MTX; IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone)	Intermediate-risk and HR arms: Chemotherapy consolidation: cyclophosphamide, mercaptopurine,[b] cytarabine, MTX, prednisone, pegaspargase[14] Post-consolidation, and HR arm not undergoing HCT: dexamethasone, 6-TG,[b] vincristine, cytarabine, daunorubicin, pegaspargase, cytarabine, prednisone, cyclophosphamide, MTX, mercaptopurine[b,14]
		LR arm: Identical approach as pediatric ALL risk-stratified chemotherapy based on genetics and MRD response (see PEDALL-I) or interfant consolidation (see above)

Risk groups: low risk (LR), 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-G) for recommended dosing alterations for 6-MP and 6-TG.
[c] Ongoing clinical trials from multi-institutional or cooperative group studies.
[g] 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.
[h] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.
[j] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.
[k] High-risk patients treated on SJCRH TXVII receive an intensification phase after induction prior to consolidation.
[l] IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone).
[m] 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).

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References

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[n,o]

Ph-negative ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• UKALL R3 regimen[22] • COG AALL01P2 regimen[23] • ALL-REZ BFM 90 regimen[24] • COG AALL07P1 regimen[25] • Blinatumomab[p,26-29] • Tisagenlecleucel (refractory disease or ≥2 relapses)[q,r,30] ▸ 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 chimeric antigen receptor (CAR) T-cell binding domains • Inotuzumab ozogamicin ± mini-hyper-CVD[s,31,32,33] • Clofarabine-containing regimens (eg, clofarabine, cyclophosphamide, etoposide)[34,35] • Fludarabine-based regimens: FLAG-IDA (fludarabine, cytarabine, G-CSF ± idarubicin)[36] • High-dose cytarabine-based regimens (eg, high-dose cytarabine, pegaspargase)[37]

[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).

[n] See Principles of Hematopoietic Cell Transplant (PEDALL-J).

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

[p] Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome (CRS) and neurologic toxicities. Understanding of the risk evaluation and mitigation strategy (REMS) program and/or 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/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125557.

[q] 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.

[r] See Principles of Systemic Therapy - Immunotherapy (PEDALL-F [10 of 12]).

[s] Inotuzumab ozogamicin is not FDA approved for children and has been associated with hepatotoxicity, including fatal and life-threatening hepatic VOD, and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.

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References

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[n,o]

Ph-positive ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• The regimens listed on (PEDALL-F [7 of 12]) for Ph-negative ALL may be considered for Ph-positive ALL with TKIs listed below.[t] ▸ TKIs to consider: ◊ Dasatinib ◊ Imatinib • Blinatumomab (TKI intolerant/refractory)[p,27,28,29,38] • Tisagenlecleucel (TKI intolerant/refractory disease or relapse post-HCT)[q,r,30] • Inotuzumab ozogamicin (TKI intolerant/refractory)[s,31,32]

[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).

[n] See Principles of Hematopoietic Cell Transplant (PEDALL-J).

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

[p] Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Understanding of the REMS program and/or 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/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125557.

[q] 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.

[r] See Principles of Systemic Therapy - Immunotherapy (PEDALL-F [10 of 12]).

[s] Inotuzumab ozogamicin is not FDA approved for children and has been associated with hepatotoxicity, including fatal and life-threatening hepatic VOD, and increased risk of post-HCT non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf.

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

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References

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[n,o]

T-ALL[a]

Preferred	Other Recommended Regimens
• Clinical trial	• Nelarabine-containing regimens: eg, nelarabine, cyclophosphamide, and etoposide[39] • Bortezomib-containing regimen: eg, bortezomib, vincristine, doxorubicin, pegaspargase, and prednisone or dexamethasone[25] • UKALL R3 Block 1: dexamethasone, mitoxantrone, pegaspargase, and vincristine[22] • BFM Intensification Block 1: high-dose MTX, high-dose cytarabine, dexamethasone, vincristine, pegaspargase, and cyclophosphamide[24] • 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).
[n] See Principles of Hematopoietic Cell Transplant (PEDALL-J).
[o] Guidelines for managing specific sites of extramedullary relapse (ie, testicular) are included in the protocols listed.

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References

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

Tisagenlecleucel[r]

- **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 cytokine release syndrome (CRS) or neurotoxicity are included in the tisagenlecleucel package insert. Tocilizumab and corticosteroids are the main options used to manage CRS and neurotoxicity.[40,41] See the American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT) consensus grading[42] and CARTOX management guidelines[43] for detailed CAR T-cell toxicity grading, monitoring, and management.**
- **Hypogammaglobulinemia: Monitor IgG levels after treatment with tisagenlecleucel and replace with IV or subcutaneous immunoglobulin 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) has been associated with durable clinical responses without subsequent HCT.[30]**
- **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.[u]**
- **Next-generation sequencing (NGS) can be used for MRD monitoring.**

[r] 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.

[u] 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

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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.**
- **Heterozygotes carry one normal function allele with normal *TPMT* activity (*1) and one no function allele (eg, *1/*2, *1/*3A). Estimated frequency is 3%–14% of patients.**
- **Homozygotes carry two no function alleles (eg, *2/*3A, *3C/*3A). Estimated frequency is 0.5%–0.03% of patients.**
- **Dosing recommendations for patients who are heterozygous or homozygous for *TPMT* no function alleles are shown in Table 1.**
- **For patients homozygous for normal function *TPMT* and *NUDT15*, who do not appear to tolerate thiopurines, consider measuring erythrocyte thiopurine metabolites and/or erythrocyte *TPMT* activity. Genetic testing may fail to identify rare or previously undiscovered no function alleles.**

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

Genotype/Phenotype	Dosing Recommendations for 6-MP	Dosing Recommendations for 6-TG
Homozygous for normal function alleles (eg, *1/*1); normal metabolizer	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.
Heterozygous for no function allele (eg, *1/*2, 3A, 3B, 3C, or 4); intermediate metabolizer[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.	Reduce starting dose by 30%–80%.[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.
Homozygous for no function alleles (eg, *2/*3A, *3C/*4); poor metabolizer	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 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.

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Continued
References

PHARMACOGENOMICS[1-5]

- **Up to 25% of Asian and Native American patients will carry a no function *NUDT15* allele. Patients of other ancestries may also carry a *NUDT15* no function allele but at a lower frequency.**
- **Patients can be categorized into three groups with varying *NUDT15* activity based on their diplotype (see Table 2 for specific genetic alterations associated with low activity alleles):**
  - **Normal metabolizer: *1/*1**
  - **Intermediate metabolizer: *1/*2, *1/*3, *1/*4, and *1/*5**
  - **Poor metabolizer: *3/*5, *2/*3, and *3/*3**

Table 2: *NUDT15* Allele Variants

***2**	**p.Val18_vAL19insGlyVal/p.Arg139/Cys**
***3**	**p.Arg139Cys**
***4**	**p.Arg139His**
***5**	**p.Val18Ile**

Table 3: Dosing Guidelines for Thiopurines Based on *NUDT15* Phenotype[a,b]

Genotype/Phenotype	Dosing Recommendations for 6-MP	Dosing Recommendations for 6-TG
Homozygous for normal function alleles (eg, *1/*1); normal metabolizer	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.
Heterozygous for no function allele (eg, *1/*2, *3, or *9); intermediate metabolizer[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.
Homozygous for no function alleles (eg, *2/*3); poor metabolizer	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 intermediate metabolizers, patients receiving already reduced starting doses (<75 mg/m^2/day of 6-MP or <40 mg/m^2/day 6-TG) of thiopurines as in the non-maintenance phases of some ALL treatment regimens, further dose reduction may not be needed.

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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% (M1) or <1% by flow or molecular testing[a]**
  - **With blood count recovery = absolute neutrophil count (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 (See PEDALL-I)**
- **Refractory disease**
  - **Failure to achieve CR 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 (see PEDALL-C) 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 lumbar punctures (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.

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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-cell 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 polymerase chain reaction (RQ-PCR) assays (eg, clonally rearranged immunoglobulin, 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 immunoglobulin 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 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.**
    - **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

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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 (See 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 indicated for Ph+ ALL in CR1 (while on TKI plus systemic chemotherapy).[c,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-J (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-J (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-F (9 of 12).**
  - **Induction failure (M3 marrow).[13]**
  - **Patients with medullary or extramedullary relapse (any time point).[14] See PEDALL-J (2 of 5).**
- **For relapsed/refractory disease, see PEDALL-J (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.
[c] 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).

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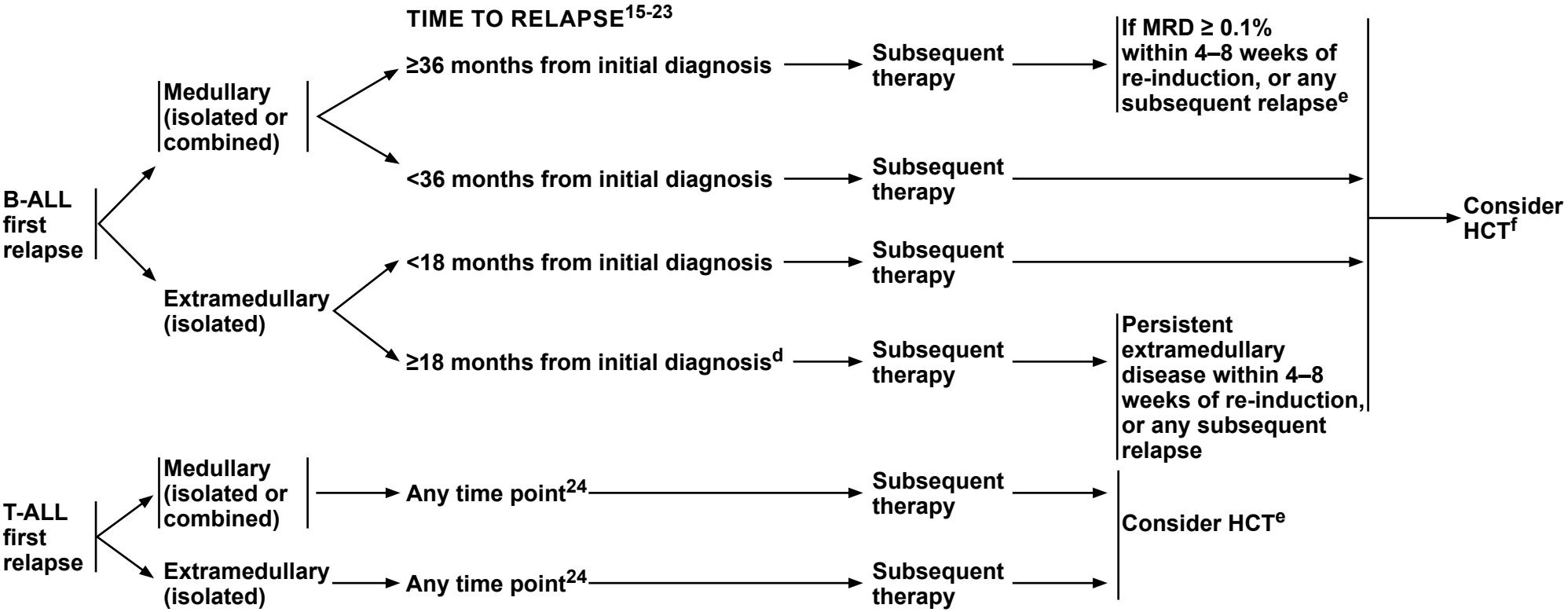
References

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT



[d] For late isolated extramedullary relapses, if patient achieves CR2 with re-induction/salvage therapy, no HCT is indicated.
[e] The recommendations may differ based on the treatment regimen.
[f] Consideration for HCT depends upon donor availability and patient's clinical status at the time of potential HCT.

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References

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Donor Type

- Unrelated vs. related donor
  - In children/young adults undergoing HCT for ALL, there is no survival advantage EFS, OS by donor type when comparing use of matched unrelated donors (URDs) to matched related donors (RDs).[25]
- Unrelated 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 cord blood (CB) vs. URD/RD.[26]
    - ◊ Possible lower relapse rates using UCB vs. URD if the patient is MRD-positive pre-HCT.[27]
    - ◊ No survival advantage for double (vs. single) CB 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]

Donor Cell Source

- When comparing bone marrow to peripheral stem cells (PSCs) as the donor cell source, there is no survival advantage for use of PSCs in URD transplantation. Higher graft-versus-host disease (GVHD) rates with equivalent survival are noted with PSCs (vs. marrow) in recipients of URD transplants. The optimal donor cell source (marrow vs. PSCs) has not been clearly defined with either RDs or haploidentical donor transplants. Due to increased risks of acute and chronic GVHD with PSCs, the use of PSCs should be considered with caution for HCT in children/young adults with ALL.[30,31]

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.[32,33,34] 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 bone marrow transplant [BMT]).[34]
- For infants: If donor available, prefer non TBI-based prep regimen and age ≥6 mo at time of HCT.[35] See PEDALL-F, 2 of 12.

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.[36,37]
- The absence of detectable MRD by NGS before and after HCT may be associated with favorable outcomes.[38]

References

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus 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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ABBREVIATIONS

AML	acute myeloid leukemia
AVN	avascular necrosis
BFM	Berlin-Frankfurt-Münster
B-ALL/LBL	B-lymphoblastic leukemia/lymphoma
CAR	chimeric antigen receptor
CB	cord blood
CMV	cytomegalovirus
CBC	complete blood count
CNS	central nervous system
CIBMTR	Center for International Blood and Marrow Transplant Research
CR	complete response
CRi	complete response with incomplete blood count recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
DT	double trisomy
EBV	epstein-barr virus
EFS	event-free survival
EOI	end of induction
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
HCT	hematopoietic cell transplant
HSV	herpes simplex virus
HR	high risk
iAMP21	intrachromosomal amplification of chromosome 21
Ig	immunoglobulin
IT	intrathecal
ITT	intrathecal triple therapy
LDH	lactate dehydrogenase
LBL	lymphoblastic lymphoma
LFT	liver function test
LP	lumbar puncture
MNCs	mononuclear cells
MRD	minimal residual disease
NGS	next-generation sequencing
OS	overall survival
PCR	polymerase chain reaction
PRES	posterior reversible encephalopathy syndrome
PSC	peripheral stem cell
REMS	risk evaluation and mitigation strategy
RBC	red blood cell
RD	related donor
RSV	respiratory syncytial virus
RT	radiation therapy
RT-PCR	reverse transcriptase-polymerase chain reaction
SAA	serum asparaginase activity
SR	standard risk
TBI	total body irradiation
TCR	T-cell receptor
TDM	therapeutic drug monitoring
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
UCB	unrelated cord blood
ULN	upper limit of normal
URD	unrelated donor
VHR	very high risk
VOD	veno-occlusive disease
VZV	varicella zoster virus
WBC	white blood cell

NCCN Guidelines Version 2.2023
Pediatric Acute Lymphoblastic Leukemia

Discussion

This discussion corresponds to the NCCN Guidelines for Pediatric Acute Lymphoblastic Leukemia. Last updated: March 10, 2023

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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 6540 new cases and 1390 deaths estimated in 2023.[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 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]

The cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.[7] 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, and the use of allogeneic hematopoietic cell transplantation (HCT). 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.[7,8] However, survival rates for adult patients remain low at approximately 20% to 40%.[9-12] 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.[10,13] 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%.[14]

Cure rates for AYAs with ALL remain suboptimal compared with those for children, although substantial improvements have been seen with the adoption of pediatric treatment regimens.[15] 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 Philadelphia chromosome (Ph)-positive and Ph-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 ALL patients 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 ALL are intended to apply to AYA patients treated in an adult oncology setting.

Literature Search Criteria and Guidelines Update Methodology

Prior to the development of this version 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.[16]

The search results were narrowed by selecting studies in humans published in English. 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 and discussed by the panel during the Guidelines update 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.

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing published studies and recommendations from other organizations, the terms used (eg, *male, female*) reflect the cited sources. The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

Clinical Presentation

Patients with ALL develop symptoms related to the infiltration of blasts in the bone marrow, lymphoid system, and extramedullary sites (including the central nervous system [CNS] and testicles).[3] These symptoms may include fatigue or lethargy, constitutional symptoms (eg, fevers, night sweats, weight loss), dyspnea, dizziness, infections, and easy bruising or bleeding.[4,17] 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 in approximately 20% of patients. Chin numbness or facial palsy may result from cranial nerve or CNS involvement.[18,19] Abdominal masses from gastrointestinal (GI) involvement are more suggestive of mature B-cell ALL (Burkitt lymphoma).[4]

The diagnosis of ALL generally requires demonstration of 20% or greater bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials. A value of greater than 25% marrow blasts is often used in treatment protocols to define leukemia.[20] 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.[20] In addition, there is no compelling evidence that failure to treat a patient when there are <20% marrow blasts has an adverse effect on outcome.[20] Peripheral blood may be substituted for bone marrow provided there is a significant amount of circulating disease,[21,22] with the NCCN Pediatric ALL Panel suggesting a general guide of ≥1,000 circulating lymphoblasts per microliter or ≥20% lymphoblasts.

The 2016 WHO classification lists ALL and lymphoblastic lymphoma as the same entity, distinguished only by the primary location of the disease.[20,23] When the disease is restricted to a mass lesion primarily involving nodal 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 lymphoblastic lymphoma.[20,23] However, based on morphologic, genetic, and immunophenotypic features, lymphoblastic lymphoma is indistinguishable from ALL. Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens versus traditional lymphoma therapy[24,25]

and should be treated in a center that has experience with lymphoblastic lymphoma.

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 (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 residual disease (MRD).

Immunophenotyping

Immunophenotypic classification of ALL involves flow cytometry to determine the presence of cell surface antigens on lymphocytes. ALL can be broadly classified into two groups based on immunophenotype, which include precursor B-cell ALL and T-cell ALL.[4,26] Among children, B-ALL constitutes approximately 80% of cases and T-ALL constitutes approximately 10% to 15% of cases.[23,27,28] In adult patients, subtypes of B-ALL represent approximately 75% of cases, whereas the remaining 25% comprise T-ALL.[28,29] 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. 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.[30,31] 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.[4,20] The definition of CD20 positivity is unclear, though most studies use 20% or greater of blasts expressing CD20.[32,33] 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.[33] 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 *CRLF2::P2RY8* and *IGH::CRLF2*.[34]

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 CD1a/CD2/CD5/CD7 and expression of TdT.[23] 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.[23,35] Most cases previously classified as pro-T or pre-T now meet the criteria for early T-cell precursor (ETP) ALL.[23] 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 or more myeloid or stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65) on at least 25% of lymphoblasts.[23,36] Initial reports demonstrated unfavorable outcomes;[36-38] however, with modern more intensive therapies, multiple groups have reported similar outcomes to those observed in non-ETP T-ALL.[39-41]

Hematologic malignancies related to ALL include acute leukemias of ambiguous lineage (ALALs), such as the mixed phenotype acute leukemias (MPALs).[42,43] 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.[42] 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.[20,23] 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 haematolymphoid tumours, ALALs/MPALs were separated into those with defining genetic abnormalities and those defined based on immunophenotyping alone.[43] Lineage assignment criteria were refined to highlight principles of intensity and pattern.

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); t(9;22)(q34.1;q11.2), *BCR::ABL1*; t(v;11q23.3), *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;* and t(17;19)(q22;p13.3)[*TCF3*::*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.[44] During the 2016 WHO classification update, two new provisional entities were added to the B-ALL classification: B-lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors (*BCR::ABL1*–like ALL or Ph-like ALL)[45,46] and B-lymphoblastic leukemia/lymphoma with *intrachromosomal amplification of chromosome 21* (*iAMP21*).[45,47] Two new provisional entities were also added to T-ALL: ETP lymphoblastic leukemia and natural killer (NK) cell lymphoblastic leukemia/lymphoma.[45] During the 2022 WHO classification update, two new subtypes of ALAL were added: MPAL with *ZNF384* rearrangement and *BCL11B* rearrangement.[43]

In these 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 with ALL, the most common chromosomal abnormality is hyperdiploidy (51–67 chromosomes) as seen in 25% of cases of B-ALL compared to 7% in the adult ALL patient population.[28,48] 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%).[28,48] 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]

Intermediate-Risk Features

Several chromosomal abnormalities are now recognized as markers of intermediate-risk disease,[50,51] including *MEF2Dr*, *ZNF384r*, *PAX5alt*, *PAX5* P80R, and *ETV6::RUNX1*-like, 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* fusion, and *BCR::ABL1*.[52,53] Hypodiploidy is associated with poor prognosis and is observed in 1% to 2% of pediatric patients.[54-56] Of note, low hypodiploidy is associated with a high frequency of *TP53* alterations, which are germline in ~50% of cases.[57,58] 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.[53]

Chromosomal rearrangements involving the *KMT2A* gene, previously referred to as the human mixed lineage leukemia (*MLL*), occur in approximately 5% of pediatric ALL cases, with a higher incidence in infants (~70%–80%).[59-62] These *KMT2A* rearrangements, including cases with t(4;11) translocation, are associated with poor outcomes, especially in infants.[31,63,64] 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.[65,66] Conversely, another translocation t(1;19) that results in the fusion gene *TCF3::PBX1* occurs in approximately 5% of pediatric ALL cases, and is associated with intermediate outcomes.[65,67]

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.[68,69] Occurring in approximately 2% of children with ALL, B-ALL with *iAMP21* is associated with adverse prognosis when treated with low-intensity regimens.[68,69] Children with *iAMP21* are typically older, with a median age of 9 years, and have low platelet counts and low white blood cell (WBC) counts.[70]

BCR::ABL1– or Ph-positive ALL is associated with poor prognosis and is relatively uncommon among childhood ALL (2%), whereas this subtype is more common among adults (25%).[28,48] The frequency of Ph-positive ALL increases with age, and younger children (1–9 years) with Ph-positive ALL have a better prognosis than adolescents with this subtype.[71,72]

In B-ALL, mutations in the Ikaros gene (*IKZF1*) mutations are seen in approximately 15% to 20% of pediatric B-ALL cases[73,74] and at a higher frequency of greater than 75% in the setting of *BCR::ABL1* positivity.[73,75] In many studies, *IKZF1* mutations are associated with a poor prognosis and a greater incidence of relapse.[75,76] *IKZF1* deletions with co-occurring deletions in *CDKN2A*, *CDKN2B*, *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.[75,77,78] 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.[79,80]

BCR::ABL1–like or Ph-like ALL is a subgroup of B-ALL associated with unfavorable prognosis that occurs in approximately 15% of pediatric ALL cases.[46,81,82] A study using gene expression signatures to classify pediatric patients with ALL into subtypes estimated the 5-year disease-free survival (DFS) in the *BCR::ABL1*–like ALL group to be 60%.[46] In adult patients with *BCR::ABL1*–like ALL, the 5-year event-free survival (EFS) is significantly lower (22.5%; 95% confidence interval [CI], 14.9%–29.3%) compared to patients with non-*BCR::ABL1*–like ALL (49.3%; 95% CI, 42.8%–56.2%).[83] Although this subgroup is Ph-negative, there is an otherwise similar genetic profile to the Ph-positive ALL subgroup including an *IKZF1* mutation.[75] A study evaluating the relationship between *BCR::ABL1*–like and *IKZF1* in children with B-cell precursor ALL showed that 40% of cases had co-occurrence of these mutations.[84] The presence of the *BCR::ABL1*–like signature and an *IKZF1* deletion were indicative of poor prognosis independent of conventional risk factors.[84] Genomically, the Ph-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,*[85] *EPOR*, *JAK1, JAK2*, *JAK3, TYK2, SH2B3*, *IL7R*), and other rearrangements in *FLT3*, *NTRK3*, *LYN*, and *PTK2B* genes.[46,86,87] Genomic profiling studies have found that at least 80% of Ph-like ALL cases 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.[86-88]

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*.[82,89] Over 50% of T-ALL cases have activating *NOTCH1* mutations, and approximately 10% to 15% of T-ALL cases have mutations in the *NOTCH1*-targeting E3 ligase *FBXW7*, which leads to prolonged *NOTCH1* activation.[90-92] In patients with T-ALL, *NOTCH1* and *FBXW7* mutations have generally been associated with favorable prognosis and lower MRD levels.[93-95] 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.[96-98]

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, and reverse transcriptase-polymerase chain reaction (RT-PCR) testing. FISH probes and RT-PCR primers should include those capable of detecting major recurrent genetic abnormalities. RT-PCR should measure 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 Ph-like ALL is encouraged in some cases, and may aid in risk stratification. Recurrent gene fusions and mutations that activate tyrosine kinase pathways and are associated with Ph-like ALL include: gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, or *PDGFRB* (gene fusions) and mutations involving *CRLF2*, *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions).[87,99] Low-density arrays (LDAs),[100] next-generation sequencing (NGS)-based assays, and multiplex RT-PCR are typically used to detect signature or cryptic rearrangements and mutations characteristic of Ph-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.[101] In cases of aneuploidy or failed karyotype, additional assessment may include a microarray comparative genomic hybridization (aCGH).

Workup

The initial workup for ALL should include a thorough medical history and physical examination, along with laboratory and imaging studies (where applicable). 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). 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 (1%–2% of males), but is slightly more common in T-ALL than B-ALL. Fertility counseling and/or preservation options should be presented to all patients.

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, a chest x-ray is recommended. If lymphoblastic lymphoma is suspected, a whole-body PET/CT scan is recommended. 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 (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 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 germline mutations associated with ALL risk have been reported.[102] Importantly, children with Down syndrome are at an increased risk for the development of ALL.[103] For non-Down syndrome–related ALL, most patients do not have an identifiable leukemia predisposition syndrome. An exception is low-hypodiploid ALL where germline *TP53* mutations are common and testing should be considered. Other germline mutations associated with ALL risk have been reported, particularly *PAX5, ETV6,* and *IKZF1*.[102] A complete family history can help identify risk for a cancer predisposition syndrome, although de novo mutations have been reported. 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, and Pancreatic).

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.[104] 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 less than 50 × 10^9 cells/L, whereas all other patients with ALL, including T-ALL (regardless of age or WBC count), were considered high risk.[56]

Different cooperative groups have used a combination of clinical, biologic, and response variables to allocate patients into risk groups based on outcome.[56,101,105] 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, Ph-positive ALL) and/or presence of *BCR::ABL1* fusion gene; hypodiploidy (<44 chromosomes);[106] *BCR::ABL1*–like or Ph-like ALL;[86] *iAMP21*;[68,107] patients <1 year of age with *KMT2A* gene rearrangement,[60,107] or inability to achieve remission with induction therapy.[56] Conversely, criteria were refined for patients with lower risk and included hyperdiploidy, especially with simultaneous trisomies of chromosomes 4, 10, and 17,[56,108] and the t(12;21) chromosomal translocation (*ETV6::RUNX1* subtype).[109] 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.[40] Although T-ALL is often categorized as high risk depending on the institute, newer treatment options have resulted in improved survival outcomes for these patients.[39,40,110,111] 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.

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.[107] In the United States, other groups have also developed standards for risk-stratified treatment approaches, including the St. Jude Consortium[112-114] and the Dana-Farber Cancer Institute (DFCI) ALL Consortium.[105,115,116] 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.[117,118]

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, Ph-positive ALL and/or presence of *BCR::ABL1* fusion protein, and have received steroid pre-treatment)].[107] After induction, a critical measure used to ascribe risk is MRD,[107] 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.[107] 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.[40] For patients requiring an EOC MRD assessment, the threshold between intermediate and very high risk is ≥0.1%.[40]

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 and have the *ETV6::RUNX1* fusion; or B-ALL with age 1–9.9 years and WBC count less than 50 × 10^9 cells/L; or if they lack standard-risk features. 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; or if the patients have T-ALL.[114] 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.[119] 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)].[105] 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 ALL 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. 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.[27] Induction regimens are typically based on a backbone that includes a combination of vincristine, corticosteroids (eg, prednisone, dexamethasone), and pegaspargase (or previously L-asparaginase) with or without anthracyclines (eg, daunorubicin, doxorubicin).[26,27,112,120]

The BFM/COG regimens are mainly based on a 4-drug induction regimen that includes a combination of vincristine, an anthracycline, a corticosteroid, and pegaspargase (or previously L-asparaginase.[118,121-124] 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.[125]

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.[126,127] The observed advantage in outcomes with dexamethasone may partly be attributed to improved penetration of dexamethasone into the CNS.[128] 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 including osteonecrosis and infection,[129,130] and an advantage for OS has yet to be conclusively shown, except in the subset of T-ALL patients with prednisone good response in the AIEOP-BFM ALL 2000 study.[129]

Several different agents exist for asparaginase 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.[27,131] Calaspargase is an asparaginase enzyme formulation with a different linker molecule that enhances its hydrolytic stability and increases its half-life relative to pegaspargase.[132] 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.[133] A phase 2/3 study[134] supports a new intramuscular dosing scheduling for ERW-rywn of 25 mg/m^2 Monday/Wednesday, 50 mg/m^2 Friday based on positive risk:benefit ratio. Moreover, *Escherichia coli*-derived L-asparaginase is currently not available in the United States and has been discontinued by the manufacturer.

Consolidation

The intent of postinduction consolidation is to eliminate any leukemic cells potentially remaining after induction therapy, further eradicating residual disease. 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. The postremission induction phase of treatment (but before long-term maintenance therapy) may also be described as *intensification therapy*. The combination of drugs and duration of therapy for consolidation regimens vary largely among studies and patient populations but can comprise combinations of drugs similar to those used during the induction phase. High-dose methotrexate (HD-MTX), cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, thioguanine, vincristine, corticosteroids, and pegaspargase (or previously L-asparaginase) are frequently incorporated into consolidation/intensification regimens.[27,112,120,123,124] 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.[112]

Maintenance

The goal of extended maintenance or continuation therapy is to prevent disease relapse after postremission induction and consolidation therapy. Most maintenance regimens are based on a backbone of daily 6-MP and weekly methotrexate (MTX) (typically with the addition of periodic vincristine and corticosteroids) for 2 to 3 years.[27,112,120] 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.[135,136] Furthermore, age, gender, and genetic polymorphisms can affect bioavailability.[137-139] The efficacy of maintenance therapy is determined by the metabolism of 6-MP to the antimetabolite chemotherapeutic agent 6-thioguanine nucleotide (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.[140-142] NUDT15 deficiency, which is more prevalent in patients of East Asian descent and patients of Hispanic ethnicity, is also associated with 6-MP intolerance.[143] 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.[143] 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.[144] 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.

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. CNS-directed therapy may include IT therapy (eg, IT MTX, cytarabine, corticosteroid), cranial irradiation, and/or systemic chemotherapy (eg, dexamethasone, HD-MTX, intermediate-/high-dose cytarabine, pegaspargase [or previously, L-asparaginase]).[27,112,120,128,145] 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.[112,146,147] In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, cord blood, or haploidentical donor).[147-149] 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.[149-151] 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.[112,152,153] 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 Ph-positive disorders with TKIs, represents an important advancement in ALL therapy.[154-158] 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 Ph-like ALL cases harboring *CRLF2* and *JAK* alterations, the utility of Janus kinase inhibitors are being explored.[159] The purine nucleoside analog nelarabine has been approved for the treatment of relapsed or refractory (R/R) T-ALL or lymphoblastic lymphoma.[160] Monoclonal antibodies to surface antigens such as CD19, CD20, CD22, and CD52 have been used in unconjugated form (eg,

rituximab, epratuzumab), conjugated to immunotoxins or chemotherapeutic agents (moxetumomab, inotuzumab ozogamicin [InO]), or in the form of a bispecific antibody (blinatumomab).[112,161-163] Chimeric antigen receptor (CAR) T cells that target CD19 have demonstrated durable remissions in pediatric and AYA patients with R/R B-ALL.[164] Overall, these agents may be incorporated as part of frontline induction, consolidation, and/or maintenance regimens during the course of initial ALL therapy, and 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.[15,120] Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense IT chemotherapy regimens.[165,166] 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.[167-171] 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.[172] 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*;[173] a greater incidence of poor-risk cytogenetics, including Ph-positive ALL, hypodiploidy, and complex karyotype;[174] and a higher incidence of ETP-ALL.[36,175] 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.[173]

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.[176] 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).[177] 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;[178] however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.[179] Pediatric patients have been shown to be more compliant to treatment protocols compared to AYA patients,[180] which may be due to greater parental supervision of the treatment and better health insurance coverage.[181]

Treatment Considerations: Vulnerable Populations

Infants (<12 months of age) make up 2% to 5% of pediatric ALL cases and represent a high-risk ALL group due to lack of response to treatment and treatment-related complications.[27,182] This is due in part to a high incidence of early bone marrow, CNS, and extramedullary relapse.[183] 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 cases.[27,183,184]

Children with trisomy 21 (Down syndrome) have an increased risk of ALL, although the basis for this increased risk is unknown.[27,103,185] 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.[185] Some reports have determined that ALL in children with Down syndrome frequently expresses *CRLF2*, which is associated with mutated *JAK2*.[186,187] Historically, children with ALL and Down syndrome have been shown to have poorer outcomes relative to non-Down syndrome–related ALL.[188] These differences may be due to poor adherence of physicians to protocol guidelines,[189] 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 cases of non-Down syndrome–related ALL.[185,190] 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 Vulnerable Populations* 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 postinduction (and/or post-consolidation) MRD measurements in predicting the likelihood of disease relapse.[41,191-199]

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 immunoglobulin and/or TCR genes.[200-207] New multiplexed PCR and NGS for MRD are emerging methodologies.

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.[201,203,205,206,208,209] 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.[202,204,206,210-212] The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.[203,210,213] 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) have been shown to be highly predictive of outcomes in children with ALL. In a study conducted by the COG, the prognostic impact of MRD was measured by flow cytometry in the peripheral blood at day 8, and in marrows at end-induction (day 29) and end-consolidation in children with B-ALL (n = 2143).[193] The presence of MRD in day 8 blood and day 29 marrow MRD was associated with shorter EFS in all risk groups (NCI standard- and high-risk).[193] In addition, 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 ($P < .001$).[193] In a study of pediatric ALL patients 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%; $P < .001$).[214] Subsequent studies confirmed these findings.[215] In another study of pediatric ALL patients 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%; $P < .001$).[216]

MRD also emerged as a highly prognostic factor in the COG AALL0232 trial, in which pediatric ALL patients (n = 2479 evaluable) were randomized in a 2 x 2 factorial design to receive either HD-MTX or Capizzi escalating-dose MTX (C-MTX) during interim maintenance (IM) or prednisone or dexamethasone during induction.[217] 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%.[217] 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).[217] Although HD-MTX was superior to C-MTX, MRD retained prognostic significance in both groups.[217]

In the AIEOP-BFM ALL 2000 study, children with Ph-negative B-ALL (n = 3184 evaluable) were risk stratified according to MRD status (PCR optimal sensitivity level ≤0.01%) at two time points (days 33 and 78), which were used to guide postinduction treatment.[194] Patients were considered to be at standard risk if MRD negativity (≤0.01%) was achieved on both days 33 and 78, at intermediate risk if MRD was greater than 0.01% (but <0.1%) on either day 33 or 78 (the other time point being MRD-negative) or on both days 33 and 78, and at high risk if MRD was 0.1% or greater on day 78. The 5-year EFS rate was 92% for patients categorized as at standard risk (n = 1348), 78% for intermediate risk (n = 1647), and 50% for 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.[194] Data from the UKALL trial have also demonstrated that treatment intensity can be modified in children and young adult ALL patients according to MRD at the EOI.[218,219]

In the COG AALL0434 trial, children with T-ALL (n = 1144) were treated using a standard 4-drug induction regimen followed by response-based risk stratification at day 29, with patients with intermediate- and high-risk disease randomized to receive (or not) nelarabine during consolidation, delayed intensification (DI), and maintenance.[41] All patients were also randomized to either receive C-MTX or HD-MTX during IM.[41] At the time of study enrollment, patients were grouped by flow cytometry as ETP, Near-ETP, or Not-ETP, and risk-stratification grouping included MRD assessment by flow cytometry using the following cutoffs: low risk, <0.1%; intermediate risk, <1%; and high risk >1%.[41] Day 29 MRD >0.01% was associated with significantly inferior EFS and OS rates for the total cohort and for Not-ETP.[41] The AIEOP-BFM ALL 2000 study also investigated the prognostic value of MRD in children with T-ALL (n = 464) using similar risk stratification measures (as described earlier) for standard, intermediate, and high risk.[197] 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 ($P < .001$).[197] MRD negativity at day 33 (time point 1 [TP1]) was the most favorable prognostic factor, and MRD >0.1%

at day 78 (TP2) was the most important predictive factor for relapse,[197] highlighting the significance of later MRD assessments on outcomes in pediatric T-ALL.

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).[220] 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.[220] 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.[220] 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.[221] 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}.[222] Patients with greater than or equal to MRD of 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 trial used a lower MRD optimal threshold (10^{-4}) to stratify patients for HCT, which may be reflective of the intensity of the induction regimen used.[223] Therefore, MRD levels may influence treatment decisions, but the application of this prognostic factor must be carefully evaluated on a regimen-by-regimen basis.

Approximately 20% of children treated with intensive therapies for ALL will experience disease relapse.[224] MRD assessment may play a prognostic role in the management of relapsed disease.[225-227] Several studies suggest early assessment of MRD during induction treatment (eg, day 15 from initiation of treatment) may be highly predictive of subsequent relapse in children with ALL.[228,229] 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.[41,191,194-198,217] 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,[201,203,208,209] and NGS methods can detect leukemic cells at an optimal/maximal sensitivity threshold of 10^{-6} (<0.0001%) bone marrow MNCs, respectively.[201,203,205,206,208,209] 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.

The timing of MRD assessment varies depending on the ALL treatment protocol used, and may occur during or after completion of initial induction therapy. Therefore, it is recommended that measurement be performed on completion of induction therapy (during treatment of *de novo* or relapsed disease); additional time points for MRD evaluation should be guided by the treatment protocol or regimen used.[208,209] Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden. In general, MRD positivity at the EOI 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 Ph-Negative or Ph-Like B-ALL

Front-Line Management of Ph-Negative or Ph-Like ALL

The management of *de novo* Ph-negative and Ph-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).[230] 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).[230] 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.[230] 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%, respectively.[230]

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.[231] 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).[231] 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.[232] In this study patients were randomly assigned to receive dexamethasone versus prednisone during induction and HD-MTX versus C-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 C-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.[232]

Relative to pediatric patients with standard-risk B-ALL, patients with high-risk B-ALL experience high relapse rates and worse clinical outcomes.[156,217] 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 1–30 years with newly diagnosed high-risk B-ALL.[233-235] Patients enrolled on 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 postinduction CNS prophylaxis with standard of care IT MTX versus triple IT therapy including MTX, hydrocortisone, and cytarabine.[235] 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 postinduction 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.[234] 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.[233] 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 Ph-like B-ALL harboring *ABL*-class lesions (AALL1131),[86] and is investigating ruxolitinib for newly diagnosed patients with high-risk Ph-like ALL harboring *CRLF2* rearrangements and/or a mutation that

activates the JAK-STAT pathway (AALL1521).[236,237] 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 Ph-negative B-ALL, and tested a new risk stratification system.[105] 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).[105] After achieving complete remission, patients with high EOI MRD (≥10^{-3} via PCR analysis of patient-specific immunoglobulin or TCR rearrangements) and/or adverse cytogenetics (*KMT2A* rearrangement or hypodiploidy) were reclassified as having very-high-risk disease and received intensified therapy.[105] 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.[105] Further analysis of outcome by age demonstrated that Ph-negative B-ALL patients 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.[105] 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.[105]

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 lymphoblastic lymphoma (n = 239).[238] 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 complete response (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 (± 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 of age) 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.[113] 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 complete remission (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.[113] 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 (3,500 U/m^2 vs. 2,500 U/m^2) and early intensification of triple IT therapy would improve systemic and CNS control in pediatric patients with ALL (n = 598).[239] 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%.[239] 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.[239]

The ongoing Total XVII study will incorporate novel precision medicine strategies based on genomic features and targeted treatment.[101] 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.[101]

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.[240,241] 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[163] evaluated the efficacy of blinatumomab in patients with MRD-positive Ph-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}.[163] After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.[242] Gökbuget et al[243] 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%.[243] 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 complete remission (including rapid MRD-negative responses) in pediatric and adult patients with R/R B-precursor ALL.[162,244-246] 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 with MRD defined as disease ≥0.1% (see *Management of Relapsed or Refractory Ph-Negative or Ph-Like ALL* for discussion of studies related to blinatumomab use in R/R B-ALL).

Hematopoietic Cell Transplant

For pediatric and AYA patients with Ph-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.[217] 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.[247-250] However, HCT for hypodiploid ALL may be considered in the context of a clinical trial.

Management of Relapsed or Refractory Ph-Negative or Ph-Like ALL

The outcomes of pediatric patients with R/R B-ALL have been historically poor. In addition, the number of previous salvage attempts and duration of CR1 impact outcomes.[224,251,252] In the guidelines, early relapse is defined as disease that recurs less than 36 months from initial diagnosis for isolated or combined BM relapse or less than 18 months from initial diagnosis for isolated extramedullary relapse. Late relapse is defined as disease that recurs greater than or equal to 36 months from initial diagnosis for isolated or combined BM relapse or greater than or equal to 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.[223,251] It has also been reported that patients who received CAR T cells can maintain long-term remission without subsequent HCT.[164] 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.[253] 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 second CR (CR2), 25 patients died during induction, and 60 patients (11%) did not experience a response. A majority of patients in each group achieved second CR (Group A: 83%; Group B: 94%; and Group C: 100%).[253] 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 $P < .001$.[253] Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HCT.[253]

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).[254] 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.[254] In addition, patients with Ph-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.[254] 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.[254] 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).[223] 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.[223] After three blocks of therapy, all patients in the high-risk group and patients in the intermediate-risk group with postinduction 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.[223] 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.[251] 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).[251]

COG AALL07P1

Bortezomib is a proteasome inhibitor that has demonstrated some activity in relapsed pediatric ALL.[255-257] 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.[255,258] Of the evaluable patients treated with bortezomib and chemotherapy (n = 135; B-ALL, n = 103; T-ALL, n = 22; T-lymphoblastic lymphoma, n = 10), overall CR2 rates were 68% ± 5% for precursor B-ALL patients (<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).[255] 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[259,260] 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.[261,262] 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).[261] The overall response rate (ORR) was 44% (7 CR, 4 complete remission with partial recovery) with a 67.3-week median duration of remission censored at last follow-up.[261]

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.[263-266] 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.[267] 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 complete remission, and in patients with primary refractory ALL, 2 of 3 achieved a complete remission—1 after a second course of FLAG-IDA and both had Ph-positive disease.[267] 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.[268] 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.[268] 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).[268]

Blinatumomab

A component of the growing arsenal of immunotherapies for cancer treatment, blinatumomab 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).[246,269] 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 Ph-negative B-cell ALL that demonstrated a CR or CR without platelet recovery in 43% of patients within the first 2 cycles of treatment.[245,270] 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).[244] 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).[244] 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 CR with incomplete count recovery [CRi], 44% vs. 25%; *P* < .001).[244] Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.[244]

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.[162] 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.[162] Of the 70 patients who received this dosage, 27 (39%) achieved complete remission within the first 2 cycles, 14 (52%) of whom achieved complete MRD response.[162]

In a phase III trial, 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).[271] 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,[272] after induction therapy and 2 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.

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 ± SD) of 1.25 ± 0.63 hours.[273,274] 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.[273] CRS typically occurs within the first 2 days following initiation of blinatumomab infusion.[273] 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.

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 the patient'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.[164,275-277] 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.[164] 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.[278] 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, and combinations of CD19 and other antigens (eg, CD22) are ongoing.[278] The manufacture 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.[279] 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.[280] 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.[164] 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.[164] 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 demonstrated an estimated RFS of 58% at 24 months and 52% at 36 months when censored for allogeneic HCT and/or further therapy and estimated RFS rates of 52.3% at 24 months and 47.8% at 36 months without censoring.[281] Among those who received no subsequent treatment while in CR, estimated RFS rates at 24 and 36 months were 81% and 76%, respectively. Estimated EFS among all patients treated with tisagenlecleucel was 44% at 36 months.

In a pilot clinical trial, 74 children and AYA patients (age range 1–29 years) with R/R B-ALL or B-lymphoblastic lymphoma were treated with huCART19, a humanized CD19 CAR T-cell product.[282] 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.[283,284] Several groups have developed comprehensive guidelines regarding grading systems for and management of CAR T-cell–associated toxicities.[285,286]

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.[287] 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 2 groups, though the study required control of CNS disease both at time of enrollment and CAR T-cell infusion.

Inotuzumab Ozogamicin

InO is a calicheamicin-based antibody-drug conjugate targeting CD22. Following the generation of encouraging single-agent phase II data,[288] a randomized study was conducted comparing InO with standard intensive chemotherapy regimens in Ph-negative or Ph-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).[289] Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with Ph-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).[289] 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 Ph-negative ALL who were treated on phase 2 clinical trials with either intensive HCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) 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 HCVAD (*P* = .001). The 3-year OS rates were 54% versus 32%, respectively (*P* = .002).[290]

However, pediatric experience with InO is limited. In a retrospective study of pediatric patients with R/R B-ALL (n = 51) who received InO in a compassionate use program, 67% of patients achieved CR and a majority of the responders were MRD-negative (71%).[291] None of the patients developed sinusoidal obstruction syndrome (SOS) during therapy, but 52% of patients who underwent HCT following InO (11 of 21; 52%) developed SOS.[291]

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.[292] 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 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.[293] Of the 27 evaluable patients, estimated ORR (including CR, CR with insufficient platelet recovery [CRp], and CRi) was 81.5%, with 81.8% of responding patients 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.

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, <1–60 years) who underwent transplant during relapse.[294] At 3 years, OS rates were 16% (95% CI, 13%–20%).[294] 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.[295]

NCCN Recommendations for Ph-Negative or Ph-Like ALL

Front-Line Management: The panel recommends that pediatric and AYA patients with Ph-negative or Ph-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 algorithm), and induction therapy consists of multiagent chemotherapy. Patients who achieve MRD negativity after induction will continue risk-stratified therapy. Patients with MRD positivity after induction may undergo intensified consolidation therapy. 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 cases, 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 and persistent B-cell aplasia has been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year RFS with and without censoring for HCT and subsequent therapy was estimated at 52% and 47.8%, respectively, and among those who received no subsequent therapy while in CR, 24- and 36-month RFS was estimated at 81% and 76%, respectively.[281]

R/R Management: For pediatric and AYA patients with Ph-negative or Ph-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 (if in early first relapse) or continue on chemotherapy 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. 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.[164] If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care.

Management of Ph-Positive B-ALL

Ph-positive ALL is relatively rare in pediatric patients, and the development of TKIs has improved previously poor treatment outcomes.[81] The management of Ph-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 Ph-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).[156] 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 Ph-positive ALL (n = 120) treated on a POG protocol, which showed a 3-year EFS rate of only 35% (P < .0001).[156] 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.[156] Subsequent follow-up after 5 years confirmed these outcomes.[157] In a phase II single-arm trial (COG AALL0622) of children and young adults with Ph-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.[158] The 5-year OS and EFS rates (± standard deviation [SD]) were 86% ± 5% and 60% ± 7%, respectively, and outcomes were similar to those observed in COG AALL0031.[158]

EsPhALL

The European intergroup study of post-induction treatment of Ph-chromosome positive ALL (EsPhALL) reported results of the randomized open-label trial designed to evaluate the safety and long-term efficacy of discontinuous postinduction imatinib plus chemotherapy with the BFM backbone intensive treatment versus chemotherapy alone.[155] 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 ($P = .64$).[155] 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.[154] However, the 5-year EFS and OS rates (57% and 71.8%, respectively) were similar in cohorts that received discontinuous postinduction imatinib and continuous imatinib plus chemotherapy with the BFM backbone intensive treatment.[154,155] 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 Ph-positive ALL (n = 109 enrolled; age range, 1–17 years).[296] 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).[296]

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 Ph-positive ALL treated in the pre-TKI era versus with the current approach of incorporating a TKI.[297] 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 Ph-positive ALL.[297] 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 ($P < .001$).[297] The 5-year EFS for the TKI versus pre-TKI groups was 68.6 ± 19.2% and 31.6 ± 9.9%, respectively ($P = .022$).[297] In the Total XVII study, dasatinib will be given to patients with Ph-positive ALL and patients with disease with ABL-class chimeric fusions (ie, involving *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, or *PDGFRB*) identified by RNA-Seq.[101] In this setting, dasatinib will be given on day 15 of remission induction.[101]

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 Ph-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.[295,298] In the large, international, collaborative MRC UKALL XII/ECOG E2993 trial conducted in patients with previously untreated ALL, the subgroup with Ph-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.[299] Among the Ph-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.[299] 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).[299]

As mentioned earlier, the COG AALL0031 trial reported similar 3-year EFS rates among patients in the very-high-risk group with Ph-positive ALL in CR1 who received imatinib with intensive chemotherapy followed by HCT or those who received chemotherapy with imatinib maintenance without HCT.[156,157,295]

Management of R/R Ph-Positive ALL

As previously mentioned, the outcomes of pediatric patients with R/R B-ALL has been historically poor. In Ph-positive ALL, several mechanisms may contribute to this including the development of resistance to TKIs.[81] Several trials referenced in the algorithm have developed regimens that are currently used to treat R/R Ph-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 Ph-positive leukemia, including cases of ALL, AML, and chronic myeloid leukemia (CML) (n = 31).[300] 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.[300] In the COG AALL0031 study, pediatric patients with Ph-positive ALL who relapsed after initial treatment with imatinib and chemotherapy were able to achieve an overall CR2 rate of 67% (n = 20/30).[157] Of the patients who attained CR2, 85% (n = 17/20) remained in remission for at least 3 months.[157]

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 Ph-positive ALL who had progressed after imatinib and at least one second- or third-generation TKI (n = 45).[301] During the first two cycles of blinatumomab, 36% achieved CR or CRh, and 88% of these responders achieved a complete MRD response.[301] In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-cell ALL (Ph-negative and Ph-positive) and clinical studies described earlier include patients with R/R Ph-positive and Ph-negative ALL.[162,244-246] Several adult studies have tested the combination of blinatumomab and a TKI.[301,302] For discussion of these studies, see *Management of Relapsed or Refractory Ph-Negative or Ph-Like ALL*.

CAR T Cells

Clinical studies described earlier include patients with R/R Ph-positive and Ph-negative ALL.[164,280,303,304] For discussion of these studies, see *Management of Relapsed or Refractory Ph-Negative or Ph-Like ALL*.

Inotuzumab Ozogamicin

Clinical studies described earlier include patients with R/R Ph-positive and Ph-negative ALL.[288,289,291] For discussion of these studies, see *Management of Relapsed or Refractory Ph-Negative or Ph-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.[295] Treatment options are extremely limited for patients with Ph-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.[305-307]

NCCN Recommendations for Ph-Positive ALL

Front-Line Management: The panel recommends that pediatric and AYA patients with Ph-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. 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 and 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 Ph-Negative or Ph-Like ALL,* Front-Line Management). Of note, HCT is not required but may be considered for Ph-positive ALL in CR1.

R/R Management: The NCCN Panel recommendations for pediatric and AYA patients with R/R Ph-positive ALL are similar to what has been summarized for R/R Ph-negative or Ph-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.

Management of T-ALL

T-ALL is biologically distinct from B-ALL, but similar to B-ALL, MRD is a key prognostic determinant.[40] 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).[308] 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.[308]

Results from the efficacy phase of this study evaluated data from 1895 patients with newly diagnosed T-ALL and T-cell lymphoblastic leukemia.[309] Patients were randomized to receive escalating-dose MTX without leucovorin rescue and polyethylene glycol (PEG) or HD-MTX with leucovorin rescue. Patients with intermediate- and high-risk T-ALL and T-cell lymphoblastic leukemia all received prophylactic or therapeutic cranial irradiation and were 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 88.9% ± 2.2% and 83.3% ± 2.5%, respectively (*P* = .0332).[309] For patients randomized to receive HD-MTX, the addition of nelarabine appeared to enhance the 4-year DFS rate: no nelarabine, 78.0% ± 3.7% versus with nelarabine, 86.2% ± 3.2%; *P* = .024.[309]

Another report from the COG AALL0434 study investigated the impact of two different approaches to MTX intensification on pediatric T-ALL outcomes.[111] All patients without CNS3 disease or testicular leukemia were randomized to receive an augmented BFM chemotherapy regimen with either C-MTX (n = 519) or HD-MTX (n = 512) during the 8-week IM phase.[111] The estimated 5-year DFS and OS rates in the C-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).[111] These data demonstrate that C-MTX combined with chemotherapy is superior to HD-MTX and chemotherapy in patients with T-ALL.[111]

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 = 97).[110] With a median follow-up of 4.3 years, the 4-year EFS and OS rates were 83% and 89%, respectively. EOI MRD, assessed by PCR, was evaluable in 58 (67%) patients who achieved CR, and high MRD was associated with inferior DFS.[110]

The DFCI ALL Consortium Protocol 11-001, as previously discussed in *Front-Line Management of Ph-Negative or Ph-Like ALL*, also included pediatric patients with newly diagnosed T-ALL.[238] 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.[310]

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.[311] However, HCT in CR1 is not indicated in the contemporary protocols unless MRD is positive.

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.[40] 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).[160] 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-cell lymphoblastic lymphoma in a phase II study (n = 39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, n = 26).[312] 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.[312]

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-cell lymphoblastic lymphoma (n = 23).[313] Of evaluable patients with R/R T-ALL (n = 12), a 33% response rate was observed.

Bortezomib-Based Regimens

The referenced study, COG AALL07P1, evaluating a bortezomib-containing regimen included pediatric patients with R/R T-ALL.[255] For a summary, refer to *Management of Relapsed or Refractory Ph-Negative or Ph-Like ALL*.

UKALL R3

The referenced study, UKALL R3, evaluating the effect of mitoxantrone in multiple risk-stratified chemotherapy blocks included pediatric patients with R/R T-ALL.[223,251] For a summary, refer to *Management of Relapsed or Refractory Ph-Negative or Ph-Like ALL*.

ALL-REZ BFM 90

The referenced study, ALL-REZ BFM 90, evaluating risk-stratified multi-chemotherapy blocks included pediatric patients with R/R T-ALL.[253] For a summary, refer to *Management of Relapsed or Refractory Ph-Negative or Ph-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.[40] In the COG AALL01P2 study, most patients with T-ALL (n = 5 of 7) did not achieve CR2.[254] In the MRC UKALL R1 trial, compared to chemotherapy alone, allogeneic HCT did not significantly improve EFS in pediatric patients with R/R ALL.[314]

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. 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 chemotherapy. 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

they subsequently respond 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.[60] However, infant patients are especially vulnerable to treatment-related toxicities, so clinical trials are continually investigating novel strategies to reduce this.[60] 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.[62] 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.[62] 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 complete remission (312 patients in the standard-risk group and 133 patients in the high-risk group).[62] At a median follow-up of 38 months (range, 1–78 months), 58% of patients (n = 260) who underwent hybrid treatment were in complete remission 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.[62] In addition, before the maintenance phase, a subset of patients in complete remission were randomly assigned to receive either standard treatment or more intensive chemotherapy with high-dose cytarabine and MTX, which did not improve outcomes.[62]

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.[14,315,316] Based on the hypothesis that early hematopoietic precursors with myeloid differentiation potential would elicit improved responses to chemotherapy regimens developed for AML,[60] the Interfant-06 trial investigated whether consolidation with myeloid-style chemotherapy was superior to lymphoid-style chemotherapy in infant patients with ALL (n = 651).[14] 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 other *KMT2A*-rearranged cases; 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.[14] The 6-year probability of DFS was comparable for the randomized arms (ADE+MAE 39.3% vs. IB 36.8%; log-rank P = .47).[14]

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*.[221] 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%).

An ongoing prospective, single arm, phase 2 study is evaluating the safety and efficacy of adding blinatumomab to the Interfant-06 backbone.[317] 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 to high MRD at EOI (76% vs. 18%; *P* = .0056). The 1-year EFS (± SE) was 96.2 ± 3.8. Longer follow-up is awaited. The addition of blinatumomab was overall well tolerated, with a total of 70 adverse events noted, with the most frequent grade >3 adverse events being febrile neutropenia (n = 2), anemia (n = 5), and elevated gamma-glutamyltransferase (GGT) (n = 2).

COG AALL0631

Based on data showing aberrant activation of FLT3 pathway in infant ALL with KMT2A rearrangements,[318-320] 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.[60,321] Initial induction consisted of 3 weeks of therapy based on a COG P9407 backbone (Cohort 1).[321,322] 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.[321] 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).[321] 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%]) vs. Cohort 1 (week 7, n = 17/25 [68%]; *P* = .0012).[321] The addition of lestaurtinib did not demonstrate a benefit in outcomes.[60]

Hematopoietic Cell Transplant

The benefit derived from using HCT in infant leukemia is unclear.[60] Several retrospective studies suggest no clinical advantage or a benefit at low EFS rates.[323] 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) appeared to benefit from HCT in CR1 over chemotherapy alone.[153]

Management of R/R Infant ALL

Infant patients with R/R ALL have poor outcomes and few studies have focused on this specific group.[324,325] 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. Alternatively, patients

who achieved MRD negativity after induction will continue risk-stratified chemotherapy similar to what has been described for Ph-negative or Ph-like ALL. Patients with MRD positivity after induction may undergo intensified consolidation therapy. For patients with MRD positivity ≥5x10^{-4} at the EOI therapy, myeloid type consolidation therapy (eg, ADE/MAE) can be considered.[221] In all cases, 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. 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 at the time of transplant.[326] 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 Ph-negative or Ph-like ALL.

Evaluation and Treatment of Extramedullary Disease

Control of CNS disease is a key part of pediatric ALL therapy[112] and CNS leukemia at diagnosis is associated with significantly decreased EFS rates.[113,118,327] CNS leukemia is defined by a WBC count of at least 5 leukocytes/μL in the cerebrospinal fluid (CSF) with the presence of lymphoblasts.[120] 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 less than 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/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% of cases), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.[120]

Factors associated with an increased risk for CNS relapse in children include T-cell immunophenotype, high WBC counts at presentation, Ph-positive disease, t(4;11) translocation, and presence of leukemic cells in the CSF.[128] CNS-directed therapy may include IT chemotherapy (eg, MTX, cytarabine, corticosteroids), cranial irradiation, and/or systemic chemotherapy (eg, HD-MTX, cytarabine, pegaspargase).[113,120]

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.[27,112,128] 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.[113,121]

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.[113,328] 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.[113,328] 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).[113,328] 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).[113] 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.[113,328]

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 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, see NCCN Guidelines for Survivorship/Long-Term Psychosocial and Physical Problems. In addition, the COG has published guidelines on long-term survivorship issues for survivors of childhood cancers.[329]

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% by flow or molecular testing. For a CR, absolute neutrophil counts (ANCs) should be greater than 1000/μL and platelet counts should be greater than 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 less than 1000/μL or the platelet count remains less than 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 greater); 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 Ph-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;[330] therefore, monitor for healthy weight and encourage healthy lifestyle choices. Further recommendations for survivorship are available in the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology and NCCN Guidelines for Survivorship. 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.[329] 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[331] or institutional standards) should be evaluated by a medical provider and treated promptly with broad-spectrum antibiotics, regardless of neutrophil count.

Patients with ALL should take appropriate antibacterial and antifungal prophylaxis throughout therapy[332,333] 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.[334] 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 high-dose 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.[332,333,335] 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.[336,337]

Some antifungal agents (azoles) have potential interactions with vincristine and should be used with caution.[338,339] G-CSF, 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 serious/life-threatening situations 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).

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.[340] 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.[341] 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.[342] 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 on admission if uric acid levels are less than 8 mg/dL and there is no evidence of renal dysfunction. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function.

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 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 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.[343] 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.[344] 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.[345] 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.[345-347] An MRI may help distinguish between MTX-induced neurotoxicity and posterior reversible encephalopathy syndrome (PRES). Patients who present with seizures may benefit from antiepileptics—preferably non-hepatic enzyme inducers such as levetiracetam[348] and lacosamide[349] 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.[350] 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.[351,352] Although a study observed that dexrazoxane may be associated with a risk of developing secondary malignancies,[353] other subsequent studies have not observed this phenomenon.[354,355]

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. 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.[356,357] In this context, adding a physiologic dose of hydrocortisone (10 mg/m^2/day) to dexamethasone may reduce the occurrence of serious neuropsychological adverse effects and sleep-related difficulties in pediatric patients with ALL.[358] In addition, 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.[358]

A potential long-term side effect associated with steroid therapy includes osteonecrosis/avascular necrosis.[359,360] 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.[359,361-365] 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.[365] There is no evidence for vitamin D and calcium replacement in pediatric patients regarding the prevention and treatment of osteonecrosis/avascular necrosis.[366-368]

Vincristine Management

Vincristine is an essential chemotherapeutic agent in many ALL regimens that is associated with dose-limiting neurotoxicity.[369] 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 or veno-occlusive disease of the liver is an adverse effect that can be associated with 6-TG.[370] Defibrotide may be used in severe cases.[371,372]

Hyperleukocytosis Management

Hyperleukocytosis (leukostasis) occurs most often in patients generally with a highly elevated WBC count (usually >200 × 10^9/L), T-cell immunophenotype, *BCR::ABL1*, and infants with *KMT2A* rearrangement.[373-375] Leukapheresis has been demonstrated to decrease complications of leukostasis in patients with ALL, but in cases of hyperleukocytosis without symptoms of leukostasis, leukapheresis does not provide clinical advantage over aggressive chemotherapy. Leukapheresis may also be associated with adverse outcomes.[376,377]

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 IT chemotherapy, neurocognitive monitoring during therapy should be

considered for all patients.[378] 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.[379] 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.[380] 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.[378] 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 greater than 10% weight loss, appetite stimulants, or enteral or parenteral nutritional support should be considered. The increased risk of obesity in pediatric patients with ALL[381] 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 employed 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.[382-384] 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, and Pancreatic).

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.[385] Three different formulations of the enzyme are in clinical use: 1) pegaspargase; 2) calaspargase; and 3) ERW-rywn. Asparaginase products are associated with potentially severe hypersensitivity reactions (including anaphylaxis) due to anti-asparaginase or anti-PEG antibodies.[386-389] These reactions may be (though not always) associated with the production of neutralizing antibodies and lack of asparaginase activity.[390-392] ERW-rywn is used for patients who develop allergic reactions to E. coli-derived asparaginase. With IV pegaspargase, 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, with concurrent infusion of saline

and use of anti-allergy premedication (eg, hydrocortisone, diphenhydramine, famotidine, acetaminophen), can reduce these reactions.[388,393]

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.[393,394] 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.[395,396] However, this practice is not currently recommended in the guidelines.

Asparaginase is associated with other toxicities, including pancreatitis[397,398] (ranging from asymptomatic cases with amylase or lipase elevation, to symptomatic cases with vomiting or severe abdominal pain), hepatotoxicity (eg, increased alanine or glutamine aminotransferase, hyperbilirubinemia), and coagulopathy (eg, thrombosis, hemorrhage). For detailed recommendations regarding the management of these toxicities, see the *Principles of Supportive Care* in the algorithm.

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