National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Aggressive Mature B-Cell Lymphomas

Version 2.2025 — April 28, 2025

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pediatric Aggressive Mature B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

***Matthew Barth, MD/Chair €**
Roswell Park Comprehensive Cancer Center | Roswell Park Oishei Children's Cancer and Blood Disorders Program

***Ana C. Xavier, MD/Vice-Chair €**
O'Neal Comprehensive Cancer Center at UAB | Children's of Alabama

Melissa Acquazzino, MD, MS € ‡
Fred & Pamela Buffett Cancer Center | Children's Hospital & Medical Center

Saro Armenian, DO, MPH € ‡
City of Hope National Medical Center

***Anthony N. Audino, MD €**
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute | Nationwide Children's Hospital

Lindsay Blazin, MD, MPH €
Indiana University Melvin and Bren Simon Comprehensive Cancer Center | Riley Children's Health

David Bloom, MD ф
University of Michigan Rogel Cancer Center | C.S. Mott Children's Hospital

Wendi Bryson, BS ¥
Thrifty Portable Buildings, Inc.

Kimberly Davies, MD €
Dana-Farber | Boston Children's Cancer and Blood Disorders Center

Jeanne Dillenbeck, MD € ф
UT Southwestern Simmons Comprehensive Cancer Center | Children's Medical Center Dallas

Hilda Ding, MD, MS €
UC San Diego Moores Cancer Center | Rady Children's Hospital-San Diego

Yang Ding, MD € ‡
Johns Hopkins Kimmel Cancer Center | Johns Hopkins Children's Center

Adam DuVall, MD, MPH € ‡
The UChicago Medicine Comprehensive Cancer Center

Nicholas Figura, MD §
Moffitt Cancer Center

Paul J. Galardy, MD €
Mayo Clinic Comprehensive Cancer Center

Amber Gibson, DO €
The University of Texas MD Anderson Cancer Center

Rabi Hanna, MD € ξ
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute | Cleveland Clinic Children's

Robert Hayashi, MD € ξ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine | St. Louis Children's Hospital

Cathy Lee-Miller, MD €
University of Wisconsin Carbone Cancer Center | American Family Children's Hospital

Kris Mahadeo, MD, MPH ξ
Duke Cancer Institute | Duke Children's Hospital & Health Center

Kelly W. Maloney, MD €
University of Colorado Cancer | Children's Hospital Colorado

***Lianna Marks, MD €**
Stanford Cancer Institute | Lucile Packard Children's Hospital

Arun Ranjan Panigrahi, MD € ‡
UC Davis Comprehensive Cancer Center

Kellee Parker, DO € ‡
Huntsman Cancer Institute at the University of Utah | Primary Children's Hospital

Anne F. Reilly, MD, MPH €
Abramson Cancer Center at the University of Pennsylvania | Children's Hospital of Philadelphia

Mikhail Roshal, MD, PhD ≠
Memorial Sloan Kettering Cancer Center

Brianna Smith, MD, MS ‡
Vanderbilt-Ingram Cancer Center | Monroe Carell Jr. Children's Hospital at Vanderbilt

***Sophie Song, MD, PhD ≠**
UCLA Jonsson Comprehensive Cancer Center | UCLA Mattel Children's Hospital

Amy Fowler Tellinghuisen, MD €
Fred Hutchinson Cancer Center | Seattle Children's Hospital

Joanna Weinstein, MD €
Robert H. Lurie Comprehensive Cancer Center of Northwestern University | Ann & Robert H. Lurie Children's Hospital of Chicago

NCCN
Ryan Schonfeld, BA
Hema Sundar, PhD

[NCCN Guidelines Panel Disclosures]

Continue

ξ Bone marrow transplantation
ф Diagnostic radiology
‡ Hematology/Hematology oncology
Þ Internal medicine
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
§ Radiotherapy/Radiation oncology
* Discussion Writing Committee Member

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pediatric Aggressive Mature B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

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 to Version 2.2025 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 1.2025 include:

MS-1
• The discussion was updated to reflect the changes in the algorithm.

Updates to Version 1.2025 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 2.2024 include:

PBCL-1
• Subtypes moved to PBCL-2.
• Additional diagnostic testing moved to header.
• New node: Post-Transplant Lymphoproliferative Disorders (PTLD) after solid organ transplant (SOT)
• Footnote c revised: Principles of Diagnostic Pathology (PBCL-A). *See also the Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A) in the NCCN Guidelines for B-Cell Lymphomas.* (Also for subsequent pages)

PBCL-2
• Additional Diagnostic Testing
  ▸ Useful Under Certain Circumstances
    ◊ Bullet 4 revised: IHC/ISH Panel: MYC *(IHC)* and Kappa/Lambda (ISH)
• Footnote e revised: Typical immunophenotype of PMBL: sIg-, B-cell antigens+ (CD19+, CD20+, CD79a+, and PAX5+), CD23+, CD30+, MUM1+, BCL2+/-, and BCL6+/-. EBV-EBER is negative. ~~See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A) in the NCCN Guidelines for B-Cell Lymphomas.~~
• Footnote i revised: Double- and triple-hit lymphomas *(HGBL with MYC and BCL2 or BCL6 rearrangements)* are currently not well described or studied in the pediatric population but FISH for BCL2 and BCL6 rearrangements may be considered in the AYA population. *Pediatric HGBL is treated with the same regimens as pediatric BL.*
• Footnote k revised: This is an uncommon variant of BL without MYC rearrangement but with 11q aberration (Campo E, et al. Blood 2022;140:1229-1253; ~~Alaggio R, et al. Leukemia 2022;36:1720-1748~~ *WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. [WHO classification of tumours series, 5th ed; vol 11]. Lyon [France]: International Agency for Research on Cancer; 2024*). Optimum management of this rare subtype is undefined, although it is most often treated like typical BL.

PBCL-3
• Workup
  ▸ Essential
    ◊ Bullet 7, sub-bullet 1 revised: *Cerebrospinal fluid (CSF)* cell count and differential
    ◊ Bullet 7, sub-bullet 2 revised: Cytology *of CSF*, including total nucleated cell count and morphologic review of cytospin
  ▸ Useful Under Certain Circumstances
    ◊ Bullet 1 revised: MRI of the head *with and without contrast*, if clinically indicated
    ◊ Bullet 2 revised: MRI of the spine *with and without contrast*, if clinically indicated
    ◊ Last bullet revised: Consider baseline immunoglobulin panel prior to using rituximab or *if there are any underlying concerns about immunodeficiency*
• Column 2, top pathway, bullets added:
  ▸ LBCL with IRF4/MUM1 rearrangement
  ▸ HGBL with 11q aberrations
  ▸ HGBL with MYC and BCL2 or BCL6 rearrangements

PBCL-4
• Staging
  ▸ Stage I revised: *Single tumor (extranodal) or single anatomical area (nodal), with exclusion of mediastinum and abdomen* ~~A single tumor not in the mediastinum and abdomen~~

Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma

PBCL-7
• Footnote ee revised: *An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.* ~~An FDA-approved biosimilar is an appropriate substitute for rituximab.~~ (Also for PBCL-8, 9, 11 and as footnote d on PMBL-1)

PBCL-10
• Late effects monitoring
  ▸ Bullet 1 revised: Attention to cardiac, gonadal, and neurocognitive function, bone health, and risk of secondary leukemia. (See Children's Oncology Group Survivorship Guidelines; *see also the NCCN Guidelines for Survivorship*) (Also for PMBL-1)
  ▸ Bullet 2 added: Psychosocial support and counseling: See NCCN Guidelines for Distress Management. (Also for PMBL-1)

Continued

Updates to Version 1.2025 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 2.2024 include:

Primary Mediastinal Large B-Cell Lymphoma

PMBL-1
- Induction therapy/initial treatment
  - Added after clinical trial (preferred): In the absence of a clinical trial, suggested regimens include: (Also for PMBL-2)
  - Bullet 1 revised: Dose-adjusted-EPOCH-R *(preferred)* (6 cycles)
- Footnote e revised: *Avoidance of RT is strongly preferred in pediatric patients to reduce the risk of late complications from normal tissue damage.* There are not enough data on the use of RT in pediatric patients *with PMBL. When RT is used, it should be delivered using advanced RT techniques to minimize dose to organ at risk (OAR) (heart, cardiac substructures, lungs, breast, spinal cord, etc). See Principles of Radiation Therapy in the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Recommendations for normal tissue dose constraints can be found in Principles of Radiation Therapy in the NCCN Guidelines for Hodgkin Lymphoma.* (Also for PMBL-2)

PMBL-2
- Treatment
  - Last bullet: Brentuximab vedotin + nivolumab was added as a category 2A recommendation.

PBCL-B 9 of 15
- Principles of Systemic Therapy
  - ◊ Header revised: ~~Preferred~~ Regimens for Induction Therapy (Also for PBCL-B 11 through 13)
  - ◊ Bullet 1 revised: Dose Adjusted-EPOCH-R (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab) *(preferred)*

PBCL-B 10 of 15
- Bullet 5 revised: If ANC <1x 10^9/l or platelets <100 x 10^9/l on day 21, delay up to 1 week. Granulocyte colony-stimulating factor (G-CSF) *(eg, pegfilgrastim)* may be started for ANC <1x 10^9/l and stopped 24 hours before treatment. If counts still low after 1-week delay, decrease 1 dose level below last course.

PBCL-B 14 of 15
- Footnote b added: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
- Footnote i revised: *Avoidance of RT is strongly preferred in pediatric patients to reduce the risk of late complications from normal tissue damage.* There are not enough data on the use of RT in pediatric patients *with PMBL. When RT is used, it should be delivered using advanced RT techniques to minimize dose to OAR (heart, cardiac substructures, lungs, breast, spinal cord, etc). See Principles of Radiation Therapy in the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Recommendations for normal tissue dose constraints can be found in Principles of Radiation Therapy in the NCCN Guidelines for Hodgkin Lymphoma.*
- Footnote removed: An FDA-approved biosimilar is an appropriate substitute for rituximab.

PBCL-D 2 of 4
- Principles of Supportive Care
  - Mass Legions at Presentation
    - ◊ Bullet 1 revised: In pediatrics, there are multiple publications of spinal cord compression, massive kidney enlargement, intussusception, ovarian masses, chest masses, and facial masses. *There may be increased risk of thrombosis due to mass lesions.*

Pediatric Post-Transplant Lymphoproliferative Disorders
- New pages added for the diagnosis and management of pediatric post-transplant lymphoproliferative disorders (PTLD).

NCCN Guidelines Version 2.2025
Pediatric Aggressive Mature B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

DIAGNOSIS[a,b,c]

- **Biopsy**
  - **Excisional or incisional biopsy of most accessible site is preferred.**
  - **Touch preparations of fresh lesional tissue should be encouraged whenever possible since, if done properly, they may reveal essential cytologic details that may be difficult to detect in small biopsies (eg, small needle core biopsy).**
  - **A core needle biopsy is less optimal but can be used in circumstances when a lymph node or tumor mass is not easily accessible for excisional or incisional biopsy.**
  - **Cores must be of sufficient size and number to allow for adequate evaluation of morphology, and all necessary ancillary studies (immunohistochemistry [IHC], flow cytometry, karyotype, and fluorescence in situ hybridization (FISH) for major translocations, as applicable).**
  - **A fine-needle aspiration (FNA) biopsy alone is not suitable for the initial diagnosis of pediatric lymphoma.**
  - **Place fresh specimen in saline, not formalin, ensuring viable diagnostic tissue for the pathologist.**
- **Pathology[c]**
  - **Hematopathology review of all slides as clinically indicated.**
  - **Touch preparation for cytologic examination is recommended.**

ADDITIONAL DIAGNOSTIC TESTING

- **Aggressive Mature B-cell Lymphomas** → **PBCL-2**
- **Posttransplant Lymphoproliferative Disorders (PTLD) after solid organ transplant (SOT)** → **PTLD-1**

[a] The Pediatric Aggressive Mature B-Cell Lymphomas Panel considers “pediatric” to include any patient aged 18 years and younger, and adolescent and young adult (AYA) patients older than 18 years of age (and <39 years of age as defined by the National Cancer Institute), who are treated in a pediatric oncology setting. Practice patterns vary with regards to AYA patients from center to center in terms of whether AYA patients with mature B-cell lymphoma are treated primarily by pediatric or adult oncologists. These guidelines are intended to apply to AYA patients with good organ function treated in a pediatric oncology setting. AYA patients treated in an adult oncology setting should be treated as per the adult NCCN Guidelines for B-Cell Lymphomas.

[b] Also see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

[c] Principles of Diagnostic Pathology (PBCL-A). See also the Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A) in the NCCN Guidelines for B-Cell Lymphomas.

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

NCCN Guidelines Version 2.2025
Pediatric Aggressive Mature B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

ADDITIONAL DIAGNOSTIC TESTING[c]

ESSENTIAL

- **Adequate immunophenotyping to establish diagnosis[d,e,f]**
  - **IHC panel for BL and DLBCL: Ki-67, BCL2, BCL6, CD3, CD10, CD20, IRF4/MUM1**
  - **IHC panel for PMBL: CD10, CD19, CD20, PAX5, CD23, CD30, BCL2, BCL6, IRF4/MUM1, and Ki-67; EBV is absent**
  - **Flow cytometry: Surface kappa/lambda, CD3, CD5, CD10, CD19, CD20, CD22, CD23, and CD45**
- **Karyotype or FISH: *MYC* rearrangement[g]**

USEFUL UNDER CERTAIN CIRCUMSTANCES

- **Karyotype: t(8;14) or variants t(2;8) or t(8;22) to identify additional chromosomal abnormalities**
- **FISH or single nucleotide polymorphism (SNP) array for 11q aberration**
- **Epstein-Barr virus-encoded RNA in-situ hybridization (EBER-ISH)[h]**
- **IHC/ISH Panel: MYC (IHC) and kappa/lambda (ISH)**
- **IHC for CD56 in absence of CD38 bright by flow cytometry (for HGBL with 11q aberrations)**
- **Karyotype or FISH for *IRF4/MUM1, BCL2,* and *BCL6* rearrangements[i]**
- **TdT IHC or flow cytometry**
- **Clonality testing by polymerase chain reaction (PCR) for immunoglobulin gene rearrangement**

→

SUBTYPES

- **Burkitt lymphoma (BL)[j]**
- **Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)[j]**
- **Large B-cell lymphoma (LBCL) with *IRF4/MUM1* rearrangement**
- **LBCL with 11q aberration (International Consensus Classification [ICC])/High-grade B-cell lymphoma (HGBL) with 11q aberrations (WHO5)[k]**
- **HGBL with *MYC* and *BCL2* or *BCL6* rearrangements (ICC); DLBCL/HGBL with *MYC* and *BCL2* rearrangements (WHO5)[i]**
- **Primary mediastinal large B-cell lymphoma (PMBL)[l]**

→ Workup (PBCL-3)

[c] Principles of Diagnostic Pathology (PBCL-A). See also the Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A) in the NCCN Guidelines for B-Cell Lymphomas.

[d] Typical immunophenotype of BL: sIg+, CD10+, CD20+, TdT-, Ki-67+ (≥95%), BCL2-, BCL6+, simple karyotype with MYC rearrangement as sole abnormality. Typical immunophenotype of DLBCL: sIg+, CD20+, TdT-, Ki-67 variably high, CD10+/-, BCL6+/-, MUM1+/-, BCL2+/-, variable karyotype with MYC, BCL6, BCL2, and/or other IGH rearrangements.

[e] Typical immunophenotype of PMBL: sIg-, B-cell antigens+ (CD19+, CD20+, CD79a+, and PAX5+), CD23+, CD30+, MUM1+, BCL2+/-, and BCL6+/-. EBV-EBER is negative.

[f] If flow cytometry is initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the results of flow cytometry.

[g] On formalin-fixed, paraffin-embedded tissue, *MYC* rearrangement is best assessed by *MYC* break apart probe to capture any partner gene.

[h] EBER-ISH is most applicable in endemic BL or immunocompromised clinical settings for either BL or DLBCL.

[i] Double- and triple-hit lymphomas (HGBL with *MYC* and *BCL2* or *BCL6* rearrangements) are currently not well described or studied in the pediatric population but FISH for *BCL2* and *BCL6* rearrangements may be considered in the AYA population. Pediatric HGBL is treated with the same regimens as pediatric BL.

[j] Pediatric BL and DLBCL are curable, but management is complex. It is preferred that treatment occur at centers with expertise in the management of these diseases.

[k] This is an uncommon variant of BL without *MYC* rearrangement but with 11q aberration (Campo E, et al. Blood 2022;140:1229-1253; WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. [WHO classification of tumours series, 5th ed; vol 11]. Lyon [France]: International Agency for Research on Cancer; 2024). Optimum management of this rare subtype is undefined, although it is most often treated like typical BL.

[l] PMBL can be defined as a clinical entity presenting with primary site of disease in the anterior mediastinum with or without other sites and histology of DLBCL. PMBL overlaps with mediastinal grey zone lymphomas that have features intermediate between PMBL and classic Hodgkin lymphoma, and have unique diagnostic characteristics.

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

WORKUP

ESSENTIAL

- History, including personal and family history of immunodeficiency
- Physical examination, with attention to lymph nodes, Waldeyer's ring, liver and spleen size, effusions, ascites, neurologic signs
- Evaluation for signs or symptoms of ureteral or bowel obstruction; spinal cord compression or cranial neuropathy
- Performance status (Lansky/Karnofsky)
- Labs
  - Complete blood count (CBC) with differential
  - Electrolytes, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, uric acid
  - Lactate dehydrogenase (LDH)
  - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin
  - Hepatitis B testing (HBcAb, HBsAb, HBsAg)
  - Consider HIV testing, if indicated
  - Consider glucose-6-phosphate dehydrogenase (G6PD) testing for male patients[m]
  - Pregnancy test for patients of childbearing age
- Bilateral bone marrow aspirate and biopsy
- Lumbar puncture
  - Cerebrospinal fluid (CSF) cell count and differential
  - Cytology of CSF, including total nucleated cell count and morphologic review of cytospin
- Imaging
  - Cross-sectional scans of the neck, chest, abdomen, and pelvis
    - ◊ Neck CT with IV contrast or MRI with and without contrast
    - ◊ Chest CT with IV contrast
    - ◊ Abdomen and pelvis CT with oral and IV contrast or MRI with and without contrast
  - FDG-PET/CT or FDG-PET/MRI, if available (do not delay treatment to obtain)[n]
  - Chest x-ray posteroanterior (PA)/lateral and abdominal ultrasound (if cross-sectional imaging not available)
- Echocardiogram (ECHO) or multigated acquisition (MUGA) scan and electrocardiogram (ECG)
- Fertility counseling recommended for all patients; fertility preservation[o] as clinically appropriate. See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology

USEFUL UNDER CERTAIN CIRCUMSTANCES

- MRI of the head with and without contrast, if clinically indicated
- MRI of the spine with and without contrast, if clinically indicated
- Flow cytometry of CSF[p]
- Flow cytometry, FISH for *MYC* rearrangement, and IHC of bone marrow[q]
- Consider baseline immunoglobulin panel prior to using rituximab or if there are any underlying concerns about immunodeficiency

- BL or DLBCL, NOS[r]
- LBCL with *IRF4/MUM1* rearrangement
- LBCL with 11q aberrations
- HGBL with *MYC* and *BCL2* or *BCL6* rearrangements

(PBCL-6)

PMBL (PMBL-1)

[m] Principles of Supportive Care (PBCL-D).
[n] Obtaining a PET/CT or PET/MRI does not exclude the need for full diagnostic quality high-resolution CT or MRI.
[o] Fertility preservation is an option for some patients. Options include sperm cryopreservation, oocyte cryopreservation, harvesting of ovarian or testicular tissue for cryopreservation, or embryo cryopreservation. Referral to a fertility preservation/reproductive health program should be considered for eligible patients prior to initiation of chemotherapy (Mulder RL, et al. Lancet Oncol 2021;22:e45-e56; Mulder RL, et al. Lancet Oncol 2021;22:e57-e67).
[p] Flow cytometry of CSF samples is not routinely recommended, but may be useful at the pathologist's discretion.
[q] For low-level or morphologically indeterminate involvement.
[r] See Staging (PBCL-4) and Risk Group Definitions (PBCL-5).

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

STAGING

International Pediatric Non-Hodgkin Lymphoma Staging System[s,t]	
Stage I	**Single tumor (extranodal) or single anatomical area (nodal), with exclusion of mediastinum and abdomen**
Stage II	**• A single extranodal tumor with regional node involvement • Two or more nodal areas on the same side of the diaphragm • A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable (if ascites or extension of the tumor to adjacent organs, it should be regarded as stage III)**
Stage III	**• Two or more extranodal tumors (including bone or skin) • Two or more nodal areas above and below the diaphragm • Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) • Intra-abdominal and retroperitoneal disease, including liver, spleen, ovary, and/or kidney localizations, regardless of degree of resection • Any paraspinal or epidural tumor, whether or not other sites are involved • Single bone lesion with concomitant involvement of extra-nodal and/or non-regional nodal sites.**
Stage IV	**Any of the above findings with initial involvement of the CNS,[u] bone marrow,[v] or both.**

See PBCL-5 for Risk Group Definitions

[s] Adapted with permission from Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. J Clin Oncol 2015;33:2112-2118.

[t] This is a revised version of the Murphy's St. Jude Staging from Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol 1980;7:332-339.

[u] The CNS is considered involved if one or more of the following applies:
- Any lymphoma cells by cytology in CSF
- Any CNS tumor mass by imaging
- Cranial nerve palsy (if not explained by extracranial tumor)
- Clinical spinal cord compression
- Parameningeal extension: cranial and/or spinal

[v] Stage IV disease, due to bone marrow involvement, is defined by morphologic evidence of any lymphoma cells in a bone marrow aspirate.

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

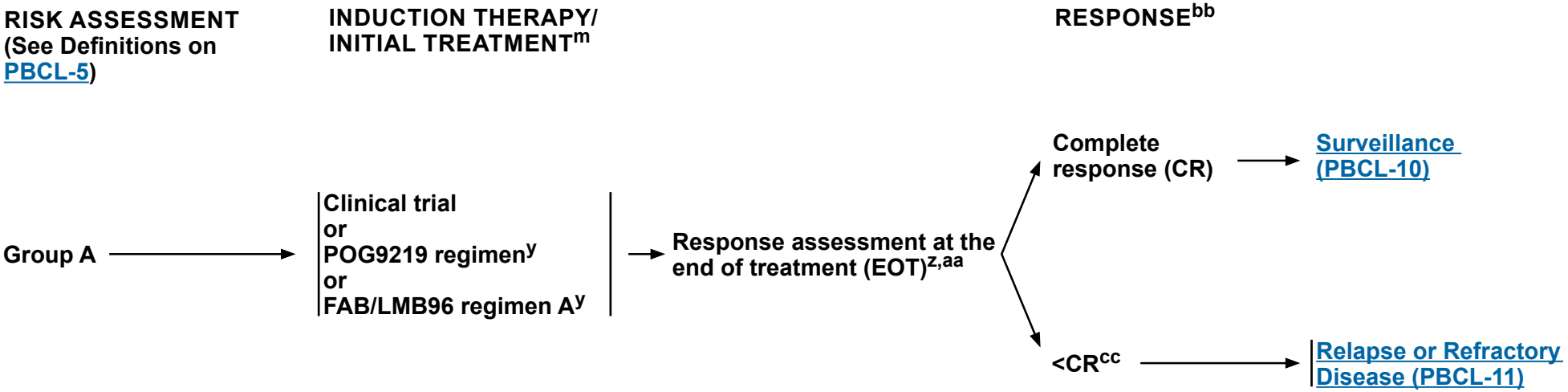
RISK GROUP DEFINITIONS

Group Classification (See PBCL-4 for Staging)		Induction Therapy/ Initial Treatment
Group A	Completely resected stage I or Completely resected abdominal stage II	PBCL-6
Group B (Low risk)[w]	Unresected stage I and non-abdominal stage II or stage III with low LDH (≤2 times the upper limit of normal [ULN])	PBCL-7
Group B (High risk)[w]	Stage III with high LDH (>2 times ULN), or all non-central nervous system (CNS) stage IV with bone marrow involvement (<25% lymphoma cells)	PBCL-8
Group C[x]	Any CNS involvement[u] and/or Bone marrow involvement (≥25% lymphoma cells)	PBCL-9

[u] The CNS is considered involved if one or more of the following applies:
- Any lymphoma cells by cytology in CSF
- Any CNS tumor mass by imaging
- Cranial nerve palsy (if not explained by extracranial tumor)
- Clinical spinal cord compression
- Parameningeal extension: cranial and/or spinal

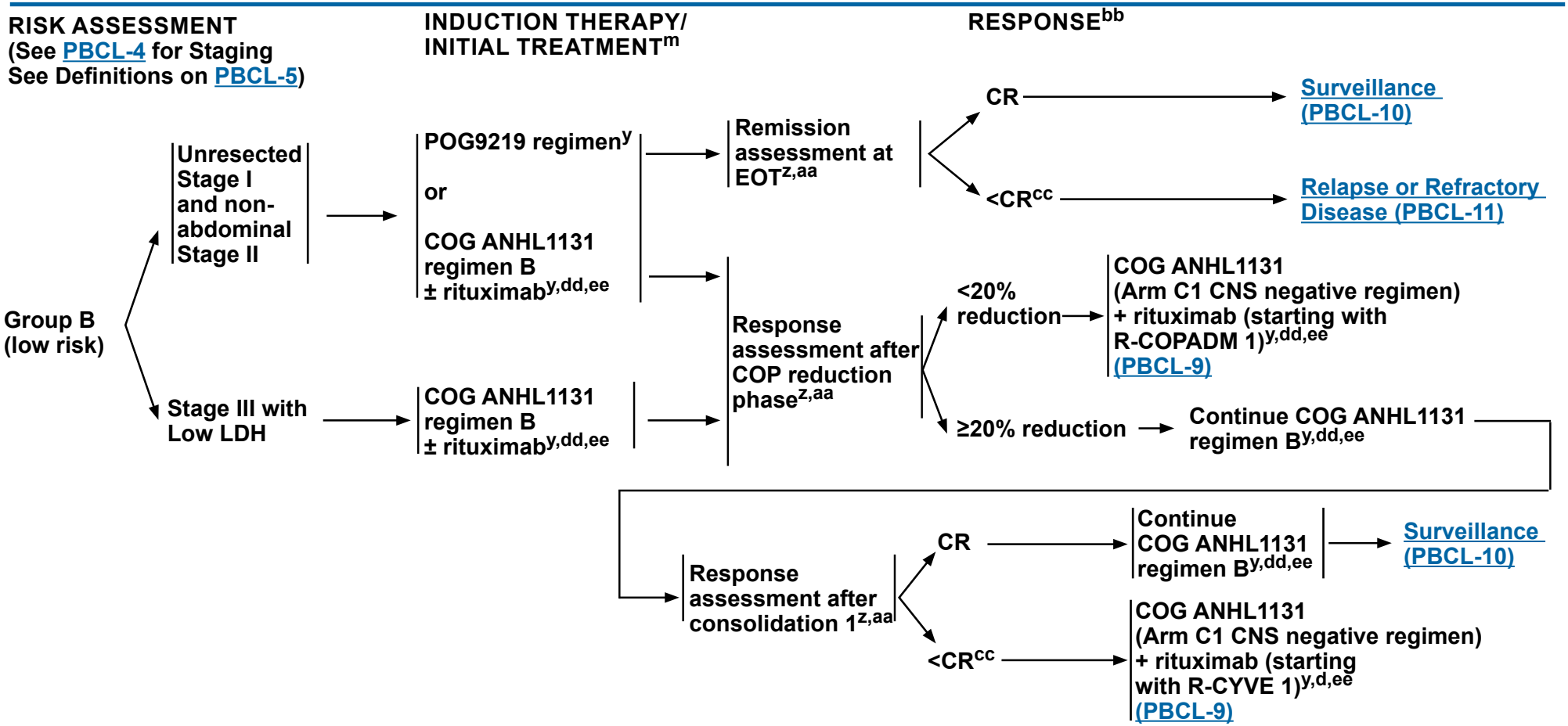
[w] Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. N Engl J Med 2020;382:2207-2219.
[x] Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736-2743.

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



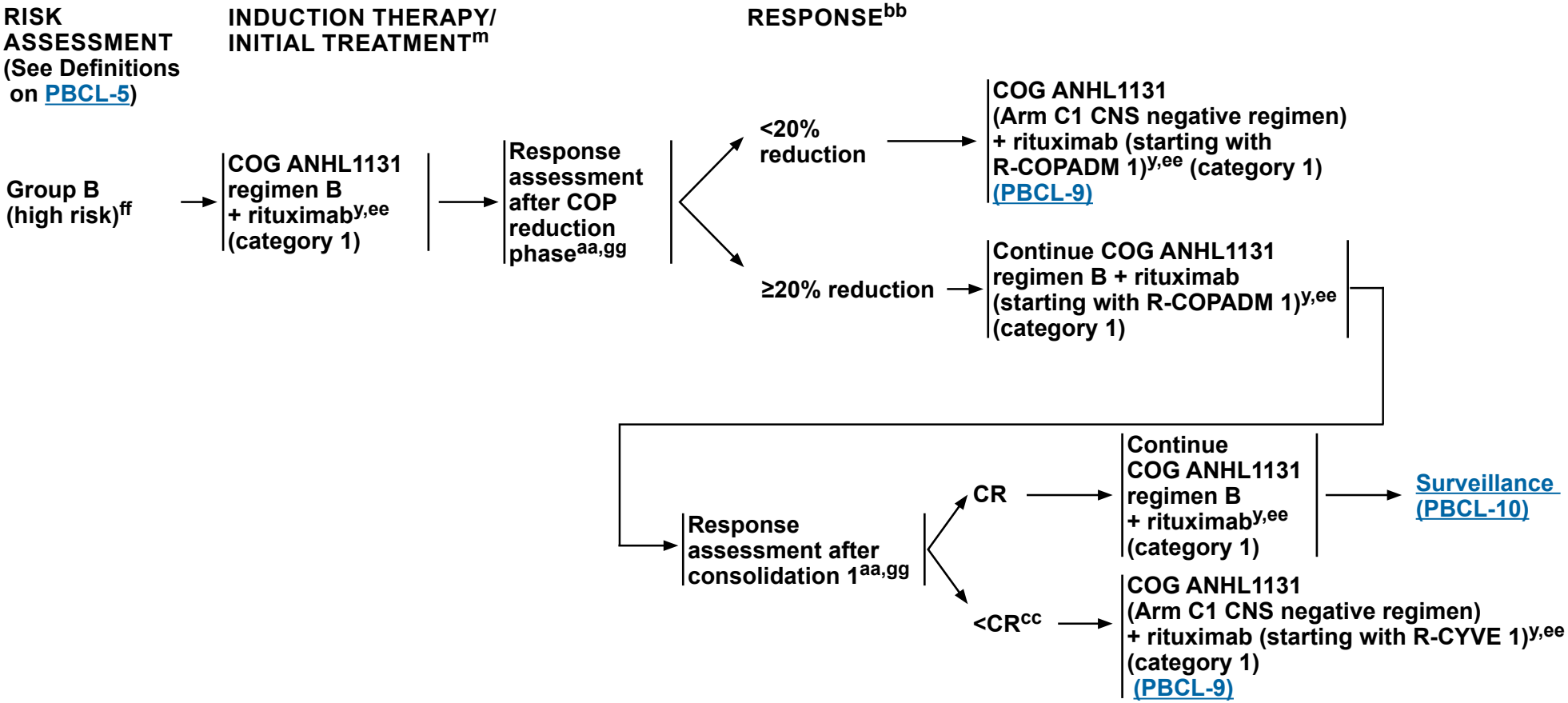
[m] Principles of Supportive Care (PBCL-D).
[y] Principles of Systemic Therapy (PBCL-B).
[z] Reassess sites of original disease with imaging studies as indicated (PBCL-3).
[aa] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. A patient's therapy should not be escalated based on FDG-PET alone. If a residual lesion is FDG-PET negative (Deauville 1, 2, or 3; PBCL-C 2 of 2), biopsy is not necessary. In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. False negatives are unusual. False positives are common.
[bb] Response Criteria (PBCL-C).
[cc] Repeat biopsy of residual mass should be considered prior to additional therapy.

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



m Principles of Supportive Care (PBCL-D).
y Principles of Systemic Therapy (PBCL-B).
z Reassess sites of original disease with imaging studies as indicated (PBCL-3).
aa FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. A patient's therapy should not be escalated based on FDG-PET alone. If a residual lesion is FDG-PET negative (Deauville 1, 2, or 3; PBCL-C 2 of 2), biopsy is not necessary. In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. False negatives are unusual. False positives are common.
bb Response Criteria (PBCL-C).
cc Repeat biopsy of residual mass should be considered prior to additional therapy.
dd Rituximab has not been tested in clinical trials in this patient group. However, in keeping with adult practice and data on efficacy and toxicity in patients at high risk, inclusion of rituximab in treatment of this patient population is deemed appropriate. Rituximab is included in induction/initial treatment, and should be continued throughout therapy. See Principles of Systemic Therapy (PBCL-B).
ee An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

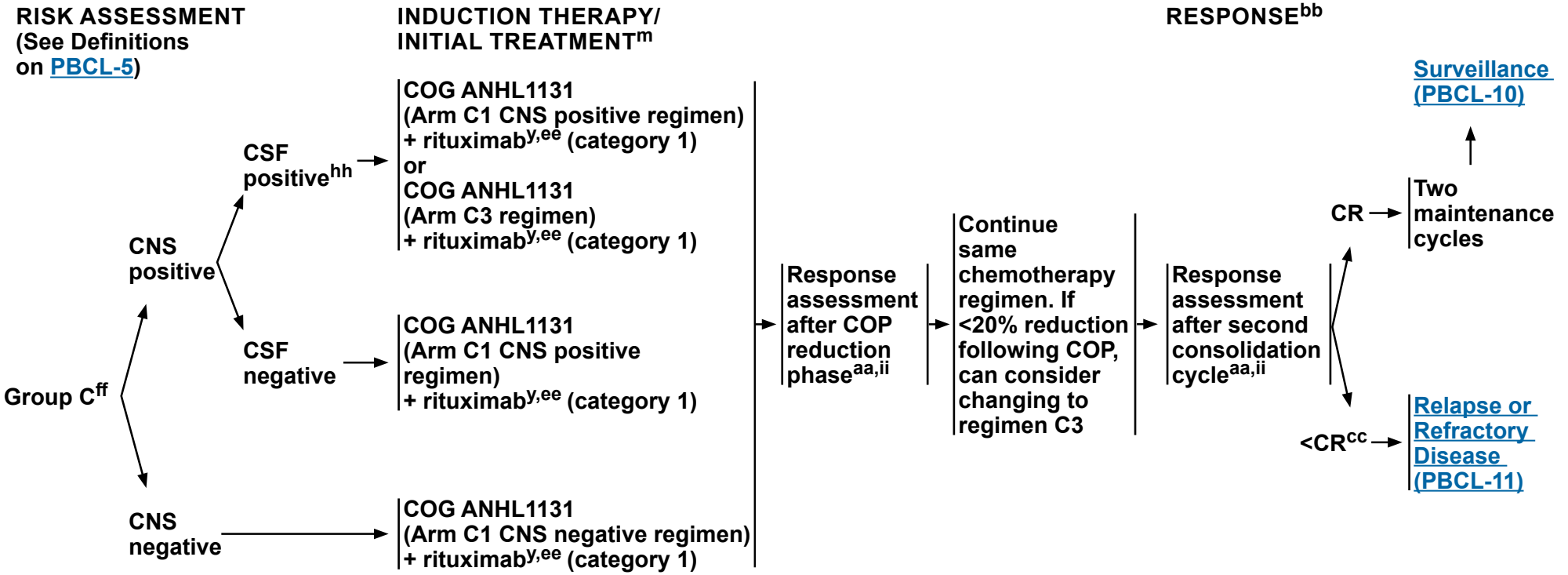
Note: All recommendations are category 2A unless otherwise indicated.



[m] Principles of Supportive Care (PBCL-D).
[y] Principles of Systemic Therapy (PBCL-B).
[aa] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. A patient's therapy should not be escalated based on FDG-PET alone. If a residual lesion is FDG-PET negative (Deauville 1, 2, or 3; PBCL-C 2 of 2), biopsy is not necessary. In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. False negatives are unusual. False positives are common.

[bb] Response Criteria (PBCL-C).
[cc] Repeat biopsy of residual mass should be considered prior to additional therapy.
[ee] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[ff] The addition of rituximab is a category 1 recommendation for patients with high-risk Group B and Group C disease. Minard-Colin V, et al. N Engl J Med 2020;382:2207-2219.
[gg] Reassess sites of original disease with imaging studies as indicated (PBCL-3). Bone marrow studies should also be performed if bone marrow was initially involved.

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



[m] Principles of Supportive Care (PBCL-D).
[y] Principles of Systemic Therapy (PBCL-B).
[aa] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. A patient's therapy should not be escalated based on FDG-PET alone. If a residual lesion is FDG-PET negative (Deauville 1, 2, or 3; PBCL-C 2 of 2), biopsy is not necessary. In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. False negatives are unusual. False positives are common.
[bb] Response Criteria (PBCL-C).
[cc] Repeat biopsy of residual mass should be considered prior to additional therapy.
[ee] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[ff] The addition of rituximab is a category 1 recommendation for patients with high-risk Group B and Group C disease. Minard-Colin V, et al. N Engl J Med 2020;382:2207-2219.
[hh] COG protocol ANHL1131 distinguished between lymphomatous CNS or parameningeal disease (CNS+) and lymphoma cells in the CSF (CSF+). Patients with CSF+ were treated on arm C3. The relative efficacy of the arm C1 and arm C3 regimens has not been evaluated. Therefore, either regimen is an acceptable choice for treatment of patients with CSF+.
[ii] Reassess sites of original disease with imaging studies as indicated (PBCL-3). Bone marrow and CSF studies should also be performed if bone marrow or CSF were initially involved.

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

SURVEILLANCE/FOLLOW-UP

- **H&P**
  - **BL[jj]**
    - ◊ **Every 1–3 months for 1 year**
    - ◊ **Then every 3 months for year 2**
    - ◊ **Then every 6 months for year 3**
    - ◊ **Then annually**
  - **DLBCL**
    - ◊ **Every 3 months for 3 years**
    - ◊ **Then annually**
- **CBC with differential**
  - **Monthly until counts are normal then at each examination visit**
- **Routine surveillance imaging is not recommended. Reassess sites of original disease with imaging studies as indicated (PBCL-3), only if clinical suspicion of relapse.**

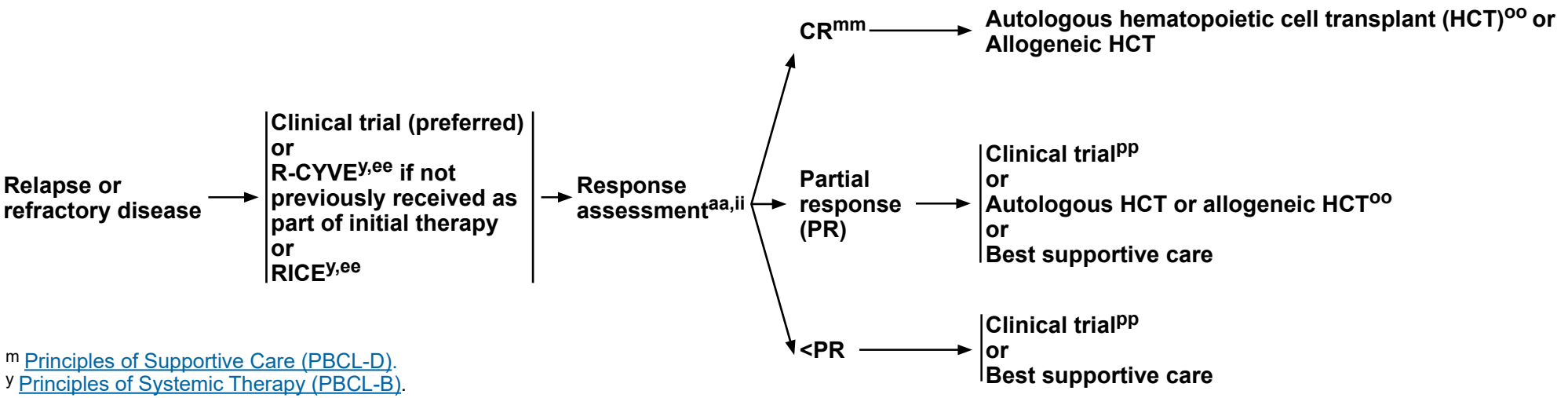
→ **Relapse[kk]** → **Relapse or Refractory Disease (PBCL-11)**

LATE EFFECTS MONITORING

- **Attention to cardiac, gonadal, and neurocognitive function, bone health, and risk of secondary leukemia.**
  (See Children's Oncology Group Survivorship Guidelines; see also the NCCN Guidelines for Survivorship)
- **Psychosocial support and counseling: See NCCN Guidelines for Distress Management.**

[jj] More frequent follow-up may be needed if the patient is symptomatic.
[kk] Pathologic confirmation of relapse is recommended before starting therapy for relapsed disease, and restaging workup should be completed as for initial diagnosis.

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



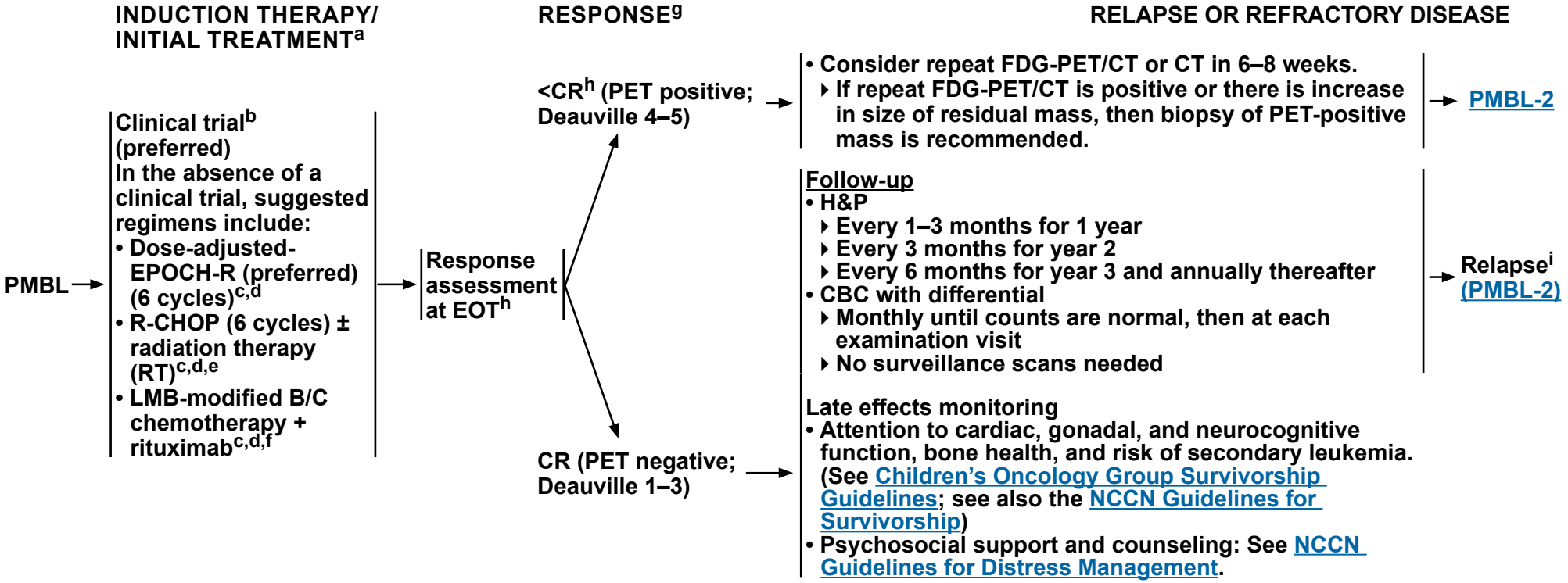
[m] Principles of Supportive Care (PBCL-D).
[y] Principles of Systemic Therapy (PBCL-B).
[aa] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. A patient's therapy should not be escalated based on FDG-PET alone. If a residual lesion is FDG-PET negative (Deauville 1, 2, or 3; PBCL-C 2 of 2), biopsy is not necessary. In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. False negatives are unusual. False positives are common.
[bb] Response Criteria (PBCL-C).
[ee] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[ii] Reassess sites of original disease with imaging studies as indicated (PBCL-3). Bone marrow and CSF studies should also be performed if bone marrow or CSF were initially involved.
[ll] It is rare for patients with Group A disease at initial diagnosis to relapse. There are little data and no proven established treatment option for these patients. Transplant is usually not considered. For patients with a low risk of relapse (defined as patients with initial Group A disease or patients with Group B low risk disease [Stage I or II] treated along POG9219), chemotherapy regimens such as COG ANHL 1131 (Arm C1 regimen) or 2 cycles of R-CYVE without consolidative transplant are options that can be considered.

[mm] Patients with late relapse from early-stage disease after a CR to relapse-refractory therapy may not require consolidation with transplant.
[nn] For conditioning therapy used in transplant, institutions can use their center's choice of myeloablative regimen. Retrospective studies showed efficacy of many regimens (eg, busulfan-cyclophosphamide, etoposide; BEAM [carmustine, etoposide, cytarabine, melphalan]; CBV[low] [low-dose cyclophosphamide, carmustine, etoposide]).
[oo] There are no data to support autologous versus allogeneic HCT; therefore, the decision regarding transplant should be based on physician preference and the availability of a suitable donor (donor options include human leukocyte antigen [HLA]-matched related donor; HLA-matched unrelated donor; cord blood or haploidentical donor).
[pp] Second-line therapy for relapsed/refractory disease should be in a clinical trial with incorporation of an investigational agent. Regimens and agents used for adults with relapsed/refractory DLBCL can also be considered. See NCCN Guidelines for B-Cell Lymphomas.

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

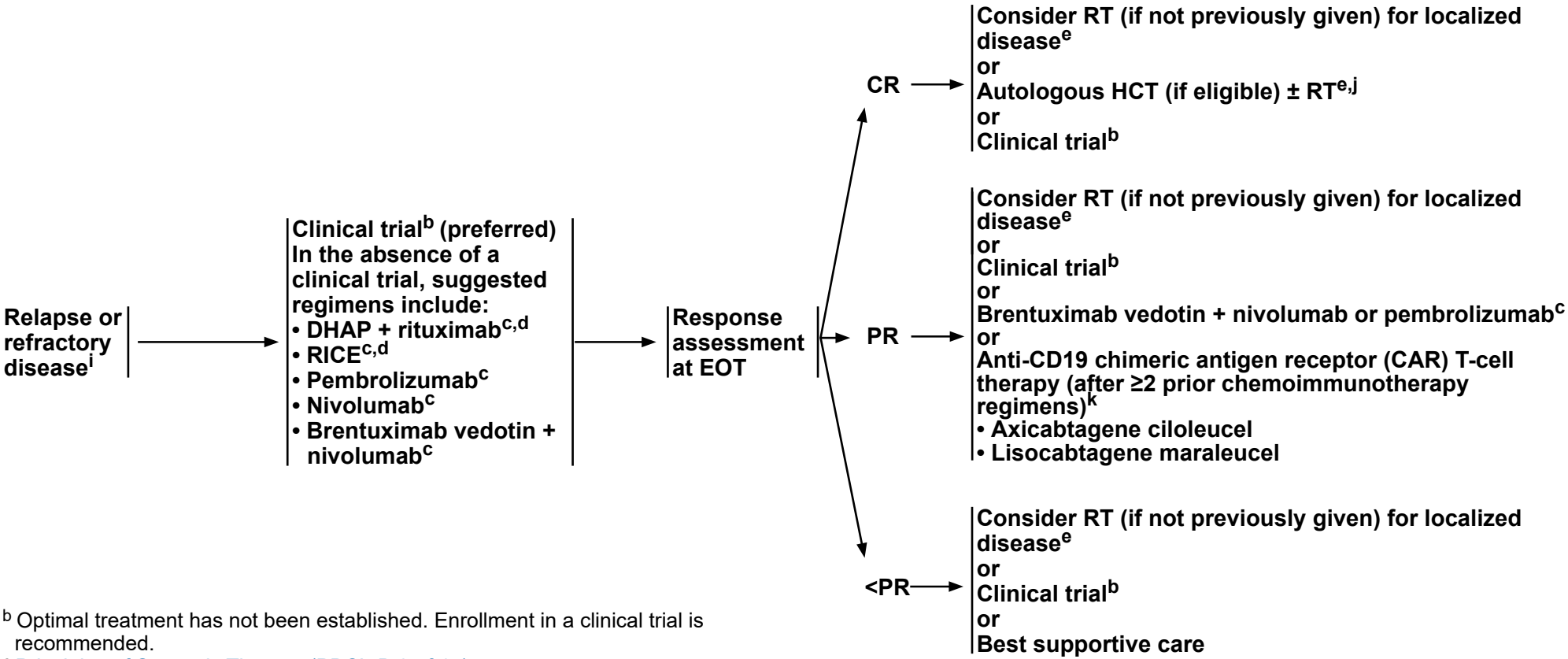
NCCN Guidelines Version 2.2025
Primary Mediastinal Large B-Cell Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion



[a] Definitive diagnosis may not be feasible before beginning treatment. Short course of COP regimen can be used while waiting to confirm the diagnosis of PMBL.
[b] Optimal treatment has not been established. Enrollment in a clinical trial is recommended.
[c] Principles of Systemic Therapy (PBCL-B 9 of 15).
[d] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[e] Avoidance of RT is strongly preferred in pediatric patients to reduce the risk of late complications from normal tissue damage. There are not enough data on the use of RT in pediatric patients with PMBL. When RT is used, it should be delivered using advanced RT techniques to minimize dose to organ at risk (OAR) (heart, cardiac substructures, lungs, breast, spinal cord, etc). See Principles of Radiation Therapy in the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Recommendations for normal tissue dose constraints can be found in Principles of Radiation Therapy in the NCCN Guidelines for Hodgkin Lymphoma.
[f] Remission assessment was performed after the second consolidation course. At the EOT, if PET/CT is positive, or a large residual tumor remains, then biopsy/removal of the residual mass is recommended. No treatment decisions were to be based on PET/CT results only.
[g] Response Criteria (PBCL-C).
[h] PET/CT scan is essential at EOT. Residual mediastinal masses are common. Biopsy of PET-positive mass should be considered if additional systemic treatment is contemplated.
[i] In the vast majority of patients, relapse occurs within 18 months of diagnosis. EOT PET scan can have a fair number of false positives. Biopsy is warranted to confirm relapse.

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



[b] Optimal treatment has not been established. Enrollment in a clinical trial is recommended.
[c] Principles of Systemic Therapy (PBCL-B 9 of 15).
[d] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[e] Avoidance of RT is strongly preferred in pediatric patients to reduce the risk of late complications from normal tissue damage. There are not enough data on the use of RT in pediatric patients with PMBL. When RT is used, it should be delivered using advanced RT techniques to minimize dose to OAR (heart, cardiac substructures, lungs, breast, spinal cord, etc). See Principles of Radiation Therapy in the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Recommendations for normal tissue dose constraints can be found in Principles of Radiation Therapy in the NCCN Guidelines for Hodgkin Lymphoma.
[g] Response Criteria (PBCL-C).
[i] In the vast majority of patients, relapse occurs within 18 months of diagnosis. EOT PET scan can have a fair number of false positives. Biopsy is warranted to confirm relapse.
[j] RT is often included in high-dose therapy regimens given prior to autologous HCT. RT could be an option for local recurrence. Allogeneic HCT is not considered an optimal approach.
[k] Management of cytokine release syndrome (CRS) and neurologic toxicity: See CAR T-Cell–Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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

PRINCIPLES OF DIAGNOSTIC PATHOLOGY

Morphology

- Touch preparations of fresh lesional tissue should be encouraged whenever possible since, if done properly, they may reveal essential cytologic details that may be difficult to detect in small biopsies (eg, small needle core biopsy).[1]
  - The morphologic appearance of typical BL is distinctive.[2] Cytologically, the lymphoid cells are intermediate in size (similar in size to a histiocyte nucleus) and have round nuclei, finely dispersed chromatin with multiple small nucleoli, and moderate amounts of densely basophilic cytoplasm. Cytoplasmic vacuoles may be seen on Wright Giemsa-stained touch preparations.
  - The cells of DLBCL are large with variable nuclear contours, vesicular chromatin, single or multiple nucleoli, and scant to moderately abundant cytoplasm.
- Tissue sections of BL, DLBCL, and PMBL are also distinctive.
  - BL is composed of patternless sheets of lymphoid cells that appear to mold to one another (pseudo-cohesion). Scattered histiocytes with apoptotic debris in the cytoplasm (tingible body macrophages) confer the so-called “starry sky” appearance indicative of high cell turnover.[2] Mitoses and apoptotic bodies are often numerous. While a morphologic spectrum is recognized in BL, with some cases bearing larger cells or cells with eccentrically oriented cytoplasm, pediatric BL tends to show little morphologic variation.[3]
  - The architecture of DLBCL also shows sheet-like growth, but the significant nuclear pleomorphism and more abundant cytoplasm confer a lighter color at low magnification. “Starry sky” is generally not prominent.
  - PMBL has a spectrum of morphologic features, and typical findings are diffuse sheets of neoplastic lymphocytes in a background of compartmentalizing fibrosis. The neoplastic lymphocytes are medium-sized to large, with round to lobulated or irregular nuclei, dispersed chromatin, prominent nucleoli, and abundant pale to clear cytoplasm. Occasionally, neoplastic lymphocytes with highly pleomorphic nuclear features including Hodgkin-Reed-Sternberg cell-like appearance may be seen.

Immunophenotyping

- As lymphomas of mature B-cell origin, BL and DLBCL express pan-B-cell markers (ie, CD20, CD19, CD79a, CD22, PAX5), do not generally express TdT, and do not express CD34.
- Clonality may be inferred by surface or cytoplasmic immunoglobulin light chain (kappa or lambda) restriction, most reliably by flow cytometry, which may be complemented by Kappa/Lambda ISH studies.
- All BL and a majority of DLBCL express markers of germinal center follicular B cells (ie, CD10, BCL6). Although an earlier study using IHC showed that one-quarter of the pediatric DLBCL demonstrated a non-germinal center immunophenotype using Hans criteria,[4,5] a recent large series by gene expression profiling showed that non-germinal center immunophenotype is rare in children and was not associated with clinical outcome.[6]
- Strong expression of MUM1/IRF4, often with BCL6 and CD10 positivity, should raise consideration of the diagnosis of LBCL with *IRF4* rearrangement.
- In BL, BCL2 is negative or weak and patchy if positive. BCL2 expression in DLBCL is variable. Demonstration of Epstein-Barr virus (EBV) association using EBER-ISH may be performed in BL and DLBCL if indicated by a history or suspicion of immunodeficiency; EBV expression by BL is predominantly seen in the endemic form. EBV-positive DLBCL, NOS (ICC)/EBV-positive DLBCL (WHO) can also be seen in pediatric patients without recognized immunodeficiency.[7]
- There are few infiltrating small T cells in BL, whereas there may be many in DLBCL, particularly in the T-cell histiocyte-rich large B-cell subtype of DLBCL.
- PMBL expresses CD23, CD30, and MUM1 in most of the cases, in addition to pan B-cell markers. BCL2 and BCL6 are variable. At least one of the biomarkers should be expressed: CD200, MAL, PD-L1, and PD-L2.

References
Continued

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

PRINCIPLES OF DIAGNOSTIC PATHOLOGY

Cytogenetic and Molecular Studies

- BL is defined by a simple karyotype including rearrangement of the *MYC* gene located on the long arm of chromosome 8 (8q24).[8] The most common translocation partner is the immunoglobulin heavy chain (*IGH)* gene (chromosome 14) followed by immunoglobulin light chain genes (kappa and lambda) on chromosomes 2 and 22, respectively.
  - Because of heterogeneity in translocation partners, FISH using a *MYC* break-apart probe is the recommended test for detection of *MYC* rearrangement.
  - Conventional karyotype analysis may also be of use to demonstrate a translocation involving *MYC* rearrangement and other karyotypic abnormalities.
  - In the absence of a *MYC* rearrangement, the diagnosis of LBCL with 11q aberration (ICC)/HGBL with 11q aberrations (WHO) may be pursued.[9,10] The epidemiology and natural history of this recently recognized entity has yet to be defined, but pediatric cases have been described. Karyotype may be complex. Optimum management of this rare subtype is undefined, although it is most often treated like typical BL.
  - The karyotype of BL is simpler than that of LBCL with 11q aberration (ICC)/HGBL with 11q aberrations (WHO). Nevertheless, few and specific chromosomal gains and losses (1q, 7, and 12 gain and 6q, 13q32–34, and 17p loss) do not exclude BL, but may indicate disease progression.[11-13]
  - In certain circumstances, including in the presence of a *MYC* rearrangement, when morphologic and/or immunophenotypic features raise consideration for a differential diagnosis of HGBL with *MYC and BCL2 or BCL6* rearrangements, *IGH/BCL2* and *BCL6* rearrangement status may be interrogated by FISH. At present, HGBL is thought to be uncommon in children,[14-17] although cases have been reported. Pediatric HGBL is treated with the same regimens as pediatric BL.[18] See the NCCN Guidelines for B-Cell Lymphomas for a full discussion on HGBL.

- DLBCL may show rearrangements of *MYC*, *BCL2*, and/or *BCL6* as well as aneuploidy of these and other loci.
  - Isolated *MYC* rearrangement is seen in up to 8% to 14% of DLCBL cases.[19-21] The *MYC* rearrangement is seen with similar frequency in children and adult patients.[6]
  - Although FISH studies for *MYC*, *IGH/BCL2*, and *BCL6* are generally recommended in all cases of DLBCL in adults, individual cases or institutional practice may be used to determine whether to pursue FISH testing in pediatric DLBCL given the rarity of “double” and “triple” hit lymphoma in this age group.
  - Mantle cell lymphoma (MCL) does not occur in children; therefore, *CCND1* interrogation for pleomorphic MCL is not needed in pediatric DLBCL.

- The molecular genetic basis of BL and to some extent DLBCL are well described,[13,22,23] but there is currently no role for molecular genetic (mutational) analysis in the routine diagnosis of BL or DLBCL.

- PMBL: Characteristic cytogenetic alterations involve major histocompatibility complex (MHC) class II transactivator (CIITA) at 16p13.13 including rearrangements or mutations, and translocations, as well as gains and amplifications of chromosome 9p24.1. Likely related to these changes, *PDL1* and *PDL2* amplification is often observed. Rearrangements involving *BCL2*, *BCL6*, and *MYC* are rare.[24-30]

References

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

PRINCIPLES OF DIAGNOSTIC PATHOLOGY – REFERENCES

[1] Iyer VK. Pediatric lymphoma diagnosis: role of FNAC, biopsy, immunohistochemistry and molecular diagnostics. Indian J Pediatr 2013;80:756-763.
[2] Huang H, Liu ZL, Zeng H, et al. Clinicopathological study of sporadic Burkitt lymphoma in children. Chin Med J (Engl) 2015;128:510-514.
[3] Leoncini L, Campo E, Stein H. Burkitt Lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Vol. 2 (ed 4th). Lyon: IARC; 2017
[4] Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-282.
[5] Miles RR, Raphael M, McCarthy K, et al. Pediatric diffuse large B-cell lymphoma demonstrates a high proliferation index, frequent c-Myc protein expression, and a high incidence of germinal center subtype: Report of the French-American-British (FAB) international study group. Pediatr Blood Cancer 2008;51:369-374.
[6] Szczepanowski M, Lange J, Kohler CW, et al. Cell-of-origin classification by gene expression and MYC-rearrangements in diffuse large B-cell lymphoma of children and adolescents. Br J Haematol 2017;179:116-119.
[7] Nicolae A, Pittaluga S, Abdullah S, et al. EBV-positive large B-cell lymphomas in young patients: a nodal lymphoma with evidence for a tolerogenic immune environment. Blood 2015;126:863-872.
[8] Boerma EG, Siebert R, Kluin PM, Baudis M. Translocations involving 8q24 in Burkitt lymphoma and other malignant lymphomas: a historical review of cytogenetics in the light of todays knowledge. Leukemia 2009;23:225-234.
[9] Aukema SM, Theil L, Rohde M, et al. Sequential karyotyping in Burkitt lymphoma reveals a linear clonal evolution with increase in karyotype complexity and a high frequency of recurrent secondary aberrations. Br J Haematol 2015;170:814-825.
[10] Pienkowska-Grela B, Rymkiewicz G, Grygalewicz B, et al. Partial trisomy 11, dup(11)(q23q13), as a defect characterizing lymphomas with Burkitt pathomorphology without MYC gene rearrangement. Med Oncol 2011;28:1589-1595.
[11] Maria Murga Penas E, Schilling G, Behrmann P, et al. Comprehensive cytogenetic and molecular cytogenetic analysis of 44 Burkitt lymphoma cell lines: secondary chromosomal changes characterization, karyotypic evolution, and comparison with primary samples. Genes Chromosomes Cancer 2014;53:497-515.
[12] Scholtysik R, Kreuz M, Klapper W, et al. Detection of genomic aberrations in molecularly defined Burkitt's lymphoma by array-based, high resolution, single nucleotide polymorphism analysis. Haematologica 2010;95:2047-2055.
[13] Toujani S, Dessen P, Ithzar N, et al. High resolution genome-wide analysis of chromosomal alterations in Burkitt's lymphoma. PLoS One 2009;4:e7089.
[14] Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114:2273-2279.
[15] Perry AM, Crockett D, Dave BJ, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma: study of 39 cases. Br J Haematol 2013;162:40-49.
[16] Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol 2010;34:327-340.
[17] Tomita N, Tokunaka M, Nakamura N, et al. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica 2009;94:935-943.
[18] Lu B, Zhou C, Yang W, et al. Morphological, immunophenotypic and molecular characterization of mature aggressive B-cell lymphomas in Chinese pediatric patients. Leuk Lymphoma 2011;52:2356-2364.
[19] Akyurek N, Uner A, Benekli M, Barista I. Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. Cancer 2012;118:4173-4183.
[20] Clipson A, Barrans S, Zeng N, et al. The prognosis of MYC translocation positive diffuse large B-cell lymphoma depends on the second hit. J Pathol Clin Res 2015;1:125-133.
[21] Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360-3365.
[22] Dave SS, Fu K, Wright GW, et al. Molecular diagnosis of Burkitt's lymphoma. N Engl J Med 2006;354:2431-2442.
[23] Hummel M, Bentink S, Berger H, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 2006;354:2419-2430.
[24] Tsang P, Cesarman E, Chadburn A, et al. Molecular characterization of primary mediastinal B cell lymphoma. Am J Pathol 1996;148:2017-2025.
[25] Joos S, Otano-Joos MI, Ziegler S, et al. Primary mediastinal (thymic) B-cell lymphoma is characterized by gains of chromosomal material including 9p and amplification of the REL gene. Blood 1996;87:1571-1578.
[26] Bentz M, Barth TF, Bruderlein S, et al. Gain of chromosome arm 9p is characteristic of primary mediastinal B-cell lymphoma (MBL): comprehensive molecular cytogenetic analysis and presentation of a novel MBL cell line. Genes Chromosomes Cancer 2001;30:393-401.
[27] Wessendorf S, Barth TF, Viardot A, et al. Further delineation of chromosomal consensus regions in primary mediastinal B-cell lymphomas: an analysis of 37 tumor samples using high-resolution genomic profiling (array-CGH). Leukemia 2007;21:2463-2469.
[28] Oschlies I, Burkhardt B, Salaverria I, et al. Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 2011;96:262-268.
[29] Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268-3277.
[30] Twa DDW, Chan FC, Ben-Neriah S, et al. Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. Blood 2014;123:2062-2065.

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Induction Therapy (Group A)

- **POG9219 Regimen[1]**
  - **Treatment Details: 9-week treatment course. No radiation.**

Drug	Dose and schedule
Cyclophosphamide	750 mg/m²/day on days 1, 22, and 43
Vincristine	1.5 mg/m²/day on days 1, 8, 15, 22, 29, 36, and 43 (Max dose 2 mg/dose. Note: Consider dose adjustment for age <1 year)
Prednisone	40 mg/m²/day divided TID on days 1–28 and days 43–47 (Max dose 60 mg/day)
Doxorubicin	40 mg/m²/day on days 1, 22, and 43 May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane:doxorubicin (eg, 400 mg/m² dexrazoxane to 40 mg/m² doxorubicin)
Intrathecal (IT) methotrexate, cytarabine, hydrocortisone	Age-based dosing[c] on days 1, 8, 22, 43, and 64 for head and neck primary tumors only

- **FAB/LMB96 Regimen A -COPAD (cyclophosphamide, vincristine, doxorubicin, prednisone)[2]**
  - **Treatment Details: Two 21-day cycles. No IT chemotherapy. No radiation.**

Drug	Dose and schedule per cycle. Two cycles.
Cyclophosphamide	250 mg/m²/dose every 12 hours on days 1–3 (6 doses per cycle)
Vincristine	2 mg/m²/day on days 1 and 6 (Max dose 2 mg/dose. Note: Consider dose adjustment for age <1 year)
Prednisone	60 mg/m²/day divided BID on days 1–6
Doxorubicin	60 mg/m²/day on day 1 May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane:doxorubicin

Useful in Certain Circumstances[d] for Group A

- **Equivalent BFM (Berlin-Frankfurt-Munster) Regimen**

BFM: Berlin-Frankfurt-Munster
POG: Pediatric Oncology Group
FAB: French-American-British
LMB: Lymphome Malin de Burkitt

Footnotes on PBCL-B (14 of 15)
References
Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Induction Therapy (Group B)

- **POG9219 Regimen (as for Group A on PBCL-B 1 of 15) – Only for Unresected Stage I and/or Nonabdominal Stage II**
- **COG ANHL1131 (based on FAB/LMB96) Regimen B[3,4,5]**
  - **Regimen B/Pre-phase COP (cyclophosphamide, vincristine, prednisone)**

Drug	Dose and schedule
Cyclophosphamide	300 mg/m²/day on day 1 (one dose)
Vincristine	1 mg/m²/day (maximum of 2 mg) on day 1
Prednisone	60 mg/m²/day divided BID on days 1–7
IT methotrexate and hydrocortisone	Age-based dosing[c] on day 1

If less than 20% size reduction after COP, proceed to Regimen C1, CNS-negative, starting with R-COPADM1 (rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate).

- **Regimen B/Induction 1 & 2 R-COPADM**
  - ◊ **Induction I starts on day 8 of the COP pre-phase. Note: If rituximab is included, the first dose is given on day 6 of the pre-phase.**
    - **– In the event the patient is too ill to proceed to COPADM1, a second COP phase may be administered.**
    - **– In the event of significant effusions or renal dysfunction on day 1, high-dose methotrexate may be delayed to day 5 or omitted in the context of persistent or large fluid collections.**
    - **– In the event the patient requires second COP pre-phase, the patient should not repeat day minus 2 (day 6 of COP pre-phase) Rituximab if already received.**
  - ◊ **Induction II starts 16–21 days after the start of Induction I, as soon as counts are recovering toward absolute neutrophil count (ANC) 750 and platelets 75,000, resolving mucositis and clinically stable. Delays are to be avoided. Give day minus 2 rituximab as counts start recovering.**

Drug	Dose and schedule
Rituximab[e]	375 mg/m²/day on day minus 2 (day 6 of COP pre-phase for R-COPADM1 [can be administered prior to response assessment]) and day 1
Cyclophosphamide	250 mg/m²/dose every 12 hours on days 2–4 (6 doses per cycle)
Vincristine	2 mg/m²/day (maximum of 2 mg) on day 1
Prednisone	60 mg/m²/day divided BID on days 1–5, then taper to zero on days 6–8
Doxorubicin	60 mg/m²/day on day 2 May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane:doxorubicin
Methotrexate	3 g/m²/day over 3 hours on day 1
Leucovorin	15 mg/m²/dose every 6 hours, starting 24 hours after start of methotrexate, until cleared
IT methotrexate and hydrocortisone	Age-based dosing[c] on day 2 (prior to start of leucovorin) and day 6

Footnotes on PBCL-B (14 of 15)
References
Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Induction Therapy (Group B)– (continued)

- **COG ANHL1131 (based on FAB/LMB96) Regimen B (continued)**
  - **Regimen B/Consolidation 1 & 2 R-CYM (rituximab, cytarabine, methotrexate)**
    - ◊ **Consolidation cycles start 16–21 days after the start of the previous cycle, as soon as counts are recovering toward ANC 750 and platelets 75,000, resolving mucositis and clinically stable. If not in remission after CYM 1, change to Group C1, CNS-negative starting with R-CYVE 1 (rituximab, cytarabine, etoposide).**

Drug	Dose and schedule
Rituximab[e]	375 mg/m²/day on day 1
Cytarabine	100 mg/m²/day continuous infusion days 2–6 (5 days total)
Methotrexate	3 g/m²/day over 3 hours on day 1
Leucovorin	15 mg/m²/dose every 6 hours, starting 24 hours after start of methotrexate, until cleared
IT methotrexate and hydrocortisone	Age-based dosing[c] on day 2
IT cytarabine and hydrocortisone	Age-based dosing[c] on day 7

Useful in Certain Circumstances[d] for Group B

- **Equivalent BFM Regimen**

Footnotes on PBCL-B (14 of 15)

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Induction Therapy (Group C)

- **COG ANHL1131 (based on FAB/LMB96 with omission of M3 and M4 cycles) Regimen C1[f,3,4,5]**
  - **Regimen C1/Pre-phase COP**

Drug	Dose and schedule
Cyclophosphamide	300 mg/m²/day on day 1 (one dose)
Vincristine	1 mg/m²/day (maximum of 2 mg) on day 1
Prednisone	60 mg/m²/day divided BID on days 1–7
IT methotrexate, cytarabine, hydrocortisone	Age-based dosing[c] on days 1, 3, and 5

  - **Regimen C1/Induction 1 & 2 R-COPADM**
    - ◊ **Induction I starts on day 8 of the COP pre-phase. Note: The first dose of rituximab is given on day 6 of the pre-phase.**
      - **– In the event the patient is too ill to proceed to R-COPADM1, a second COP phase may be administered.**
      - **– In the event of significant effusions or renal dysfunction on day 1, high-dose methotrexate may be delayed to day 5 or omitted in the context of persistent or large fluid collections.**
    - ◊ **Induction II starts 16–21 days after the start of Induction I, as soon as counts are recovering toward ANC 750 and platelets 75,000, resolving mucositis and clinically stable. Delays are to be avoided. Give day minus 2 rituximab as counts start recovering.**

Drug	Dose and schedule
Rituximab[e]	375 mg/m² on day minus 2 (day 6 of COP pre-phase for R-COPADM1 [can be administered prior to response assessment]) and day 1
Cyclophosphamide	• Induction I cycle: 250 mg/m²/dose every 12 hours on days 2–4 (6 doses) • Induction II cycle: 500 mg/m²/dose every 12 hours on days 2–4 (6 doses)
Vincristine	2 mg/m²/day (maximum of 2 mg) on day 1
Prednisone	60 mg/m²/day divided BID on days 1–5, then taper to zero on days 6–8
Doxorubicin	60 mg/m²/day on day 2 May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane:doxorubicin
Methotrexate	8 g/m²/day over 4 hours on day 1
Leucovorin	15 mg/m²/dose every 6 hours, starting 24 hours after start of methotrexate, until cleared
IT methotrexate, cytarabine, hydrocortisone	Age-based dosing[c] on day 2 (prior to start of leucovorin), day 4, and day 6

Footnotes on PBCL-B (14 of 15)
References
Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Induction Therapy (Group C) (continued)

- **COG ANHL1131 (based on FAB/LMB96) Regimen C1 (continued)**
  - **Regimen C1/Consolidation 1 & 2 R-CYVE**
    - ◊ **Consolidation cycles start 16–21 days after the start of the previous cycle, as soon as counts are recovering toward ANC 750 and platelets 75,000, resolving mucositis and clinically stable. If not in remission after R-CYVE 2 cycle, proceed to treatment for refractory disease.**

Drug	Dose and schedule
Rituximab[e]	375 mg/m² on day 1
Cytarabine	50 mg/m²/day continuous infusion over 12 hours (8 PM to 8 AM) on days 1–5 (5 days total)
High-dose cytarabine	3 g/m²/day over 3 hours after completion of low-dose cytarabine (8 AM to 11 AM) on days 2–5 (4 days total)
Etoposide	200 mg/m²/day over 2 hours, starting 3 hours after end of high-dose cytarabine (2 PM to 4 PM) on days 2–5 (4 days total)
IT methotrexate and hydrocortisone	Age-based dosing[a] on day 1 at least 6 hours before cytarabine *ONLY IF CNS POSITIVE*
IF CNS POSITIVE, ADMINISTER HIGH-DOSE METHOTREXATE AND IT AFTER R-CYVE 1 ONLY, AS BELOW:	
Methotrexate	8 g/m²/day over 4 hours on day ~18, when ANC is >500 and platelets are >50,000
Leucovorin	15 mg/m²/dose every 6 hours, starting 24 hours after start of methotrexate, until cleared
IT methotrexate, cytarabine, hydrocortisone	Age-based dosing[c] on day after high-dose methotrexate (prior to start of leucovorin)

Footnotes on PBCL-B (14 of 15)

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Induction Therapy (Group C) (continued)

- **COG ANHL1131 (based on FAB/LMB96) Regimen C1 (continued)**
  - **Regimen C1/Maintenance 1**
    - ◊ **Maintenance starts when ANC >750 and platelets >75,000, generally day 25–28 after start of Consolidation 2.**

Drug	Dose and schedule
Cyclophosphamide	250 mg/m²/dose every 12 hours on days 2–3 (4 doses total)
Vincristine	2 mg/m²/day (maximum of 2 mg) on day 1
Prednisone	60 mg/m²/day divided BID on days 1–5, then taper to zero on days 6–8
Doxorubicin	60 mg/m²/day on day 2 May administer dexrazoxane: Dexrazoxane dosing as 10:1 ratio of dexrazoxane:doxorubicin
Methotrexate	8 g/m²/day over 4 hours on day 1
Leucovorin	15 mg/m²/dose every 6 hours, starting 24 hours after start of methotrexate, until cleared
IT methotrexate, cytarabine, hydrocortisone	Age-based dosing[c] on day 2 (prior to start of leucovorin)

  - **Regimen C1/Maintenance 2**
    - ◊ **Starts on day 28 of Maintenance 1**

Drug	Dose and schedule
Cytarabine	50 mg/m²/dose every 12 hours on days 1–5 (10 doses)
Etoposide	150 mg/m²/day on days 1–3 (3 doses)

- **COG ANHL1131 Regimen C3[f,3,4,5]**
  - **This regimen is identical to Regimen C1 with the following exception:**
    - ◊ **The high-dose methotrexate (8 gm/m²) during R-COPADM2, at day 18 of R-CYVE 1, and in maintenance 1 is infused over 24 hours with leucovorin beginning at hour 36 after start of methotrexate. (Methotrexate 1.6 gm/m² over 30 minutes followed by 6.4 gm/m² over 23.5 hours)**

Useful in Certain Circumstances[d] for Group C

- **Equivalent BFM Regimen**

Footnotes on PBCL-B (14 of 15)
References

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

Preferred Regimens for Relapsed/Refractory Disease

• R-CYVE[6]

Drug	Dose and schedule
Rituximab	375 mg/m² IV on day 1
Cytarabine	50 mg/m² CIV over 12 hours (8 PM to 8 AM) on days 1 through 5
High-dose cytarabine	3 g/m² IV over 3 hours (8 AM to 11 AM) on days 2 through 5
Etoposide	200 mg/m² IV over 2 hours (2 PM to 4 PM) on days 2 through 5
IT methotrexate and hydrocortisone	Age-based dosing[c] on day 1 at least 6 hours before cytarabine

• RICE (Rituximab, ifosfamide, carboplatin, etoposide)[7]

Drug	Dose and schedule
Rituximab	375 mg/m² IV on days 1 and 3 of courses 1 and 2, and on day 1 only of course 3, if administered
Ifosfamide	3 g/m² IV over 2 hours daily on days 3, 4, and 5
Carboplatin	635 mg/m² (no maximum dose) IV over 1 hour on day 3 only
Etoposide	100 mg/m² IV over 1 hour daily on days 3, 4, and 5
Mesna[g]	600 mg/m² IV over 15 minutes before the start of ifosfamide and then at 3, 6, 9, and 12 hours after the start of ifosfamide daily on days 3, 4, and 5[g]
IT methotrexate and cytarabine	Age-based dosing[c]: • CNS disease with any histology: days 3, 10, and 17 of courses 1 and 2 • CNS-negative disease with large cell lymphoma: day 3 of course 1 only • CNS-negative disease with B-cell lymphoma and B-cell acute lymphoblastic leukemia: day 3 of each cycle

Footnotes on PBCL-B (14 of 15)
References
Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(BL and DLBCL)

• Age-Based Dosing for IT Methotrexate, Cytarabine, Hydrocortisone for Therapies Other than RICE[h] (PBCL-B 1–7 of 15)

Age-Based IT Therapy[h]					
Drug		**<1 year old**	**1 to <2 years old**	**≥2 to <3 years old**	**≥3 years old**
Methotrexate	**IT**	**8 mg**	**10 mg**	**12 mg**	**15 mg**
Cytarabine	**IT**	**15 mg**	**20 mg**	**25 mg**	**30 mg**
Hydrocortisone	**IT**	**8 mg**	**10 mg**	**12 mg**	**15 mg**

• Age-Based Dosing for IT Methotrexate, Cytarabine for RICE[h] (PBCL-B 7 of 15)

Age-Based IT Therapy[h,7]					
Drug		**<2 years old**	**2 to <3 years old**	**3 to <9 years old**	**≥9 years old**
Methotrexate	**IT**	**8 mg**	**10 mg**	**12 mg**	**15 mg**
Cytarabine	**IT**	**16 mg**	**20 mg**	**24 mg**	**30 mg**

Footnotes on PBCL-B (14 of 15)
References
Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(PMBL)

Regimens for Induction Therapy

- **Dose Adjusted-EPOCH-R (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab) (preferred)[8]**
  - **Treatment details: 21-day cycle for 6 cycles.**
  - **Refer to PBCL-B (10 of 15) for dose adjustments for etoposide, doxorubicin, and cyclophosphamide.**

Drug	Dose and schedule
Etoposide	(Dose adjusted) 50 mg/m²/day continuous infusion over 24 hours daily on days 1–4
Prednisolone	120 mg/m²/day divided BID on days 1–5
Vincristine	0.4 mg/m²/day continuous infusion over 24 hours daily on days 1–4
Cyclophosphamide	(Dose adjusted) 750 mg/m²/day on day 5
Doxorubicin	(Dose adjusted) 10 mg/m²/day continuous infusion over 24 hours daily on days 1–4
Rituximab	375 mg/m²/day on day 1

- **R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)[i,9]**
  - **Treatment Details: 21-day cycle for 6 cycles.**
  - **This regimen is more likely to be used in adolescents and young adults.**
  - **This regimen may be accompanied by RT as an initial treatment for PMBL.**

Drug	Dose and schedule
Cyclophosphamide	750 mg/m²/day on day 1
Doxorubicin	50 mg/m²/day on day 1
Vincristine	1.4 mg/m²/day on day 1 (Max dose 2 mg/dose. Note: Consider dose adjustment for age <1 year)
Prednisone	60 mg/m²/day daily on days 1–5
Rituximab	375 mg/m²/day on day 1

- **LMB-Modified B/C Chemotherapy + Rituximab[10] (based on FAB/LMB96). See PBCL-B (11 of 15) for Treatment Details.**

Footnotes on PBCL-B (14 of 15)
References
Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(PMBL)

Dose Adjustment Paradigm for the following Dose Adjusted-EPOCH-R Course*

Basic principles of treatment regulation

- **Dose adjustments above starting dose (level 1) apply to etoposide, doxorubicin, and cyclophosphamide.**
- **Dose adjustments below starting dose (level 1) apply to cyclophosphamide only.**
- **Doses of drugs are based on the previous course of ANC nadir according to the following two tables:**

ANC nadir after previous course	Dose level for next course
≥0.5x10^9/l on all measurements	Increase 1 dose level above last course
<0.5x10^9/l on 1 or 2 measurements	Same dose as last course
<0.5x10^9/l on ≥3 measurements	Decrease 1 dose level below last course

OR

Platelet nadir after previous course	Dose level for next course
<25 x 10^9/l on ≥1 measurement	Decrease 1 dose level below last course

- **If ANC ≥1x 10^9/l and platelets ≥100 x 10^9/l on day 21, begin next course.**
- **If ANC <1x 10^9/l or platelets <100 x 10^9/l on day 21, delay up to 1 week. Granulocyte colony-stimulating factor (G-CSF) (eg, pegfilgrastim[b]) may be started for ANC <1x 10^9/l and stopped 24 hours before treatment. If counts still low after 1-week delay, decrease 1 dose level below last course.**

- **Important: Measurement of ANC nadir is based on twice-weekly blood counts only (3 days apart). Only use twice-weekly blood counts for dose adjustment, even if additional blood counts are obtained.**
  - **If a patient has severe life-threatening complications, such as infection requiring intubation or pressor support, the responsible physician has the option not to escalate or to reduce doses.**
  - **In the absence of severe complications, the dose-adjusted principles should be followed.**

Table of doses per level for adjusted agents:

Drugs	Drug doses per dose levels							
	-2	-1	1 "starting dose"	2	3	4	5	6
Doxorubicin (mg/m^2/day)			10	12	14.4	17.3	20.7	24.8
Etoposide (mg/m^2/day)			50	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m^2/day)	480	600	750	900	1080	1296**	1555**	1866**

* Adapted with permission from Burke GAA, Minard-Colin V, Aupérin A, et al. Dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab therapy in children and adolescents with primary mediastinal B-cell lymphoma: A multicenter phase II trial. J Clin Oncol 2021;39:3716-3724.

** These dose levels should be accompanied by at least 12-hour hydration. Mesna may also be added.

Footnotes on PBCL-B (14 of 15)

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY[a,b] (PMBL)

Regimens for Induction Therapy

- **LMB-Modified B/C Chemotherapy + Rituximab[10] (based on FAB/LMB96)**
  - **Pre-phase COP**
    - ◊ **COP pre-phase is not mandatory but may be required 1 week prior to commencement of course 1 for patients requiring urgent treatment while awaiting histological confirmation. In case of COP pre-phase more intrathecal chemotherapy are administered.**

Drug	Dose and schedule
Cyclophosphamide	300 mg/m^2/day on day 1
Vincristine	2 mg/m^2/day on day 1
Prednisone	60 mg/m^2/day divided BID on days 1–7
IT Methotrexate and Hydrocortisone	Age based dosing[c] on day 1

- **Induction – 2 cycles of R-COPADM**

Drug	Dose and schedule
Rituximab[e]	375 mg/m^2/day on day 1
Vincristine	2 mg/m^2/day on day 1
Methotrexate	3 g/m^2/day on day 1
Cyclophosphamide	250 mg/m^2/every 12 hours on days 2–4
Doxorubicin	60 mg/m^2/day on day 2 May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane: doxorubicin
Prednisone	60 mg/m^2/day divided BID on days 1–5
Leucovorin	15 mg/m^2/dose every 6 hours, starting 24 hours after start of methotrexate, until cleared
IT Methotrexate and Hydrocortisone)	Age based dosing[c] on day 2 (prior to start of leucovorin)

Footnotes on PBCL-B (14 of 15)
References Continued

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b] (PMBL)

Regimens for Induction Therapy (continued)

- **LMB-Modified B/C Chemotherapy + Rituximab[e,10] (based on FAB/LMB96) (continued)**
  - **Consolidation – 2 cycles of R-CYVE**

Drug	Dose and schedule
Rituximab[e]	375 mg/m^2 on day 1
Cytarabine	50 mg/m^2/day continuous infusion over 12 hours days 1–5
High-dose cytarabine	3 g/m^2/day over 3 hours after completion of low dose cytarabine on days 2–5
Etoposide	200 mg/m^2/day over 2 hours, starting 3 hours after end of high dose cytarabine on days 2–5

  - **Maintenance – 2 cycles**

Drug	Dose and schedule
Vincristine	2 mg/m^2/day on day 1
Cyclophosphamide	500 mg/m^2/day on days 1–2
Doxorubicin	60 mg/m^2/day on day 1 May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane: doxorubicin
Prednisone	60 mg/m^2/day divided BID on days 1–5

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

Footnotes on PBCL-B (14 of 15)
References
Continued

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(PMBL)

Regimens for Relapsed/Refractory Disease

- **DHAP (dexamethasone, cytarabine, cisplatin, or carboplatin) + Rituximab[e,11]**
  - **Treatment Details: 21- or 28-day cycle for 3–6 cycles.**

Drug	Dose and schedule
Dexamethasone	Age ≥5 years: 40 mg/day IV daily on days 1–4 Age <5 years: 20 mg/m^2/day (max dose 40 mg) IV daily on days 1–4
Cytarabine	2000 mg/m^2/day over 3 hours every 12 hours for 2 doses on day 2
Cisplatin*	100 mg/m^2/day continuous infusion over 24 hours on day 1
Rituximab[e]	375 mg/m^2/day on day 1

*May substitute with carboplatin as a continuous infusion over 24 hours on day 1 to achieve an area under the concentration versus time curve (AUC) of 8 mg/mL/min.

- **RICE[7]**

Drug	Dose and schedule
Rituximab[e]	375 mg/m² IV on days 1 and 3 of courses 1 and 2, and on day 1 only of course 3, if administered
Ifosfamide	3 g/m² IV over 2 hours daily on days 3, 4, and 5
Carboplatin	635 mg/m² (no maximum dose) IV over 1 hour on day 3 only
Etoposide	100 mg/m² IV over 1 hour daily on days 3, 4, and 5
Mesna[g]	600 mg/m² IV over 15 minutes before the start of ifosfamide and then at 3, 6, 9, and 12 hours after the start of ifosfamide daily on days 3, 4, and 5

- **Pembrolizumab[12,13]**
  - **Treatment details: 2 mg/kg/day (max 200 mg/dose) on day 1 once every 3 weeks.**
- **Nivolumab[14]**
  - **Treatment details: 3 mg/kg/day on day 1 once every 2 weeks; a cycle is 28 days.**
- **Brentuximab vedotin + nivolumab[15]**
  - **Brentuximab vedotin 1.8 mg/kg/day (max 180 mg/dose) on day 1 once every 3 weeks.**
  - **Nivolumab 3 mg/kg on day 1 once every 2 weeks; a cycle is 28 days.**
- **Brentuximab vedotin + pembrolizumab[12,13]**
  - **Brentuximab vedotin 1.8 mg/kg/day (max 180 mg/dose) on day 1 once every 3 weeks.**
  - **Pembrolizumab 2 mg/kg/day (max 200 mg/dose) on day 1 once every 3 weeks.**

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

Footnotes on PBCL-B (14 of 15)
References

PRINCIPLES OF SYSTEMIC THERAPY
FOOTNOTES

[a] Radiation therapy rarely has a role in pediatric aggressive mature B-cell lymphomas.
[b] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[c] For age-based dosing for IT therapy, see PBCL-B 8 of 15.
[d] A large body of mature data shows that the BFM regimens are as safe and efficacious as the POG, FAB/LMB, and COG regimens. However, they are not routinely used in North America.
[e] Rituximab is optional for patients with low-risk Group B disease (PBCL-7). The addition of rituximab is a category 1 recommendation for patients with high-risk Group B (PBCL-8) and Group C (PBCL-9) disease. Minard-Colin V, et al. N Engl J Med 2020;382:2207-2219.
[f] COG protocol ANHL1131 distinguished between lymphomatous central nervous system or parameningeal disease (CNS+) and lymphoma cells in the CSF (CSF+). Patients with CSF+ were treated on arm C3. The relative efficacy of the arm C1 and arm C3 regimens has not been evaluated. Therefore, either regimen is an acceptable choice for treatment of patients with CSF+.
[g] Consider changing mesna to 3 g/m^2 continuous IV infusion over 24 hours if microscopic or gross hematuria occurs.
[h] For full details on all phases of therapy, see References.
[i] Avoidance of RT is strongly preferred in pediatric patients to reduce the risk of late complications from normal tissue damage. There are not enough data on the use of RT in pediatric patients with PMBL. When RT is used, it should be delivered using advanced RT techniques to minimize dose to OAR (heart, cardiac substructures, lungs, breast, spinal cord, etc). See Principles of Radiation Therapy in the NCCN Guidelines for Pediatric Hodgkin Lymphoma. Recommendations for normal tissue dose constraints can be found in Principles of Radiation Therapy in the NCCN Guidelines for Hodgkin Lymphoma.

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

PRINCIPLES OF SYSTEMIC THERAPY
REFERENCES

[1] Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. N Engl J Med 1997;337:1259-1266.
[2] Gerrard M, Cairo MS, Weston C, et al. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin lymphoma: results of the FAB/LMB96 international study. Br J Haematol 2008;141:840-847.
[3] Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736-2743.
[4] Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood 2007;109:2773-2780.
[5] Minard-Colin V, Auperin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in Children. N Engl J Med 2020;382:2207-2219.
[6] Jourdain A, Auperin A, Minard-Colin V, et al. Outcome of and prognostic factors for relapse in children and adolescents with mature B-cell lymphoma and leukemia treated in three consecutive prospective "Lymphomes Malins B" protocols. A Société Française des Cancers de l'Enfant study. Haematologica 2015;100:810-817.
[7] Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181.
[8] Burke GAA, Minard-Colin V, Aupérin A, et al. Dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab therapy in children and adolescents with primary mediastinal c-cell lymphoma: A multicenter phase II trial. J Clin Oncol 2021;39:3716-3724.
[9] Hayden AR, Tonseth PT, Lee DG, et al. Outcome of primary mediastinal large B-cell lymphoma using R-CHOP: impact of a PET-adapted approach. Blood 2020;136:2803-2811.
[10] Dourthe ME, Phulpin A, Auperin A, et al. Rituximab in addition to LMB-based chemotherapy regimen in children and adolescents with primary mediastinal large B-cell lymphoma: results of the French LMB2001 prospective study. Haematologica 2022;107:2173-2182.
[11] Sandlund JT, Santana VM, Hudson MM, et al. Combination of dexamethasone, high-dose cytarabine, and carboplatin is effective for advanced large-cell non-Hodgkin lymphoma of childhood. Cancer 2008;113:782-790.
[12] Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol 2019;37:3291-3299.
[13] Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood 2017:267-270.
[14] Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020-21:541-550.
[15] Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II CheckMate 436 study. J Clin Oncol 2019;37:3081-3089.

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

RESPONSE CRITERIA

Table 1: International Pediatric Non-Hodgkin Lymphoma Response Criteria[a]

Criterion	Definition
CR	**Disappearance of all disease**
CR	**• CT or MRI reveals no residual and no new lesions • Residual mass pathologically negative for disease BM and CSF free of disease pathologically**
CRb	**• Residual mass with no pathologic evidence of disease from limited or core biopsy; no new lesions by imaging examination • BM and CSF free of disease pathologically • No new and/or progressive disease elsewhere**
CRu	**• Residual mass negative by FDG-PET; no new lesions by imaging examination • BM and CSF free of disease pathologically • No new and/or progressive disease elsewhere**
PR	**• ≥50% decrease in SPD on CT or MRI; FDG-PET may be positive (Deauville score 4 or 5 with reduced lesional uptake compared to baseline [Table 2]). • May have evidence of disease in BM or CSF if present at diagnosis, but should have 50% reduction in percentage of lymphoma cells. • No new and/or progressive disease**
MR	**• Decrease in SPD >25%, but <50% on CT or MRI • May have evidence of disease in BM or CSF if present at diagnosis, but should have 25% to 50% reduction in percentage of lymphoma cells • No new and/or progressive disease**
NR	**Not meeting CR, PR, MR, or PD criteria**
PD	**• >25% increase in SPD on CT or MRI; Deauville score 4 or 5 (Table 2) on FDG-PET with increase in lesional uptake from baseline; or new morphologic disease in BM or CSF**

[a] Adapted with permission from Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 2015;33:2106-2111.

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

RESPONSE CRITERIA

Table 2: The Deauville Five-Point Scale[b]	
Score	**Definition**
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Markedly increased uptake at any site or new lesions
X	New areas of uptake unlikely to be due to lymphoma

[b] Adapted with permission from Meignan M, Gallamini A, Meignan M, et al. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. Leuk Lymphoma 2009;50:1257-1260.

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

PRINCIPLES OF SUPPORTIVE CARE

Tumor Lysis Syndrome (TLS)[1-6]

- Laboratory TLS (presence of 2 or more metabolic abnormalities in the same 24-hour period)
  - High uric acid (> ULN for children)
  - High phosphorus (>6.5 mg/dL in children)
  - High potassium (>6.0 mmol/L)
  - Low calcium (corrected calcium <7.0 mg/dL)

- TLS can be asymptomatic or can cause seizures, cardiac arrhythmias, acute renal failure, neuromuscular abnormalities, hypotension, and/or death

- TLS risk factors
  - BL and occasionally DLBCL
  - Elevated LDH (>2X ULN)
  - Bulky disease
  - Evidence of TLS prior to initiation of therapy
  - Oliguria
  - Preexisting renal impairment
  - Dehydration

- Prophylaxis/management of TLS
  - Begin hyperhydration with 1.5–2X maintenance IV fluids without potassium and without bicarbonate; initiate frequent monitoring of potassium, phosphorus, calcium, creatinine, and uric acid.
  - Hyperuricemia
    - ◊ Allopurinol should be started prior to initiation of chemotherapy for patients with low tumor burden and LDH <2X ULN. Discontinuation of allopurinol and prompt initiation of rasburicase is recommended if there is a concern for TLS, because it has been shown to be safe and effective in preventing new-onset renal failure and was associated with an improved glomerular filtration rate.
    - ◊ For ongoing control of TLS, consider restarting allopurinol after rasburicase therapy is completed.
    - ◊ Rasburicase is indicated prophylactically for patients with high tumor burden, LDH >2X ULN, or those presenting with renal dysfunction, elevated uric acid, or inability to tolerate hydration. The first dose of rasburicase should be given prior to starting chemotherapy.
    - ◊ Rasburicase is contraindicated in patients with G6PD deficiency due to an increased risk of methemoglobinemia or hemolysis. However, in patients with TLS at risk for end-organ injury with unknown G6PD status, the benefit of rasburicase may outweigh the risk.
    - ◊ Rasburicase is given as a single dose of 0.1–0.2 mg/kg. The maximum dose is 6 mg and should be repeated only if necessary based on laboratory values.
    - ◊ If rasburicase is used, blood samples for the measurement of the uric acid level must be placed on ice to prevent ex vivo breakdown of uric acid by rasburicase and thus a spuriously low level.
  - Hyperkalemia: Manage per standard hyperkalemia algorithms, such as in Pediatric Advanced Life Support (PALS). Ensure that all exogenous sources of potassium, such as in IV fluids, have been removed. Frequent measurement of potassium levels (every 4–6 hours), continuous cardiac monitoring, and the administration of oral sodium polystyrene sulfonate are recommended. Glucose plus insulin or beta agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of dysrhythmia while awaiting hemodialysis and/or hemofiltration, which most effectively remove potassium.
  - Hyperphosphatemia: Manage with phosphorous-restricted diet; consider phosphate binder such as sevelamer. Do not use calcium carbonate in patients at risk for TLS as this may prompt formation of calcium phosphate crystals and worsen renal and other organ function, especially if the calcium phosphate product is >60 mg^2/dL^2.
  - Hypocalcemia: Correct hypocalcemia; calcium supplementation should not be used unless the 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.

References on PBCL-D 4 of 4

Continued

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

PRINCIPLES OF SUPPORTIVE CARE

Risk of Infection[7-9]

- Recommended treatment regimens are associated with a high risk of serious infections.
- Antiviral prophylaxis is recommended for at least 12–18 months after the last dose of rituximab for patients with HBsAg-positive.
- Patients on treatment should be on pneumocystis jiroveci pneumonia (PJP) prophylaxis.
- There is a risk of hypogammaglobulinemia during and for months after rituximab. If the patient has frequent infections, gammaglobulin level may be measured and consideration given to intravenous IgG (immunoglobulin G) replacement.
- Rituximab-related neutropenia may occur weeks to months following last rituximab exposure in up to 10% of patients. While it can be severe, it is not generally associated with infectious complications.

Viral Reactivation

- There may be a risk of hepatitis B reactivation during treatment with rituximab. Screening for chronic or resolved hepatitis B viral infection should be performed before starting treatment with rituximab. If the patient is positive for hepatitis B, consult with an infectious disease specialist and monitor for reactivation during and after treatment with rituximab.
- Screen for herpes simplex virus (HSV) if the patient develops mucositis. If positive, the patient should be treated for HSV to potentially improve mucositis earlier.[10,11]
- Progressive multifocal leukoencephalopathy (PML) caused by reactivation of John Cunningham virus (JCV) has been noted as a rare complication of rituximab therapy and is usually fatal. Clinical signs may include confusion, dizziness, altered speech, unstable gait, visual changes, and behavioral changes. There is no known effective treatment.

Mass Lesions at Presentation[12]

- In pediatrics, there are multiple publications of spinal cord compression, massive kidney enlargement, intussusception, ovarian masses, chest masses, and facial masses. There may be increased risk of thrombosis due to mass lesions.
- For obstruction of the urinary tract, it may be necessary to deviate the urine by transcutaneous pyelostomy.
- Chemotherapy should be started as soon as possible to preserve organ function and improve complications.

References on PBCL-D 4 of 4
Continued

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

PRINCIPLES OF SUPPORTIVE CARE

Supportive Care Related to Systemic Therapy

- Abdominal pain, bowel obstruction, and bowel perforation have been described in patients treated with rituximab. These symptoms should prompt early diagnostic evaluation to include plain films and/or CT of the abdomen and pelvis.[13]
- Growth factors
  - There is a high incidence of fever, neutropenia, and bacteremia in COPADM cycles.
  - Growth factors have been used in some North American chemotherapy trials, but not in European trials.
  - There are little published guiding data, but growth factors can be used according to patient stability and physician preference.

- Methotrexate toxicity[14]
  - If a patient receiving high-dose methotrexate experiences delayed elimination due to renal impairment, glucarpidase is strongly recommended when:
    - plasma methotrexate concentrations are two standard deviations above the mean expected plasma concentration as determined by MTXPK.org,
      or
    - plasma methotrexate level is >30 µM at 36 hours, >10 µM at 42 hours, or >5 µM at 48 hours.
  - Optimal administration of glucarpidase is within 48 to 60 hours from the start of methotrexate infusion. Leucovorin should be administered at least 2 hours before or 2 hours after glucarpidase administration. For the first 48 hours following glucarpidase administration, administer the same leucovorin dose as that given prior to glucarpidase. Beyond 48 hours after glucarpidase administration, determine the appropriate leucovorin dose for administration based on the measured methotrexate concentration.
  - Methotrexate neurotoxicity can occur following high-dose or IT methotrexate. MRI may allow for discrimination between methotrexate neurotoxicity and posterior reversible encephalopathy syndrome (PRES). Most patients make a full recovery without intervention. Potential interventions include aminophylline and dextromethorphan, but there is limited evidence for any of these. Risk of recurrence with continued methotrexate treatment is low.

- Mucositis
  - Prevention
    - Use chlorhexidine mouthwash for its bactericidal effect.
    - Bland rinses such as 0.9% saline solution, sodium bicarbonate, or fluoride topical mouthwash (nonalcoholic and unsweetened) may be used twice daily and after meals.
  - Management
    - Maintain hydration
    - Provide adequate nutrition with enteral or parenteral sources
    - Control bleeding
    - Manage viral (HSV) or fungal (candida) mouth infections
    - Manage pain with topical anesthetics and oral or IV analgesics.

References on PBCL-D 4 of 4

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

PRINCIPLES OF SUPPORTIVE CARE – REFERENCES

[1] Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008;26:2767-2778.
[2] Cairo MS, Coiffier B, Reiter A, Younes A. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol 2010;149:578-586.
[3] Hough R, Vora A. Crisis management in the treatment of childhood acute lymphoblastic leukemia: putting right what can go wrong (emergency complications of disease and treatment). Hematology Am Soc Hematol Educ Program 2017;2017:251-258.
[4] Pession A, Masetti R, Gaidano G, et al. Risk evaluation, prophylaxis, and treatment of tumor lysis syndrome: consensus of an Italian expert panel. Adv Ther 2011;28:684-697.
[5] Galardy PJ, Hochberg J, Perkins SL, et al. Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: a Children's Oncology Group Report. Br J Haematol 2013;163:365-372.
[6] Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med 2011;364:1844-1854.
[7] Mikulska M, Lanini S, Gudiol C, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect 2018;24 Suppl 2:S71-S82.
[8] Barmettler S, Ong MS, Farmer JR, et al. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Netw Open 2018;1:e184169.
[9] Kado R, Sanders G, McCune WJ. Diagnostic and therapeutic considerations in patients with hypogammaglobulinemia after rituximab therapy. Curr Opin Rheumatol 2017;29:228-233.
[10] Redding SW. Role of herpes simplex virus reactivation in chemotherapy-induced oral mucositis. NCI Monogr 1990:103-105.
[11] Righini-Grunder F, Hurni M, Warschkow R, Rischewski J. Frequency of oral mucositis and local virus reactivation in herpes simplex virus seropositive children with myelosuppressive therapy. Klin Padiatr 2015;227:335-338.
[12] Derinkuyu BE, Boyunaga O, Oztunali C, et al. Imaging features of Burkitt lymphoma in pediatric patients. Diagn Interv Radiol 2016;22:95-100.
[13] Fallon SC, Redell MS, El-Bietar J, et al. Intestinal perforation after treatment of Burkitt's lymphoma: case report and review of the literature. J Pediatr Surg 2013;48:436-440.
[14] Howard SC, McCormick J, Pui CH, et al. Preventing and managing toxicities of high-dose methotrexate. Oncologist 2016;21:1471-1482.

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

ADDITIONAL DIAGNOSTIC TESTING FOR PTLD[a]

ESSENTIAL

- **Adequate immunophenotyping to establish diagnosis[b]**
- **Hyperplastic non-destructive PTLD (hyperplastic ND-PTLD)[c]**
  - **Morphology (See PTLD-A)**
  - **Flow cytometry: CD3, CD5, CD10, CD19, CD20, CD45, and surface kappa/lambda**
  - **IHC/ISH panel: CD3, CD19, CD20, PAX5, CD138, MUM1, kappa (ISH), and lambda (ISH)**
  - **EBER-ISH**
- **Polymorphic PTLD (P-PTLD)**
  - **Morphology (See PTLD-A)**
  - **Flow cytometry: CD2, CD3, CD5, CD7, CD10, CD19, CD20, CD22, CD23, CD45, and surface kappa/lambda**
  - **IHC/ISH panel: CD3, CD5, CD10, CD15, CD19, CD20, PAX5, CD30, CD45, BCL1, BCL2, BCL6, CD138, MUM1, kappa (ISH), and lambda (ISH)**
  - **EBER-ISH**
- **Monomorphic PTLD (M-PTLD)[d]**
  - **Morphology (See PTLD-A)**
  - **Flow cytometry: CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD22, CD23, CD38, CD45, CD56, and surface kappa/lambda**
  - **IHC/ISH panel: CD3, CD5, CD10, CD19, CD20, PAX5, CD30, CD45, BCL1, BCL2, BCL6, CD138, MUM1, kappa (ISH), and lambda (ISH)**
  - **EBER-ISH**

USEFUL UNDER CERTAIN CIRCUMSTANCES

- **Additional immunophenotypic studies may be needed for further assessment including subclassification of M-PTLD[d]**
- **Molecular analysis to assess clonality (See PTLD-A)**
- **Additional cytogenetics/FISH and mutational analysis may be indicated when specific type of M-PTLD is suspected or considered[d]**

→ Workup (PTLD-2)

[a] Clinical Presentation and Diagnostic Pathology (PTLD-A).
[b] Interpretation of the flow cytometry utilizes the standard approach of pattern recognition, and it is clinically important to report CD20 expression (positive vs. negative; and if positive, the pattern of expression) on B-cells in all subtypes of PTLD.
[c] Hyperplastic ND-PTLD lesions include florid follicular hyperplasia, plasmacytic hyperplasia, and infectious mononucleosis–like hyperplasia. (WHO Classification of Tumours Editorial Board. Paediatric tumours. [WHO classification of tumours series, 5th ed; vol 7]. Lyon [France]: International Agency for Research on Cancer; 2022).
[d] See relevant sections in the NCCN Guidelines for B-Cell Lymphomas, T-Cell Lymphomas, Multiple Myeloma, and Hodgkin Lymphoma.

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

WORKUP

ESSENTIAL

- History including:
  - Transplant history (orthotopic transplant or SOT), including timing since transplant, current/past immunosuppressive therapies, recurrent infections, or immunodeficiency.
  - Infection history, in particular, EBV viral load status and recurrent infections prior to transplant.
- Baseline re-evaluation of graft organ function and any episodes of graft rejection by a graft transplant specialist, as appropriate.
- Physical examination, with attention to lymph nodes, tonsils, liver and spleen, effusions, ascites, neurologic signs/symptoms.
- EBV PCR (whole blood or plasma)[e]
- Laboratory tests
  - CBC with differential
  - Electrolytes, calcium, phosphorus, BUN, creatinine, uric acid, LDH, AST, ALT, bilirubin, albumin
  - Immunosuppressive medication levels
  - Consider hepatitis B testing (HBcAb, HBsAb, HBsAg), HIV testing (if indicated)
  - Consider G6PD testing for male patients[f]
  - Pregnancy test for patients of childbearing age
- Bilateral bone marrow aspirate and biopsy (in select cases)[g]
- Lumbar puncture
  - CSF cell count and differential
  - Cytology of CSF, including total nucleated cell count and morphologic review of cytospin[g]
- Imaging
  - Cross-sectional scans of the neck, chest, abdomen, and pelvis
    - ◊ Neck CT with IV contrast or MRI with and without contrast
    - ◊ Chest CT with IV contrast
    - ◊ Abdomen and pelvis CT with oral and IV contrast or MRI with and without contrast
  - FDG-PET/CT or FDG-PET/MRI, if available (do not delay treatment to obtain)[h]
  - For CNS PTLD, MRI of the brain with and without contrast and MRI of the spine with and without contrast.
- Fertility counseling recommended for all patients; fertility preservation as clinically appropriate.[i] See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology

→ Treatment based on PTLD subtype (PTLD-3)

USEFUL UNDER CERTAIN CIRCUMSTANCES

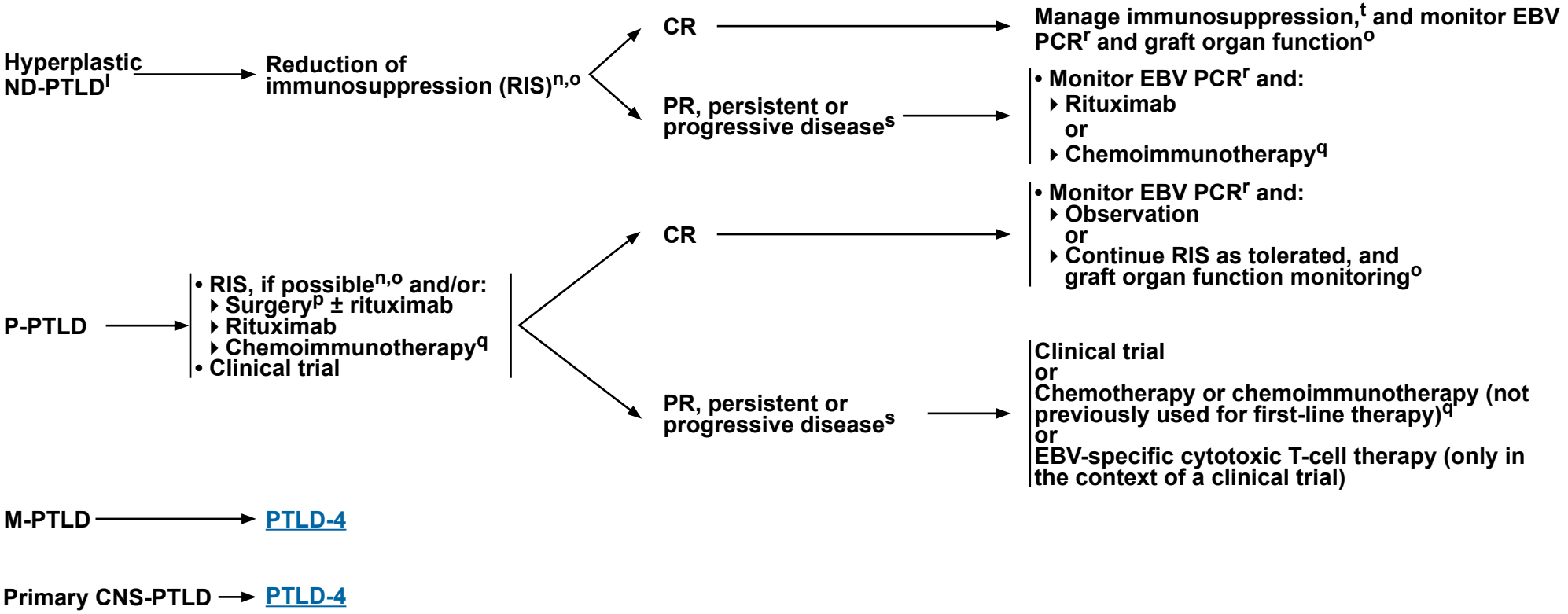
- MRI of the head with and without contrast
- MRI of the spine with and without contrast
- Flow cytometry of CSF[j]
- EBV PCR of CSF
- Flow cytometry, FISH for *MYC* rearrangement, and IHC of bone marrow aspirate and biopsy[k]
- Consider baseline immunoglobulin panel prior to using rituximab or if there are any underlying concerns about immunodeficiency.

[e] An elevated EBV PCR is not diagnostic of PTLD, and EBV viral load cannot be used for response assessment in PTLD.
[f] Principles of Supportive Care (PBCL-D).
[g] Useful in selected cases of M-PTLD; not essential for hyperplastic ND-PTLD, P-PTLD and in localized tonsillar disease.
[h] Obtaining a PET/CT or PET/MRI does not exclude the need for full diagnostic quality high-resolution CT or MRI.
[i] Fertility preservation is an option for some patients. Options include sperm cryopreservation, oocyte cryopreservation, harvesting of ovarian or testicular tissue for cryopreservation, or embryo cryopreservation. Referral to a fertility preservation/reproductive health program should be considered for eligible patients prior to initiation of chemotherapy (Mulder RL, et al. Lancet Oncol 2021;22:e45-e56; Mulder RL, et al. Lancet Oncol 2021;22:e57-e67).
[j] Flow cytometry of CSF samples is not routinely recommended, but may be useful at the pathologist's discretion.
[k] For low-level or morphologically indeterminate involvement

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

NCCN Guidelines Version 2.2025
Pediatric Post-Transplant Lymphoproliferative Disorders

NCCN Guidelines Index
Table of Contents
Discussion



[f] Principles of Supportive Care (PBCL-D).
[l] Treatment is based on the unique histology.
[m] Rituximab can be used if CD20 is only partially or dimly expressed but is not essential for CD20-negative PTLD. The status and pattern of CD20 expression by flow cytometry should be reported in all subtypes of PTLD.
[n] Response to RIS is variable and patients need to be closely monitored; RIS: reduction in calcineurin inhibition (cyclosporin and tacrolimus), discontinuation of antimetabolic agents (azathioprine and mycophenolate mofetil), and consider discontinuation of non-glucocorticoid immunosuppression in patients who are critically ill.
[o] Collaboration with a graft transplant specialist is recommended to coordinate immunosuppressive medication assessment, dose modifications, and graft organ function monitoring.
[p] Completely resected PTLD without disease elsewhere can be managed without additional therapy with the exception of RIS.
[q] Suggested Treatment Regimens (PTLD-B).
[r] EBV viral load cannot be used for response assessment in PTLD.
[s] Rebiopsy should be considered prior to additional therapy.
[t] Re-escalation of immunosuppressive therapy should be individualized, taking into account the extent of initial RIS and the nature of the organ allograft.

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

PTLD SUBTYPE	FIRST-LINE THERAPY[f,m]	INITIAL RESPONSE[r]	FOLLOW-UP/SECOND-LINE THERAPY[f,m]
M-PTLD (B-cell type, Burkitt lymphoma-type)	• RIS if possible[n,o] and treatment for BL (PBCL-6 through PBCL-9)		
M-PTLD (B-cell type, non-Burkitt lymphoma-type)[l]	• RIS, if possible[n,o] ± surgery[p] and/or: ▸ Rituximab ▸ Chemoimmunotherapy[q] • Clinical trial	CR	See appropriate histologic subtype for follow-up (PBCL-10 or PMBL-1) or RIS and graft organ function monitoring[o]
		PR, persistent or progressive disease[s]	Clinical trial or If RIS ± surgery was initial therapy, then rituximab or chemoimmunotherapy or chemotherapy[q] or If RIS ± surgery and rituximab or chemoimmunotherapy was initial therapy, then chemotherapy or chemoimmunotherapy (not previously used for first-line therapy)[q] or EBV-specific cytotoxic T-cell therapy (only in the context of a clinical trial)
M-PTLD (T/NK-cell type[l] or Plasmacytic-type)	• Other than reduction of RIS,[n,o] there are no established treatment options. • M-PLTD, T/NK-cell type: HDT/ASCR may not be appropriate. Treatment should be individualized based on histologic subtype and the nature of the organ allograft. • Plasmacytic PTLD: Multiple myeloma type treatment can be considered for aggressive/refractory disease.		
M-PTLD (CHL-type)	RIS, if possible[n,o] and treatment for CHL (See NCCN Guidelines for Pediatric Hodgkin Lymphoma)		
Primary CNS PTLD (B-cell type)	• High-dose methotrexate + rituximab • Chemoimmunotherapy[q] including methotrexate • Consider RT for selected cases		

[f] Principles of Supportive Care (PBCL-D).
[l] Treatment is based on the unique histology.
[m] Rituximab can be used if CD20 is only partially or dimly expressed but is not essential for CD20-negative PTLD. The status and pattern of CD20 expression by flow cytometry should be reported in all subtypes of PTLD.
[n] Response to RIS is variable and patients need to be closely monitored; RIS: reduction in calcineurin inhibition (cyclosporin and tacrolimus), discontinuation of antimetabolic agents (azathioprine and mycophenolate mofetil), and consider discontinuation of non-glucocorticoid immunosuppression in patients who are critically ill.
[o] Collaboration with a graft transplant specialist is recommended to coordinate immunosuppressive medication assessment, dose modifications, and graft organ function monitoring.
[p] Completely resected PTLD without disease elsewhere can be managed without additional therapy with the exception of RIS.
[q] Suggested Treatment Regimens (PTLD-B).
[r] EBV viral load cannot be used for response assessment in PTLD.
[s] Rebiopsy should be considered prior to additional therapy.

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

CLINICAL PRESENTATION AND DIAGNOSTIC PATHOLOGY[a,b]

Clinical Presentation
- **Localized or disseminated disease that affects the transplanted organ**
- **Symptoms are related to the affected organ and age of patient at the time of transplant**
- **Symptoms are usually preceded by elevation of EBV viremia (detectable using EBV-PCR)**
- **Symptoms can simulate organ rejection or graft versus host disease (GVHD)**
- **Hyperplastic ND-PTLD and P-PTLD have nodal manifestations**
- **M-PTLD presents with symptoms of lymphoma**

Morphology
- **Histopathologic findings and classifications of pediatric PTLD are similar to those described in adults.**
  - **Hyperplastic ND-PTLD: Mass-forming lesions with expanded but retained lymphoid organ architecture by prominent proliferation of secondary follicles (florid follicular hyperplasia), or paracortical proliferation of plasma cells in large aggregates to sheets (plasmacytic hyperplasia), or paracortical proliferation of mixed small to intermediate-sized lymphocytes, immunoblasts, and plasma cells (infectious mononucleosis-like hyperplasia).**
  - **P-PTLD: Lesions demonstrate nodal architectural effacement by mixed infiltrate of small to intermediate-sized lymphocytes, immunoblasts, plasma cells, and histiocytes. Large atypical lymphocytes resembling Hodgkin/Reed-Sternberg cells (HRS-like cells) may be present.**
  - **M-PTLD: Lesions fulfill the criteria of lymphoma seen in immunocompetent individuals.**

Diagnosis
- **Biopsy and adequate immunophenotyping are essential for accurate diagnosis of PTLD and its subtype.**
- **If biopsy is not feasible, consider presumed treatment of PTLD subtype (see PTLD-3), once infection is excluded.**

Assessment of Clonality
- **Hyperplastic ND-PTLDs: polyclonal;**
- **P-PTLDs: variable and can be polyclonal, oligoclonal, and monoclonal;**
- **M-PTLDs: monoclonal**

Footnotes

[a] In the WHO Classification of Haematolymphoid Tumors (5th Edition; WHO5), posttransplant lymphoproliferative disorders (PTLD) are classified under the category of immunodeficiency and dysregulation-associated lymphoproliferative disorders (IDD-LPD), where diagnosis requires a three-part nomenclature including histologic lesion, status of oncogenic viruses, and the clinical setting of IDD.[1]

[b] On the other hand, in the section of Haematolymphoid Disorders of the WHO Classification of Paediatric Tumors (5th Edition), PTLD are listed as an independent category within the group of IDD-LPD.[2]

References

[1] WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed; vol 11). Lyon (France): International Agency for Research on Cancer; 2024.

[2] WHO Classification of Tumours Editorial Board. Paediatric tumours. (WHO classification of tumours series, 5th ed.; vol. 7). Lyon (France): International Agency for Research on Cancer; 2022.

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

PRINCIPLES OF SYSTEMIC THERAPY[a]
(PTLD)

- There are no established treatment options. Selection of a regimen is dependent on patient characteristics and the subtype of PTLD. Suggested regimens are listed below.[b]
- Rituximab[1,b]

Drug	Dose and schedule
Rituximab[b,c]	375 mg/m^2 dose IV x 3–4 doses weekly x 4 weeks[c]

Chemoimmunotherapy

- Low-dose R-CP[2] (rituximab, cyclophosphamide, prednisone); 21-day cycle

Drug	Dose and schedule
Cycle 1 and 2	
Cyclophosphamide	600 mg/m^2 IV over 30–60 min on day 1 of each cycle
Prednisone	1 mg/kg PO every 12 h or methylprednisolone 0.8 mg/kg IV every 12 h on days 1-5 of each cycle
Rituximab[b]	375 mg/m^2 IV on days 1, 8, and 15 of cycles 1 and 2
Cycle 3, 4, 5, 6	
Cyclophosphamide	600 mg/m^2 IV over 30–60 min on day 1 of each cycle
Prednisone	1 mg/kg PO every 12 h or methylprednisolone 0.8 mg/kg IV every 12 h on days 1-5 of each cycle

- R-CHOP (rituximab,[b] cyclophosphamide, doxorubicin, vincristine, prednisone)
- R-CEPP (rituximab,[b] cyclophosphamide, etoposide, prednisone, procarbazine)
- R-CEOP (rituximab,[b] cyclophosphamide, etoposide, vincristine, prednisone)
- R-CVP (rituximab,[b] cyclophosphamide, vincristine, prednisone)

Chemotherapy (used after poor response to rituximab)

- CHOP[3] (cyclophosphamide, doxorubicin, vincristine, prednisone); 21-day cycle

Drug	Dose and schedule
Cycle 1, 2, 3, 4	
Cyclophosphamide	750 mg/m^2 IV over 30–60 min on day 1 of each cycle
Vincristine	1.4 mg/m^2 IV on day 1
Prednisone	50 mg/m^2 PO days 1–5
Doxorubicin	50 mg/m^2 IV on day 1
G-CSF (eg, filgrastim or pegfilgrastim)[b]	

- Moderate dose COMP (mCOMP; modified cyclophosphamide, vincrinstine, methotrexate, prednisone; 28-day cycle)[4]

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

Footnotes and References on PTLD-B 2 of 2

PRINCIPLES OF SYSTEMIC THERAPY (PTLD)

Footnotes

[a] Principles of Supportive Care (PBCL-D).
[b] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[c] The role of additional therapy with rituximab if CR not achieved after 4 to 8 doses is not established in children. If there is no response after 4 weeks, switch to chemoimmunotherapy or chemotherapy.

References

1 Webber S, Harmon W, Faro A, et al. Anti-CD20 Monoclonal Antibody (rituximab) for Refractory PTLD after Pediatric Solid Organ Transplantation: Multicenter Experience from a Registry and from a Prospective Clinical Trial [abstract]. Blood 2004;104:Abstract 746.
2 Gross TG, Orjuela MA, Perkins SL, et al. Low-dose chemotherapy and rituximab for posttransplant lymphoproliferative disease (PTLD): a Children's Oncology Group Report. Am J Transplant 2012;12:3069-3075.
3 Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 2012;13:196-206.
4 Maecker-Kolhoff B, Beier R, Zimmermann M, et al. Response-adapted sequential immuno-chemotherapy of post-transplant lymphoproliferative disorders in pediatric solid organ transplant recipients: results from the prospective Ped-PTLD 2005 trial [abstract]. Blood 2014;124:Abstract 4468.

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

ABBREVIATIONS

ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AYA	adolescent and young adult
BFM	Berlin-Frankfurt-Munster
BL	Burkitt lymphoma
BM	bone marrow
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CBC	complete blood count
CIITA	class II transactivator
CIV	continuous intravenous infusion
CNS	central nervous system
CR	complete response
CRb	complete response biopsy negative
CRu	complete response unconfirmed
CRRT	continuous renal replacement therapies
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
DLBCL	diffuse large B-cell lymphoma
EBER	Epstein-Barr virus-encoded RNA
EBER-ISH	Epstein-Barr virus-encoded RNA in situ hybridization
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECHO	echocardiogram
EOT	end of treatment
FAB	French American British
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
G6PD	glucose-6-phosphate dehydrogenase
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
H&P	history and physical
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCT	hematopoietic cell transplant
HGBL	high-grade B-cell lymphoma
HLA	human leukocyte antigen
HRS	Hodgkin-Reed-Sternberg
HSV	herpes simplex virus
ICC	International Consensus Classification
IDD-LPD	immunodeficiency and dysregulation-associated lymphoproliferative disorders
IHC	immunohistochemistry
IT	intrathecal
JCV	John Cunningham virus
LBCL	large B-cell lymphoma
LDH	lactate dehydrogenase
LMB	Lymphome Malin de Burkitt
MCL	mantle cell lymphoma
MHC	major histocompatibility complex
M-PTLD	monomorphic post-transplant lymphoproliferative disorders
ND-PTLD	non-destructive post-transplant lymphoproliferative disorders
MR	minor response
MUGA	multigated acquisition
NOS	not otherwise specified
NR	no response
OAR	organ at risk
PA	posteroanterior
PALS	Pediatric Advanced Life Support
PCR	polymerase chain reaction
PD	progressive disease
PMBL	primary mediastinal large B-cell lymphoma
PJP	pneumocystis jiroveci pneumonia
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRES	posterior reversible encephalopathy syndrome
P-PTLD	polymorphic post-transplant lymphoproliferative disorders
PTLD	posttransplant lymphoproliferative disorders
RIS	reduction of immunosuppression
SNP	single nucleotide polymorphism
SOT	solid organ transplant
SPD	sum of product of greatest perpendicular diameters
TLS	tumor lysis syndrome
ULN	upper limit of normal

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Pediatric Aggressive Mature B-Cell Lymphomas

This discussion corresponds to the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas. Last updated: April 28, 2025.

Discussion

Table of Contents

NCCN Guidelines Version 2.2025
Pediatric Aggressive Mature B-Cell Lymphomas

Overview

An estimated 9550 children (≤14 years of age) and 5140 adolescents (aged 15–19 years) will be diagnosed with cancer in the United States in 2025, and 1050 children and 600 adolescents will die from the disease.[1]

Non-Hodgkin lymphomas (NHLs) account for 6% and 7% of all cancers, respectively, in children and adolescents with the 5-year relative survival rates of 91% and 89%, respectively. Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are the most common types of aggressive mature B-cell lymphomas in children and adolescents, and the incidence of DLBCL markedly increases with age, especially in adolescents.[2-5]

BL and DLBCL account for about 38% and 20% of NHLs, respectively, in children aged 0 to 14 years. DLBCL accounts for about 37% of NHLs in adolescents aged 15 to 19 years and BL accounts for about 21% of NHLs in the same age group.[3]

Endemic, sporadic, and immunodeficiency-associated BL are the three clinical variants of BL described in the updated World Health Organization classification of Hematolymphoid Tumors (WHO5).[6] The endemic variant of DLBCL has also been described and may be associated with EBV, hepatitis B virus (HBV), and/or John Cunningham virus (JCV) infection.[7,8]

BL associated with EBV infection, formerly known as “endemic variant,” is more common in equatorial Africa, as well as in South America, and Papua New Guinea.[9-14] The endemic variant classically presents in the jaw, orbit, mesentery, and central nervous system (CNS). The sporadic variant (EBV negative) mainly occurs in North America and Europe. However, EBV infection is found in 15% of the BL occurring in Western countries and EBV positive BL is genetically similar across different areas of the globe.[10] The sporadic variant most commonly presents in the abdomen, lymph nodes, bone marrow, or cerebrospinal fluid (CSF). Immunodeficiency-associated BL occurs primarily in people living with HIV (PLWH), in individuals with inborne errors of immunology and immune deficiency/dysregulation (IEI/IDD), and in patients who have received hematopoietic cell transplant (HCT) or solid organ transplant (SOT) or in those with post-transplant lymphoproliferative disorders (PTLD).

Primary mediastinal B-cell lymphoma (PMBL) is considered a distinct entity of NHL arising from mature thymic B cells, accounting for 2% of mature B-cell lymphomas in children and adolescents.[6]

PTLD are a heterogeneous group of lymphoproliferative disorders (LPD) occurring after SOT or allogeneic HCT that are related to immunosuppression and in most cases, EBV infection.[6,15,16]

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Aggressive Mature B-Cell Lymphomas provide recommendations for diagnostic workup, treatment, and surveillance strategies in addition to a general discussion on the classification systems and supportive care considerations. The subtypes that are covered in these guidelines are listed below. These guidelines do not address the management of endemic variant of BL or DLBCL.

- Burkitt lymphoma (BL)
- Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)
- Large B-cell lymphomas (LBCL) with *IRF4/MUM1* rearrangement
- LBCL with 11q aberration
- High-grade B-Cell lymphomas (HGBL) with *MYC* and *BCL2* or *BCL6* rearrangements; DLBCL/HGBL with *MYC* and *BCL2* rearrangements
- Primary mediastinal large B-cell lymphoma (PMBL)
- Post-transplant lymphoproliferative disorders (PTLD) following SOT

NCCN Guidelines® for Pediatric Aggressive Mature B-Cell Lymphomas are intended to apply to all pediatric patients and adolescent and young adult (AYA) patients with good organ function treated in a pediatric oncology setting. The Panel considers "pediatric" to include any patients aged 18 years and younger, and AYAs over 18 years (and <39 years as defined by the National Cancer Institute), who are treated in a pediatric oncology setting. Practice patterns vary from center to center in terms of whether AYA patients with mature B-cell lymphomas are treated primarily by pediatric or adult oncologists.

AYA patients treated in an adult oncology setting should be treated as per the adult NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org).

Although the guidelines are believed to represent the optimal treatment strategy, the Panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.

Guidelines Update Methodology

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

Literature Search Criteria

Prior to the initial development of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas, an electronic search of the PubMed database was performed to obtain key literature using the following search terms: pediatric Burkitt lymphoma, pediatric diffuse large B-cell lymphoma, pediatric primary mediastinal large B-cell lymphoma, and pediatric post-transplant lymphoproliferative disorders. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[17]

The search results were narrowed by selecting relevant studies in humans published in English. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

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

Burkitt Lymphoma and Other Large B-Cell Lymphomas

Pediatric aggressive mature B-cell lymphomas (BL and other LBCL, including DLBCL, NOS and HGBL) are highly aggressive but curable, and

the treatment is complex. It is preferred that treatment occur at centers with expertise in the management of these diseases.

Clinical Presentation

Patients with aggressive mature B-cell lymphomas present with painless regional or diffuse lymphadenopathy in the head/neck and inguinal region, hepatomegaly, splenomegaly, and B symptoms including fever, chills, night sweats, unexplained/unintentional weight loss, fatigue, bone pain, and/or irritability.[18] Extranodal involvement (including the abdomen, skin, and other organs) on presentation is common.[19] Patients with abdominal tumors may have a history of abdominal pain/swelling, poor appetite/early satiety, constipation, and/or nausea/vomiting.[20] Intrathoracic masses can cause cough, dyspnea, wheezing, stridor, chest pain, and/or reduced endurance. Tumors in the head and neck may be associated with swollen glands; swelling in the neck, jaw, gingival area, or maxilla; difficulty swallowing; choking; and/or vision changes.

Finally, CNS involvement can lead to bladder or bowel dysfunction, lower extremity weakness, and/or headaches. Oncologic emergencies related to rapid tumor growth (tumor lysis syndrome [TLS], superior vena cava [SVC] syndrome, spinal cord compression, and respiratory distress due to airway compression) may also be the reason for initial presentation.[18]

Diagnosis

Excisional or incisional biopsy of the most accessible site is preferred, with fresh biopsy tissue sent to pathology in saline to ensure viable diagnostic tissue. Fine-needle aspiration (FNA) biopsy alone is not suitable for the initial diagnosis of pediatric lymphoma.[21]

A core needle biopsy is not optimal but can be used when a lymph node or tumor mass is not easily accessible for excisional or incisional biopsy. Touch preparation of fresh tissue samples is recommended whenever possible to obtain essential cytologic details that may be difficult to detect in small core needle biopsy samples, and morphologic review should be performed as clinically indicated.[22]

BL is composed of patternless sheets of lymphoid cells that appear to mold to one another (pseudo-cohesion). The lymphoid cells are intermediate in size (similar in size to a histiocyte nucleus) with a round nuclei, relatively coarse chromatin that is finely dispersed with multiple small nucleoli, and moderate amounts of densely basophilic cytoplasm.[6] Clear cytoplasmic vacuoles may be seen on Wright Giemsa-stained touch preparations. Scattered histiocytes with apoptotic debris in the cytoplasm (tangible body macrophages) confer the so-called “starry sky” appearance indicative of high cell turnover. Mitosis and apoptotic bodies are often numerous.

Other LBCL are characterized by large cells with variable nuclear contours, condensed to vesicular chromatin, single or multiple nucleoli, and scant to moderately abundant cytoplasm.[6] Cytoplasmic vacuoles are not typically present. The architecture of LBCL may have a diffuse and/or follicular pattern and also shows sheet-like growth, but the significant nuclear pleomorphism and more abundant cytoplasm confer a lighter color at low magnification. “Starry sky” appearance is generally not prominent.

Additional Diagnostic Testing

Immunophenotyping is essential for the differentiation of subtypes, and it can be performed using immunohistochemistry (IHC) and flow cytometry. Cytogenetic or molecular genetic analysis may be necessary under certain circumstances to identify the specific chromosomal translocations that are characteristic of each subtype or to establish clonality.

Pediatric aggressive mature B-cell lymphomas express surface immunoglobulin and B-cell antigens that confirm mature phenotype. BL and other LBCL are both typically negative for terminal deoxynucleotidyl

transferase (TdT), a marker of cellular immaturity, and negative for CD3, a T-cell marker. TdT, CD3, and CD34 should be checked to exclude lymphoblastic lymphomas.

BL is characterized by CD10+, CD20+, Ki-67+ (≥95%) and MYC+. BL generally exhibits a simple karyotype with *MYC* rearrangement resulting in the juxtaposition of the *MYC* gene on chromosome 8, with the immunoglobulin heavy chain (*IGH*) region on chromosome 14 or the immunoglobulin light chain genes as their sole cytogenetic abnormality [t(8;14) present in 80% of cases, and its variants t(2;8) and t(8:22) present in the remaining 20% of cases].[23-26]

Pediatric DLBCL, NOS is CD20+ with variable expression of CD10, BCL2, MUM1, and high Ki-67. Pediatric DLBCL, NOS is considered an exclusion diagnosis. They are predominantly of germinal center B-cell (GCB) subtype (CD10+; or BCL2+ and MUM1-) with abnormalities involving 8q24, including *MYC* rearrangement.[27-32] Genetic abnormalities in DLBCL, NOS, involving chromosomes 4, 19, and 16 are unique to pediatric population suggesting distinct etiology.[33] Additional abnormalities involving *BCL2* or *BCL6* are very rare in pediatric DLBCL-NOS and in most instances, lymphomas with *MYC* rearrangement are in fact BL.

Aggressive mature B-cell lymphomas without *MYC* rearrangement that are morphologically similar to BL with a more complex karyotype than BL have also been described in pediatric patients.[6] HGBL with *BCL2 and/or BCL6* rearrangements are also rare in the pediatric population, but may be more common in AYA patients.[34-39] In patients older than 18 years, it is essential to differentiate BL from HGBL with *MYC* and *BCL2* or *BCL6* rearrangements, DLBCL/HGBL with *MYC* and *BCL2* rearrangements, LBCL that are *MYC* negative with *BCL6* rearrangements or HGBL, NOS.

Karyotype or fluorescence in situ hybridization (FISH) for *MYC* rearrangement is essential for the diagnosis of pediatric aggressive mature B-cell lymphomas. FISH using a break-apart probe is more reliable for the detection of t(8;14) as well as to detect any partner gene involved in *MYC* rearrangement.[39,40] Cytogenetic analysis for detection of t(8;14) or variants [t(2;8) or t(8;22)] may be useful under certain circumstances. Importantly, FISH for *BCL2* and *BCL6* rearrangements should be done for patients older than 18 years with lymphomas suggestive of BL histology.

FISH for *IRF4/MUM1* rearrangement is recommended for lymphomas that are MYC negative and MUM1 positive to confirm the diagnosis of LBCL with *IRF4/MUM1* rearrangement.[6,33,41-43] Lymphomas that are MUM1 negative and MYC negative should be tested for BCL2. Molecular analysis for 11q aberrations should be done to confirm the diagnosis of HGBL with 11q aberration, if both MUM1 and BCL2 are negative.[6,33,44-47] IHC for CD56 (in absence of CD38 bright by flow cytometry) and FISH or single nucleotide polymorphism (SNP) array for the detection of 11q aberration is useful to confirm the diagnosis of HGBL with 11q aberration. The epidemiology, natural history and optimal management of these entities in pediatric population are yet to be defined. LBCL with *IRF4/MUM1* rearrangement are most often treated like DLBCL. HGBL with 11q aberration are most often treated like typical sporadic BL.

Epstein-Barr encoding region in situ hybridization (EBER-ISH) is useful to demonstrate EBV association, if indicated by a history or suspicion of IEI/IDD. EBV expression is predominantly seen in BL occurring in certain geographic areas. However, EBV-positive mature B-Cell lymphomas can be seen in pediatric patients without recognized IEI/IDD, and some evidence suggests that EBV positivity in sporadic BL may be associated with older age at diagnosis, higher incidence of nodal involvement, and distinct pathogenic features that are similar independent of the geographic area of occurrence.[48-51]

Workup

Workup for patients with a diagnosis of pediatric aggressive mature B-cell lymphomas (as outlined on PBCL-3) includes history and physical examination, laboratory analysis, bilateral bone marrow aspirate and biopsy, lumbar puncture, and imaging.

Baseline immunoglobulin (Ig) panel should be obtained prior to using rituximab if there are any concerns about IDD.[52,53] In the Inter B NHL Ritux 2010 trial, the percentage of patients receiving Ig replacement therapy was higher in the chemotherapy with rituximab group than in the chemotherapy group (16% and 7%, respectively) mainly due to low Ig concentration.[54] IgG replacement therapy should be considered in patients with hypogammaglobulinemia and recurrent infections.

CNS involvement is found in approximately 9% and 3% of pediatric patients with BL and DLBCL, respectively.[55,56] CSF cell count with differential and cytology of CSF are recommended as part of essential diagnostic workup.

Imaging studies should include cross-sectional scans of the neck, chest, abdomen, and pelvis. Fluorodeoxyglucose (FDG)-PET/CT or FDG-PET/MRI is recommended if available.[57] However, treatment should not be delayed in order to obtain this scan, and FDG-PET does not exclude the need for full diagnostic quality, high-resolution CT or MRI. In addition, a baseline echocardiogram (ECHO) or multigated acquisition (MUGA) scan, and electrocardiogram (ECG) is recommended.

Pediatric and AYA patients treated with chemotherapy are at increased risk for infertility. Fertility counseling is recommended for all patients. Fertility preservation is an option for some patients and referral to fertility preservation/reproductive health program should be considered for eligible patients prior to initiation of chemotherapy.[58,59]

Response Criteria

The Panel recommends use of the International Pediatric NHL Response Criteria.[60] In this response criteria, disease is classified as progressive disease (PD), no response (NR), minimal response (MR), partial response (PR), and complete response (CR). For patients with less than CR by these criteria at the end of treatment (EOT), the residual mass should be biopsied to confirm the presence or absence of residual disease. The majority of residual masses at the EOT are necrotic tumor. Response assessment using PET/CT scans is done according to the Deauville 5-point scale (PS), which is based on the visual assessment of FDG uptake in the involved sites relative to that of the mediastinum and the liver.[61] A Deauville score of 1 to 3 is now widely considered to be PET negative, and a Deauville score of 4 to 5 is universally considered to be PET positive. A score of 4 on an interim or EOT restaging scan may be consistent with a PR if the FDG avidity has declined from initial staging, while a score of 5 denotes PD.

Sites of original disease should be reassessed with imaging studies as indicated (abdominal ultrasound, chest/abdomen/pelvis CT with contrast, and/or MRI of the head, neck, abdomen, and/or pelvis). Bone marrow and CSF studies should also be performed if they were initially involved. FDG-PET/CT or FDG-PET/MRI may be considered if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. Treatment should not be escalated based on the results of FDG-PET alone. Repeat biopsy of residual mass should be considered prior to additional therapy. If the residual lesion is FDG-PET negative (Deauville 1–3), biopsy is not required because of the high negative predictive value of FDG-PET.[62-66] In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. It is important to note, however, that the positive predictive value of FDG-PET is fairly low.[67] False-positive findings may

include inflammation, necrotic tumor, reactive lymphadenitis, brown fat, thymic rebound, and secondary malignancy.

Staging and Risk Group Classification

Historically, the Murphy/St. Jude Childhood NHL staging classification, published in 1980, was used for the staging of pediatric BL and DLBCL.[68] A revised system, the International Pediatric NHL Staging System (IPNHLSS), was published in 2015 to address some limitations of the original system by including newer histologic entities; recognizing frequent skin, bone, kidney, ovarian, and other organ involvement; and accounting for improved detection of bone marrow and CNS involvement and distant spread.[69] The NCCN Pediatric Aggressive Mature B-Cell Lymphoma Panel supports use of the revised IPNHLSS. Information regarding bone marrow and CNS involvement and distant spread is important for staging and risk group classification.

Bone marrow involvement is defined by morphologic evidence of lymphoma cells in a bone marrow aspirate.[69] Patients with bone marrow and CNS involvement have stage IV disease. CNS is considered involved if one or more of the following applies:

- Any lymphoma cells by cytology in CSF
- Any CNS tumor mass by imaging
- Cranial nerve palsy (if not explained by extracranial tumor)
- Clinical spinal cord compression
- Parameningeal extension: cranial and/or spinal

The treatment recommendations for patients with BL and other LBCL are based on the risk group classification used in the French-American-British (FAB) /Lymphoma Malignancy B (LMB) group trial (FAB/LMB96)[70,71]:

- *Group A:* Completely resected stage I or abdominal stage II disease
- *Group B (low risk):* Unresected stage I and non-abdominal stage II or stage III with low lactate dehydrogenase (LDH)
- *Group B (high risk):* Stage III with high LDH or all CNS stage IV disease with bone marrow involvement (<25% lymphoma cells)
- *Group C:* Any CNS involvement and/or with ≥25% lymphoma cells in the bone marrow

Response Assessment

Response assessment is critical during therapy for patients with pediatric aggressive mature B-cell lymphomas, especially for risk Group B patients treated per Inter-B-NHL therapy protocol (COG ANHL1131 regimen B), since additional treatment options depend on the response to initial therapy.

Initial Treatment

Intensive multiagent chemotherapy is the mainstay of initial treatment for patients with BL or other LBCL and is highly effective for most patients (based on many clinical trials, including those discussed below). Several cooperative groups have been instrumental in establishing the standard regimens for these patients, including the Children's Oncology Group (COG), the Pediatric Oncology Group (POG), the French Society of Pediatric Oncology, the United Kingdom Children's Cancer Study Group, and the German Berlin-Frankfurt-Münster (BFM) group.

Rituximab, an anti-CD20 monoclonal antibody with indications in certain adults with B-cell lymphomas, may be included for low-risk Group B patients (see below) and is recommended for patients with high-risk Group B and Group C BL and DLBCL. In 2021, the U.S. Food and Drug Administration (FDA) approved rituximab in combination with chemotherapy for BL and DLBCL in pediatric patients based on the results of the Inter-B-NHL-Ritux-2010 (COG ANHL1131) study, which showed that the addition of rituximab to standard Lymphome Malin B (LMB)

chemotherapy markedly prolonged event-free survival (EFS) and overall survival (OS) among children and adolescents with high-grade, high-risk, mature B-cell NHL.[71]

Group A

POG 9219 regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone for 9 weeks) or the FAB/LMB96 Regimen A (COPAD [cyclophosphamide, vincristine, prednisone, and doxorubicin] without intrathecal therapy) are included as preferred regimens if they are not enrolled in a clinical trial.[72,73]

The POG 9219 regimen is based on two trials with a total of 340 pediatric patients with stage I or II NHL, resected or not (Group A and low-risk Group B), conducted by the POG between 1983 and 1991.[72] Chemotherapy consisted of induction/consolidation chemotherapy (POG 9219 regimen for 9 weeks) and continuation chemotherapy (mercaptopurine and methotrexate) for 24 weeks. CNS prophylaxis with intrathecal therapy (methotrexate, cytarabine, and hydrocortisone) was given only for patients with primary tumors in the head and neck region.

In the first trial, patients were randomized to receive either 8 months of chemotherapy (induction/consolidation followed by continuation of chemotherapy) with radiation therapy (RT) or 8 months of chemotherapy alone. In the second trial, all patients received induction/consolidation chemotherapy without RT for 9 weeks, and those with CR after 9 weeks were randomized to continuation chemotherapy or no further therapy. The 5-year rates of continuous CR were 89%, 86%, and 88%, respectively, for those who received 9 weeks of chemotherapy without RT, 8 months of chemotherapy without RT, and 8 months of chemotherapy with RT. These results indicate that 9 weeks of induction chemotherapy (vincristine, doxorubicin, cyclophosphamide, and prednisone) is sufficient in this group of patients.

The international FAB/LMB96 study included pediatric patients with all stages of NHL.[73] All patients with resected stage I or completely resected abdominal stage II disease received two courses of COPAD without intrathecal therapy after surgery (Regimen A). After a median follow-up of 51 months, the 4-year EFS with events defined as treatment failure for any reason was 98% and OS was 99%.

Alternatively, an equivalent BFM regimen can be considered. The NHL-BFM95 trial was a randomized non-inferiority study that compared methotrexate infused over 4 hours with a 24-hour infusion in patients with stage I or II B-cell NHL in an attempt to reduce toxicity.[74] Patients in Group A received two cycles of chemotherapy; failure-free survival at 1 year in this group was 95% ± 5% (n = 20) versus 100% (n = 19) for the 4-hour and 24-hour arms, respectively, meeting the non-inferiority endpoint. The incidence of grade 3/4 mucositis was significantly lower in the 4-hour arm in all risk groups.

The Panel emphasizes that there is no data to favor the use of one regimen over the other. It should however be noted that the duration of cumulative doses of steroids is longer with POG 9219 regimen (9 weeks) compared to COPAD chemotherapy (FAB/LMB96 Regimen A) and the incidences of acute toxicity are also higher with POG 9219 regimen.

No further treatment is necessary for patients achieving CR at the completion of induction therapy and those with a less than CR should be treated as described for relapsed/refractory disease.

Group B (Low Risk)

COG ANHL1131 regimen B with or without rituximab is recommended for patients with Group B low risk disease. POG 9219 regimen (as described above for patients with Group A disease) is also an option for patients with unresected stage I and non-abdominal stage II disease.

Rituximab has not been evaluated in clinical trials for patients with low-risk Group B disease. However, in keeping with adult practice and data on its efficacy and safety in patients with high-risk disease (discussed below), the Panel deems the inclusion of rituximab in the treatment of this patient population to be appropriate. The Panel recommends COG ANHL1131 regimen B starting with a COP reduction phase with or without rituximab for patients with Group B low-risk disease.

Patients with <20% tumor reduction after COP should start induction therapy with rituximab + COPADM (R-COPADM) of COG ANHL1131 regimen C1 CNS-negative with rituximab, even if rituximab was not included initially (see *Group C*, below). Patients with ≥20% tumor reduction after COP reduction phase should proceed to COPADM1 induction of COG ANHL1131 regimen B with or without rituximab, based on initial therapy (ie, if rituximab was included at day 6 of COP reduction, it should be continued throughout therapy). A second response assessment is performed in these initial responders after consolidation 1. Those with CR continue regimen B with or without rituximab based on initial therapy, while those with a less than CR should change to COG ANHL1131 regimen C1 CNS-negative with rituximab, starting with R-CYVE1 (rituximab, cytarabine, and etoposide) (see *Group C*, below).

As discussed earlier for Group B (low-risk disease), there is no data to favor the use of one regimen over the other. While the long-term safety profile is similar to both regimens, POG 9219 regimen is associated with higher incidences of acute toxicity and longer duration of cumulative doses of steroids.

Group B (High Risk)

COG ANHL1131 regimen B with rituximab is recommended for patients with high-risk Group B disease based on the results from COG ANHL01P1 trial and Inter-B-NHL-Ritux-2010 (COG ANHL1131) trial.[71,75]

In the COG ANHL01P1 trial of patients younger than 30 years with high-risk (stage III/IV) Group B mature B-cell lymphoma, 45 patients received FAB/LMB96 chemotherapy plus rituximab. No serious adverse events were attributed to rituximab, and 3-year EFS was 93% (95% CI, 79%–98%).[75] The COG ANHL1131 regimen B used in the Inter-B-NHL-Ritux-2010 study[71] is based on the chemotherapy regimen used for Group B patients in the FAB/LMB96 trial.[76] In the FAB/LMB96 trial, patients with Group B disease received pre-phase therapy with the COP regimen (cyclophosphamide, vincristine, prednisone), followed by induction with two courses of COPADM (rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin, and methotrexate) with either full-dose or half-dose cyclophosphamide for those with good response, followed by consolidation with two courses of CYM (cytarabine and methotrexate), and then followed by maintenance or no maintenance for those with continued response.[76] Intrathecal therapy was included. The results showed that treatment reductions did not have significant effects on EFS.

Therefore, the Inter-B-NHL-Ritux-2010 (COG ANHL1131) trial that assessed the EFS outcomes in pediatric patients with high-risk Group B or Group C NHL treated with and without rituximab used the lower-intensity chemotherapy used for Group B patients in the FAB/LMB96 trial as its backbone.[71] The results of the COG ANHL1131 trial demonstrated the improved efficacy of rituximab + LMB chemotherapy in children and adolescents with high-risk BL and DLBCL. The 3-year EFS rate was 94% in the rituximab plus LMB chemotherapy group versus 82% in the chemotherapy alone group.[71] The 3-year OS was 95% for the rituximab/chemotherapy group versus 87% in the chemotherapy alone group. CR was observed in 95% of patients. This led to the category 1 recommendation for the addition of rituximab in high-risk Group B disease.

The Panel recommends COG ANHL1131 regimen B starting with a COP reduction phase with rituximab for patients with Group B high-risk disease. Response assessment (after COP reduction phase) and additional treatment is similar to that described for Group B low-risk disease.

Alternatively, an equivalent BFM regimen can be used. In the NHL-BFM95 trial (see Group A, above), patients with non-resected stage I or stage II disease and those with stage III disease and LDH <500 U/L received five cycles of therapy, including a cytoreductive pre-phase.[74] Failure-free survival (FFS) at 1 year for the 4-hour versus the 24-hour infusion was 94% ± 2% versus 96% ± 2% in these patients. The NHL-BFM90 trial included a cytoreductive pre-phase, followed by six courses of chemotherapy with intrathecal therapy for patients with high-risk Group B and Group C disease.[77] The 6-year EFS was 78% ± 3% in this group of patients.

Group C

COG ANHL1131 regimen + rituximab is included with a category 1 recommendation for all patients in Group C. See *Group B* (above) for the results of the randomized comparison of chemotherapy with and without rituximab in the COG ANHL1131 trial.[71] Other studies have also demonstrated high cure rates with the use of rituximab in patients with Group C disease.[78-80] In the COG ANHL01P1 study (40 evaluable pediatric patients with CNS and/or bone marrow-positive BL), FAB/LMB96 chemotherapy with rituximab was well tolerated resulting in a 3-year EFS/OS of 90%.[79] In addition, a combined analysis of FAB/LMB96 C1 arm and COG ANHL01P1, which include the use of rituximab for patients with CNS involvement showed that EFS and OS were improved with rituximab compared with historic LMB89 results.[81]

Regimens recommended for patients in Group C are those being used in the Inter-B-NHL-Ritux-2010 (COG ANHL1131) trial (see above) and are dependent on CNS and CSF involvement. COG ANHL1131 Arm C1 CNS-positive regimen is recommended for patients with CNS-positive disease, regardless of CSF positivity. Switching to COG ANHL1131 Arm C3 regimen can be considered if there is <20% tumor reduction following COP reduction phase. Patients with CSF-positive disease can alternatively be treated according to the Arm C3 regimen, although the relative efficacy of the C3 versus the C1 regimen for patients with CSF-positive disease has not been established. Patients without CNS involvement should receive the Arm C1 CNS-negative regimen.

An equivalent BFM regimen can be used for patients in Group C. In the NHL-BFM90 and NHL-BFM95 trials, Group C patients received a cytoreductive pre-phase and six courses of chemotherapy.[74,77]

Surveillance

Very few patients (about 5%) with BL or other LBCL experience a relapse, and the majority of these relapses occur in the first 6 months after completion of treatment, with <10% of relapses occurring after 15 months.[82,83] DLBCL relapses tend to occur later than BL relapses and may be seen up to 3 years post treatment. Therefore, patients with a CR to initial treatment should undergo routine clinical surveillance.

History and physical examination are recommended more frequently in the first 3 years, and then annually. Monthly monitoring of complete blood count (CBC) with differential is recommended until counts are normal, and then at each examination visit. Routine surveillance imaging is not recommended. Sites of original disease should be reassessed with imaging studies as indicated if there is a clinical suspicion of relapse.[84]

In addition, patients should be monitored for late effects of treatment as per the COG Survivorship Guidelines and NCCN Guidelines for Survivorship (available at www.NCCN.org). Particular attention should be paid to cardiac, gonadal, and neurocognitive function; bone health; and the risk for secondary leukemia. Additionally, AYA patients are also at risk

of developing psychosocial issues (eg, emotional distress symptoms, depression, anxiety).[85,86] Psychosocial support and counseling is recommended as outlined in the NCCN Guidelines for Distress Management (available at www.NCCN.org).

Treatment for Relapsed or Refractory Disease

Treatment of relapsed/refractory disease can lead to sustained complete second remissions in some patients.[82,83,87,88] CYVE and ICE (ifosfamide, carboplatin, and etoposide) have been evaluated for relapsed/refractory disease in the LMB89, LMB96, and LMB2001 studies resulting in a 5-year survival rate of 30% with manageable toxicity.[82] After 1996, 16 patients with relapsed/refractory disease received CYVE + rituximab (R-CYVE) or ICE + rituximab (R-ICE). Six of them were in CR, but there was no difference in survival rates between those who did and did not receive rituximab.[82,83]

The addition of rituximab to chemotherapy in the relapsed/refractory setting has also been evaluated in other small studies.[89-91] In a small COG study, second-line therapy with R-ICE for relapsed/refractory NHL resulted in a CR/PR rate of 60% in 20 evaluable patients, with 30% able to complete consolidation therapy.[89] A Japanese study reported a 73% response rate for 223 patients treated with R-ICE in the relapsed or refractory setting.[91] A multicenter case series from the United Kingdom also demonstrated an association between rituximab and survival in the relapse/refractory setting.[90] In this series, 9 of 16 patients who received HCT survived for >6 years; no patient who did not receive HCT survived.

In another report that analyzed the outcomes of 639 children and adolescents with relapsed or refractory NHL, the estimated 8-year probability of OS was 34% ± 2% for the entire study population with significant differences between the NHL subtypes.[92] R-ICE and R-VICI (rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone) and variants were the most commonly used regimens in the relapsed or refractory setting. The estimated 8-year OS rates were 28% ± 3% for BL, 50% ± 6% for DLBCL, and 57% ± 8% for PMBL.

Clinical trial is the preferred option for patients with relapsed or refractory disease. Second-line therapy followed by consolidation with autologous or allogeneic HCT (based on response to second-line therapy) is recommended for most patients if they are not enrolled in a clinical trial. The exception is for patients with Group A or stage I/II Group B disease at diagnosis (see *Treatment for Relapsed or Refractory Disease,* above). It is rare for patients with Group A disease at initial diagnosis to relapse, and there are little data and no established treatment options for these patients.

R-CYVE (if not previously received as part of initial therapy) or R-ICE are included as options for second-line therapy.[82,83,89,91] Chemotherapy regimens such as COG ANHL 1131 (Arm C1 regimen) or two cycles of R-CYVE (*without* consolidative HCT) can be considered for patients with a low risk of relapse (defined as patients with initial Group A disease or patients with low-stage [stage I or II] Group B treated according to POG9219).

Most patients with relapsed or refractory disease achieving a CR to second-line therapy should receive an autologous or allogeneic HCT. Donor options for allogeneic HCT include human leukocyte antigen (HLA)-matched related donor; HLA-matched unrelated donor, cord blood or a haploidentical donor.[93,94] Autologous or allogeneic HCT is also an appropriate option for patients with a PR to second-line therapy. For patients with a PR or less than a PR, a clinical trial of second-line therapy with incorporation of investigational agents can be considered, as can regimens and agents used for adults with relapsed or refractory DLBCL. Best supportive care is another option.

While some case series have reported better OS rates for patients who received HCT compared with patients who did not receive HCT,[90,92,95] other studies have shown comparable survival rates.[87,88,96,97] Disease status at the time of transplant was predictive of both PFS and OS for pediatric and AYA patients undergoing autologous HCT for relapsed or refractory disease.[98] There are no data to support the use of autologous versus allogeneic HCT; therefore, the decision regarding the type of HCT should be based on the donor availability and physician preference.[96,99]

Chimeric antigen receptor (CAR) T-cell therapy (CD19-directed) and bispecific antibodies have demonstrated significant efficacy for the treatment of relapsed or refractory DLBCL in adult patients after ≥2 prior systemic therapy regimens. Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel are the 3 CD19-directed CAR T-cell therapies approved for relapsed or refractory DLBCL in adults.[100] Tisagenlecleucel is also approved for relapsed or refractory ALL in pediatric and young adult patients.[101] Epcoritamab and glofitamab are the two bispecific antibodies that are approved for the treatment of relapsed or refractory DLBCL in adults.[102,103] The feasibility of CD19-directed CAR T-cell therapy in pediatric patients with relapsed or refractory BL has been demonstrated only in a small cohort of patients.[104] Ongoing clinical trials are evaluating CAR T-cell therapy and bispecific antibodies (NCT05206357; NCT05533775) for relapsed or refractory mature B-cell lymphomas in pediatric and AYA patients.[105]

CAR T-cell therapy is currently not recommended in the guidelines for the treatment of pediatric patients with relapsed or refractory BL or other LBCL due to lack of clinical trial data for the use of CAR T-cell therapy in this patient population.

Primary Mediastinal Large B-Cell Lymphoma

Clinical Presentation

PMBL usually presents as a bulky mediastinal mass in the anterior mediastinum (primary site of disease) with or without locoregional spread to adjacent organs such as the chest wall, pleura, pericardium, and lung.[6,106,107] While extrathoracic dissemination to the kidney or liver may occur, CNS and bone marrow involvement are generally rare. Patients may also present with clinical symptoms related to rapid growth of a mediastinal mass (TLS, SVC syndrome, respiratory distress due to airway compression, pericardial and pleural effusions), abdominal distention (in patients with abdominal disease) and nausea/vomiting.[6,107]

Diagnosis

Excisional or incisional biopsy of the most accessible site is preferred, with fresh biopsy tissue sent to pathology in saline to ensure viable diagnostic tissue. FNA biopsy alone is not suitable for the initial diagnosis of pediatric lymphoma.[21]

A core needle biopsy is not optimal but can be used when a lymph node or tumor mass is not easily accessible for excisional or incisional biopsy

Additional Diagnostic Testing

PMBL expresses CD23, CD30, and MUM1 in most of the cases, in addition to pan T-cell markers and lacks slg. PMBL is CD19+, CD20+, CD79a+, PAX5+, CD23+, and MUM1+ with a variable expression of BCL2 and BCL6.[107] At least one of the biomarkers should be expressed: CD200, MAL, PD-L1, and PD-L2. CD30 is heterogeneously expressed in more than 80% of cases. *BCL2*, *BCL6*, and *MYC* rearrangements are very rare. PMBL is almost always negative for EBV, and the presence or absence of EBV is useful to differentiate PMBL from other mediastinal lymphomas with overlapping pathologic features.

Gene expression profiling has shown that adult PMBL has molecular features that overlap with classic Hodgkin lymphoma (CHL) and the biology of pediatric PMBL has also been reported to be similar to that of adult PMBL.[108-111] Genetic alterations involving the major histocompatibility complex (MHC) class II transactivator (*CIITA*) gene at chromosome 16p are highly recurrent in PMBL.[112,113] Gains or amplifications in chromosome 9p24 (including *JAK2, PD1*, *and PD2*) and chromosome 2p16 (including *REL* and *BCL11A*) have also been detected in PMBL.[114-119]

PMBL is almost always negative for EBV, and the presence or absence of EBV is useful to differentiate PMBL from other mediastinal lymphomas due to the presence of overlapping pathologic features.

Workup

Workup for patients with a diagnosis of PMBL is similar to that described for BL or other LBCL and is outlined on PBCL-3.

Initial Treatment

Historically, pediatric patients with PMBL enrolled in prospective clinical trials of pediatric aggressive mature B-cell lymphomas have been treated with the same protocols used for BL and (dose-intensive multiagent chemotherapy regimens and intrathecal therapy for CNS prophylaxis). However, outcomes in the subset of patients with PMBL differs from those with BL and DLBCL, with reported 5-year EFS rates of 66% to 70%.[120,121]

The BFM Group reported the pooled outcomes of 30 patients with PMBL (median age was 14 years) enrolled in three consecutive NHL-BFM trials.[120] Treatment consisted of four to six courses of intensified chemotherapy using steroids, oxazaphosphorine alkylating agents, methotrexate, cytarabine, etoposide, and doxorubicin. With a median follow-up of 5 years, the estimated EFS rate was 70%. Residual mediastinal masses were present in 15 patients after the EOT, and elevated LDH (≥500 U/L) was associated with increased risk of failure in multivariate analysis. In the international FAB/LMB96 mature B-cell NHL trial that enrolled 42 patients with PMBL, the estimated 5-year EFS and OS rates were 66% and 73%, respectively.[121] Patients received pre-phase therapy with COP (low-dose cyclophosphamide, vincristine, and prednisone) followed by an induction course of COPADM (cyclophosphamide, vincristine, prednisone, doxorubicin, and methotrexate) and a consolidation course of CYM (cytarabine and high-dose methotrexate).

The French LMB2001 prospective study evaluated intensive LMB-based chemotherapy (based on the FAB/LMB96 protocol) in pediatric patients with PMBL (42 of 773 patients with newly diagnosed B-cell NHL had PMBL).[122] All patients received pre-phase COP followed by four to eight courses (induction, consolidation, and maintenance) of chemotherapy, and rituximab was added to chemotherapy after 2008. In 2010, the protocol was modified to recommend six courses of LMB-modified chemotherapy (B/C) with rituximab for all patients (2 induction courses of R-COPADM followed by two consolidation courses of R-CYVE [rituximab, cytarabine, and etoposide] and two courses of maintenance therapy [vincristine, cytarabine, doxorubicin, prednisone, and rituximab]). The cumulative dose of doxorubicin was limited at 240 mg/m^2. The median follow-up was 7 years (11 years for patients treated without rituximab and 6 years for those treated with rituximab). The 5-year EFS and OS rates were 88% and 95%, respectively, for the entire population. This study also showed that the addition of rituximab to chemotherapy improves the outcome (not based on a randomized comparison but based on a comparison of two periods using different intensity chemotherapy). The 5-year EFS rate was 95% with rituximab and 81% without rituximab. The corresponding 5-year OS rates were 100% and 91%. The results of a large cohort analysis of 44 patients with newly diagnosed PMLBL (confirmed either through central review in the LMB2001 prospective study [n = 21] or by assessment from

a referent pathologist of the French Lymphoma Study Association [LYSA; n = 23]) also confirmed the efficacy of LMB-based chemotherapy as initial treatment.[123]

Dose-adjusted EPOCH-R without RT has been shown to be effective in adult patients with PMBL without the routine use of RT, and the use of RCHOP with a PET-adapted approach has also been associated with favorable outcomes in adult patients with PMBL.[124,125] There are limited data with dose-adjusted EPOCH-R in pediatric patients (as discussed below).

In a multicenter retrospective analysis of 156 children and adults with PMBL treated with dose-adjusted EPOCH-R, with a median follow-up of 23 months, the estimated 3-year EFS and OS rates were 86% and 95%, respectively.[126] The outcomes were not statistically different between pediatric and adult patients in terms of both EFS (81% vs. 87%; $P = .338$) and OS (91% vs. 97%; $P = .170$). Thrombotic complications were more common in pediatric patients (46% compared to 23% in adult patients; $P = .011$). Another analysis that compared the outcomes of pediatric patients with PMBL from three different trials also reported that modified dose-adjusted EPOCH-R (with at least one dose of intrathecal therapy and cumulative dose of doxorubicin limited at 360 mg/m^2) resulted in a superior 5-year EFS rate (84%) compared to intensive chemotherapy regimens used in the B-NHL-BFM-04 (59%; $P = .016$) and NHL-BFM 95 (39%; $P < .001$) studies.[127] The corresponding 5-year OS rates were 90%, 72%, and 70%, respectively.

Another multicenter, single-arm, prospective phase II study of 46 pediatric patients with PMBL showed that dose-adjusted EPOCH-R did not improve EFS compared to survival rates from the FAB/LMB96 study (discussed above).[128] After a median follow-up of 59 months, the 4-year EFS and OS rates were 70% and 85%, respectively. Although the EFS rates were not better in this study, dose-adjusted EPOCH-R had a favorable toxicity profile (grade 2 or higher adverse cardiac events occurred only in 9% of patients). In this study, adherence to dose intensity was not followed in 29% of patients. These results are in contrast to the EFS and OS rates for dose-adjusted EPOCH-R reported in the aforementioned analyses,[126,127] and the survival rates reported in this phase II study are also inferior to those reported in the LMB2001 prospective study (discussed above).[122]

In the absence of data from randomized trials, optimal first-line treatment for patients with PMBL has not been established. Enrollment in a clinical trial is preferred for all patients. Based on the available data (as discussed above), the following regimens are included as options for first-line therapy: dose-adjusted EPOCH-R (6 cycles)[126,127] or R-CHOP (6 cycles)[125] with ot without RT or LMB-modified B/C chemotherapy with rituximab.[122] There are not enough data on the use of RT in pediatric patients and RT was not part of the protocol for pediatric patients with PMBL. Definitive diagnosis may not be feasible prior to the initiation of initial treatment. A short course of COP regimen can be used while waiting to confirm the diagnosis of PMBL.

Response Assessment

PET/CT at EOT is essential since residual mediastinal masses are common and negative EOT PET scan has been reported to be a prognostic indicator of improved survival outcomes.[125,126,129] In the aforementioned multicenter retrospective analysis of 156 patients with children and adults with PMBL, patients with a negative PET scan at EOT had improved 3-year EFS compared to those with a positive PET (95% vs. 55%; $P < .001$).[126] In a retrospective and prospective series of pediatric patients with PMBL, although PET/CT was used for response assessment after a few cycles of chemotherapy and at EOT, no treatment decisions were based on the results of PET/CT scans.[122,126,128] In the LMB2001 study, response assessment was required after four or six courses of chemotherapy. At the EOT, if PET/CT was positive, or a large residual

tumor remained, then biopsy and removal of the residual mass was recommended.[122] A PET-adapted treatment approach has also been used to identify adult patients for whom RT can be safely omitted, and only those with a PET-positive scan at the EOT received RT.[125] However, the role of RT in patients with a positive EOT PET remains undefined in pediatric patients due to the increased late effects of RT.[111]

The guidelines recommend response assessment at EOT with PET/CT. In the vast majority of patients, relapse occurs within 18 months of diagnosis.[129] Routine clinical surveillance (as described below) is recommended for patients with a CR to initial treatment (negative PET; Deauville 1–3).[84]

Repeat PET/CT or CT in 6 to 8 weeks after EOT should be considered for patients achieving less than a CR (positive PET; Deauville 4–5). If repeat PET/CT is positive or there is increase in size of residual mass, biopsy of PET-positive mass is recommended prior to initiation of additional treatment for persistent or refractory disease.

Surveillance

History and physical examination are recommended every 3 to 6 months in the first 3 years, and then annually. Monthly monitoring of CBC with differential is recommended until counts are normal, and then at each examination visit.

In addition, patients should be monitored for late effects of treatment as per the COG Survivorship Guidelines and NCCN Guidelines for Survivorship (available at www.NCCN.org). Particular attention should be paid to cardiac, gonadal, and neurocognitive function; bone health; and the risk for secondary leukemia. In addition, as noted earlier, psychosocial support and counseling is recommended as outlined in the NCCN Guidelines for Distress Management (available at www.NCCN.org).[85,86]

Treatment for Relapsed or Refractory Disease

There are very limited data on the outcome of relapsed or refractory PMBL in pediatric patients.[130] Enrollment in clinical trials is recommended for all patients.

The management of relapsed or refractory PMBL in both pediatric and adult patients is similar to the management of relapsed or refractory DLBCL. Second-line therapy with cross-resistant chemoimmunotherapy regimens followed by autologous HCT is recommended for patients with relapsed or refractory disease and outcomes following HCT are more favorable in patients with chemosensitive disease.[130-132]

Immune checkpoint inhibitors (pembrolizumab and nivolumab), either as monotherapy or in combination with anti-CD30 antibody drug conjugate (brentuximab vedotin) have demonstrated activity in relapsed or refractory PMBL.[133-137]

R-ICE, R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), nivolumab (monotherapy or in combination with brentuximab vedotin) and pembrolizumab, are included as options for second-line therapy for relapsed or refractory PMBL.

Patients with a CR to second-line therapy should receive an autologous HCT. Allogeneic HCT is not considered an optimal approach.

Brentuximab vedotin in combination with nivolumab or pembrolizumab is also an option for patients with a PR to second-line therapy.[137] CAR T-cell therapy (axicabtagene ciloleucel or lisocabtagene maraleucel) is included as an option based on the extrapolation of data from clinical trials that have included adult patients with relapsed or refractory PMBL (ZUMA-1 [axicabtagene ciloleucel] and TRANSCEND-NHL-001 trials [lisocabtagene maraleucel]).[100]

Clinical trial or best supportive care are recommended for patients achieving less than a PR to second-line therapy.

RT is often included in high-dose therapy regimens given prior to autologous HCT and RT alone could be considered an option for local recurrence with disease restricted to the mediastinum, although there are not enough data on the use of RT in pediatric patients with PMBL.[129] Avoidance of RT is strongly preferred in pediatric patients to reduce the risk of late complications from normal tissue damage. When RT is used, it should be delivered using advanced RT techniques to minimize dose to organs at risk (OARs; eg, heart, cardiac substructures, lungs, breast, spinal cord). Recommendations for normal tissue dose constraints can be found in the Principles of Radiation Therapy section of the NCCN Guidelines for Pediatric Hodgkin Lymphoma (available at www.NCCN.org).

Post-Transplant Lymphoproliferative Disorders

PTLD are a heterogeneous group of LPD occurring after SOT or allogeneic HCT that are related to immunosuppression and, in most cases, EBV infection.[6,15] The NCCN Guidelines include recommendations for the diagnosis and treatment of PTLD following SOT in pediatric patients.

PTLD remains the most common malignancy diagnosed in children following SOT and the incidence varies depending on the transplanted organ.[138,139] The incidence of PTLD are higher following lung (7% to 20%), intestinal (12% to 17%) and heart (4% to 13%) transplant compared to the incidences following liver (2% to 6%) and kidney transplant (1% to 7%).[138,139]

Early-onset PTLD (diagnosed within 1 year after SOT) are EBV-positive in the majority of patients whereas late-onset PTLD (diagnosed >1 year after transplant) are more likely to be EBV-negative.[139-141] The onset of EBV-negative pediatric PTLD was at 8.5 years following SOT in one series and the survival outcomes were similar to that of pediatric EBV-positive PTLD.[141] Gene expression-profiling studies have also shown that EBV-negative PTLD are clinically and biologically distinct from EBV-positive PTLD.[15,142,143] EBV-negative PTLD are characterized by the presence of complex genetic alterations similar to DLBCL in immunocompetent individuals whereas EBV-positive PTLD are associated with minor molecular or genetic alterations.

Recipient EBV-seronegativity, donor EBV-seropositivity, increased immunosuppression after SOT are considered as risk factors for developing PTLD.[144-150] EBV seronegativity is the most important risk factor for the development of PTLD in children likely due to the fact that the majority of pediatric patients are EBV-seronegative at the time of transplant and the risk for primary EBV infection after SOT is higher in this group of patients.[146] A prospective multicenter study that included 34 pediatric patients with EBV-positive PTLD, also identified recipient EBV-seronegativity and donor EBV-seropositivity as significant risk factors for the development of PTLD following SOT.[150] Mutations in EBV latent membrane protein 1 (EBV-LMP1) have also been reported as indicators of increased risk for developing EBV-positive PTLD in children.[151] Bone marrow and/or CNS involvement is considered a predictor of poor survival.[152]

Classification

In the updated World Health Organization (WHO) classification of Hematolymphoid Tumors (WHO5), PTLD are classified under IDD-associated LPD (IDD-LPD) based on the histology and the clinical setting of IDD[6]: (1) Nondestructive PTLD (ND-PTLD) are classified as hyperplasias arising in the setting of IDD; (2) Polymorphic PTLD (P-PTLD) are included under polymorphic LPD arising in individuals with IDD; (3)

Monomorphic PTLD (M-PTLD) are classified as lymphomas arising in the setting of IDD.

In the WHO Classification of Pediatric Tumors (5th Edition), PTLD are listed as an independent category within the group of IDD-LPD and are categorized into three different subtypes (as listed below).[15] The NCCN Guidelines Panel supports use of this classification for pediatric PTLD.

Hyperplastic Nondestructive PTLD

Hyperplastic ND-PTLD include plasmacytic hyperplasia, infectious mononucleosis-like hyperplasia, and florid follicular hyperplasia.[15] Hyperplastic ND-PTLD are polyclonal, typically develop within a year of SOT, and are always EBV-positive.

Polymorphic PTLD (P-PTLD)

P-PTLD are the most common type of PTLD among children and is mostly EBV positive.[153-155] P-PTLD can be either polyclonal or monoclonal, characterized by a mixture of immunoblasts, plasma cells, and small to intermediate-sized lymphoid cells comprised of mixed B-cells and T-cells by immunophenotyping.[15] However, in the WHO classification, P-PTLD are not categorized into subtypes based on cell lineage since this does not reliably predict clinical behavior.

Monomorphic PTLD

M-PTLD are monoclonal and can be EBV-positive or negative. M-PTLD fulfill the criteria of lymphoma seen in immunocompetent individuals and are further divided into four subtypes based on the cell lineage: B-cell, T-cell, or natural killer (NK)-cell, or plasmacytic type.[15]

The majority of M-PTLD are of B-cell origin (involving B-lymphocytes of recipient origin). DLBCL is the most frequent subtype. BL is the less common subtype and presents with an aggressive clinical course.[139,156]

Primary CNS PTLD is also an uncommon subtype of B-cell origin and is EBV-positive.[157,158]

T-cell/NK-cell type (although very rare) tend to have a late onset following SOT and are also associated with a poor prognosis.[159] Peripheral T-cell lymphoma not otherwise specified (PTCL, NOS) is the most prevalent subtype followed by anaplastic large cell lymphoma (ALCL).[160,161]

Plasma cell myeloma or plasmacytoma are the subtypes of plasmacytic type M-PTLD that have been described in few reports.[162,163]

CHL type M-PTLD is usually EBV-positive and is the least common subtype of M-PTLD.[164] CHL type M-PTLD is not included in WHO5, but it is listed as a subtype in the revised 2017 WHO classification (WHO4R) and 2022 International Consensus Classification (ICC).[165,166]

Clinical Presentation

PTLD present either as localized or disseminated disease that affects the transplanted organ. Gastrointestinal tract, lung or airways, and cervical adenopathy were the most common sites in one series.[153]

Hyperplastic ND-PTLD and P-PTLD are characterized by nodal involvement and M-PTLD presents with symptoms of lymphoma. Symptoms are related to the affected organ and age of patient at the time of transplant, usually preceded by elevation of EBV viremia (detectable using quantitative polymerase chain reaction [PCR]) and can simulate organ rejection or graft versus host disease (GVHD).

Diagnosis

Biopsy and adequate immunophenotyping (flow cytometry and IHC as outlined in PTLD-1) are essential to confirm the diagnosis of PTLD subtype.[15] If biopsy is not feasible, preemptive treatment for PTLD subtype should be considered.[167]

CD20 expression has been reported as a predictor of timing for the onset of PTLD following SOT and survival. In a retrospective analysis of 45 pediatric patients diagnosed with PTLD following SOT, CD20 expression correlated with shorter interval of onset for PTLD (28 months compared to 64 months for EBV positivity) and higher rates of EFS(5-year rates were 84% for CD20-positive PTLD vs. 29% for CD20-negative PTLD; $P < \cdot 001$) and OS(5-year rates were 96% and 56% respectively; $P = .01$).[168] It is clinically important to report the status and pattern of CD20 expression on B-cells in all subtypes of PTLD.

Evaluation of EBV infection status by EBER-ISH is an essential component of the diagnostic workup, although an association with EBV infection status is not required for the diagnosis of PTLD. Molecular analysis may be useful for the assessment of clonality.

Cytogenetics or FISH for mutational analysis may be useful to confirm the specific subtype if the diagnosis of M-PTLD is suspected. In a study that investigated the mutational landscape of pediatric M-PTLD after SOT (n = 31; DLBCL-type, n = 24 and BL-type, n=7), the mutation profile of BL-type was similar to that of BL diagnosed in immunocompetent individuals (*MYC* mutations identified in all 7 cases) whereas DLBCL-type had a mutation profile that was less complex than that of DLBCL diagnosed in immunocompetent individuals.[169] BL-type also had a higher mutational burden than DLBCL-type.

Workup

Workup for patients diagnosed with PTLD includes history and physical examination, laboratory analysis, lumbar puncture, bone marrow aspiration and biopsy (in certain cases), and imaging (as outlined on PTLD-2).

Patients should be evaluated for history of transplant (orthotopic transplant or SOT, including timing since transplant, current/past immunosuppressive therapies, recurrent infections, or immunodeficiency) and infections (EBV viral load status and recurrent infections prior to transplant). Baseline re-evaluation of graft organ function and any episodes of graft rejection should also be done by a graft transplant specialist, if appropriate.

Evaluation of EBV viral load by EBV-PCR (whole blood or plasma) is recommended for measuring EBV DNA.[170] Graft organ function and EBV viral load should be monitored for all patients during treatment. The guidelines emphasize that an elevated EBV-PCR is not diagnostic of PTLD, and EBV viral load cannot be used for response assessment.

Treatment Options

Treatment options are largely dependent on the PTLD subtype but the optimal treatment for PTLD is not well defined due to the lack of randomized controlled trials and the heterogeneity of the disease.

Reduction in immunosuppression (RIS) remains the initial treatment for nearly all patients with PTLD.[155] Surgery (with no additional therapy, with the exception of RIS) can be a curative treatment option following complete resection of the affected lesion.[171] Anti-CD20 monoclonal antibody monotherapy (eg, rituximab), chemotherapy and chemoimmunotherapy have also been evaluated.[172-178] However, it should be noted that none of the aforementioned treatment options have been evaluated in head-to-head randomized clinical trials.

Two multicenter studies have reported the use of chemoimmunotherapy as first-line therapy for pediatric patients with PTLD.[153,177] In one study that evaluated the outcomes of PTLD in 56 pediatric patients following heart transplant, chemotherapy was the initial treatment for 16 patients (29%; P-PTLD, 11% and M-PTLD, 61%).[153] The estimated survival rates at 1-year, 3-years, and 5-years after diagnosis were 75%, 68%, and 67%, respectively. In another study that evaluated the treatment of M-PTLD in pediatric patients (n = 48), 39 patients received rituximab in combination

with chemotherapy, with or without RIS. After a median follow-up of 48 months, the 3-year EFS and OS rates were 62% and 77%, respectively.[177]

The results of a multicenter registry trial and a prospective clinical trial demonstrated the safety and efficacy of rituximab monotherapy in patients with refractory PTLD (no response to RIS, progressive or relapsed disease, or concomitant allograft rejection).[172] In the registry cohort (n = 26; 17 patients with P-PTLD and 7 patients with M-PTLD), rituximab (375 mg/m^2 x 4 doses) resulted in an overall response rate (ORR) of 85% (69% CR). After a median follow-up of 41 months, the OS rate was 73%. In a prospective clinical trial cohort (n = 14; 10 patients with P-PTLD), all patients received rituximab (375 mg/m^2 x 4 doses). No further treatment was needed for those achieving a CR and 4 additional doses of rituximab were given for those achieving a PR. After a median follow-up of 1.5 years, CR rate and OS rate were 75% and 83%, respectively.

Two phase II studies have shown that low-dose chemotherapy (cyclophosphamide and prednisone) with or without rituximab is also effective for the treatment of pediatric patients with refractory PTLD (progressive disease or persistent disease with concurrent allograft rejection) following initial treatment (RIS, surgery, or rituximab monotherapy).[174,176] In the initial phase II study (n = 36; majority of the patients had stage III or IV disease with extranodal involvement and ≥3 sites of disease), low dose chemotherapy (cyclophosphamide and prednisone) resulted in an ORR of 83% (75% CR).[174] The 2-year relapse-free survival (RFS), failure-free survival (with functioning original allograft and no PTLD), and OS rates were 69%, 67%, and 73%, respectively. In the subsequent phase II study (n = 55), the addition of rituximab to the same low dose chemotherapy regimen resulted in a CR rate of 69%. After a median follow-up of 5 years, the 2-year EFS (alive with functioning original allograft and no PTLD) and OS rates were 71% and 83%, respectively.[176]

Ped-PTLD 2005 trial evaluated a response-adapted sequential treatment (rituximab with or without chemotherapy) in pediatric patients with CD20-positive PTLD (n = 49; P-PTLD, n =12; DLBCL, n = 24; BL, n =7). All patients received rituximab (375 mg/m^2; 3 weekly infusions).[179] Patients achieving PR received 3 additional doses of rituximab and those with progressive or stable disease received 6 cycles of moderate dose chemotherapy (mCOMP – modified cyclophosphamide, vincristine, methotrexate and prednisone). After a median follow-up of 4.5 years, 32 patients (64%) had received rituximab alone and 15 patients with stable or progressive disease after rituximab monotherapy received mCOMP regimen, which resulted in a CR rate of 66%. The estimated 5-year EFS and OS rates were 67% and 83%, respectively. The results of the study demonstrated that chemotherapy could be omitted in patients achieving at least a PR to rituximab monotherapy. In this study, all patients with BL-type PTLD received chemotherapy with mCOMP after initial treatment with rituximab.

Autologous or allogeneic EBV-specific cytotoxic T-cell therapy may be an effective treatment approach for patients with PTLD not responding to conventional treatments.[180-182] An off-the-shelf, allogeneic EBV-specific cytotoxic T-cell therapy has demonstrated efficacy in the treatment of PTLD refractory to rituximab with or without chemotherapy in a phase III trial (that also included 11 patients <18 years of age).[183-185]

NCCN Recommendations

Graft organ function monitoring is essential to allow for early detection of allograft rejection. Collaboration with graft transplant specialist is recommended to coordinate immunosuppressive medication assessment, dose modifications and graft organ function monitoring for all patients receiving RIS.

Surgery alone (without any additional systemic therapy) is considered sufficient therapy following complete resection of the affected lesion (in the absence of disease elsewhere). Rituximab can be used if CD20 is only partially or dimly expressed but is not essential for CD20-negative PTLD. The role of additional therapy with rituximab if CR not achieved after first-line therapy with 4 to 8 doses of rituximab monotherapy is not established in children. Switching to chemotherapy or chemoimmunotherapy is recommended, if there is no response to rituximab after 4 weekly doses of rituximab monotherapy.[172,174,176,179] Rebiopsy should be considered prior to additional therapy.

Recommendations for first-line and second-line therapy based on the subtype are discussed below. Participation in a suitable clinical trial is recommended for patients with P-PTLD and M-PTLD (DLBCL or non-BL type) that is refractory (partial response, persistent or progressive disease) to first-line therapy. EBV-specific cytotoxic T-cell therapy (in the context of a clinical trial) can be considered for patients with P-PTLD and M-PTLD (DLBCL or non-BL type) that is refractory to conventional treatment options.

Hyperplastic ND-PTLD

RIS alone is an appropriate first-line therapy for patients with hyperplastic ND-PTLD. RIS strategies include reduction of calcineurin inhibition (cyclosporin or tacrolimus) and discontinuation of antimetabolic agents (azathioprine or mycophenolate mofetil). Discontinuation of all nonsteroidal immunosuppression should be considered in patients who are critically ill with extensive and life-threatening disease. The response to RIS is variable and patients should be closely monitored during RIS.

Re-escalation of immunosuppressive therapy should be individualized in patients who achieve a CR, considering the extent of initial RIS and the nature of the organ allograft. Rituximab or chemoimmunotherapy are included as second-line therapy options for patients with refractory disease after RIS.

P-PTLD

RIS alone or in combination surgery (with or without rituximab) or systemic therapy (rituximab monotherapy or chemoimmunotherapy) are appropriate first-line therapy options for patients with P-PTLD.[153,155,177]

Observation or continuation of RIS (as tolerated) with graft function monitoring is recommended for patients achieving a CR to first-line therapy. Chemotherapy or chemoimmunotherapy (not previously used for first-line therapy) are included as options for patients with refractory disease after first-line therapy.

M-PTLD (BL- Type)

M-PTLD (BL type) has an aggressive clinical course and multiagent chemotherapy regimens used for the treatment of BL in immunocompetent patients result in comparable clinical outcomes.[186] The guidelines recommend that pediatric patients with M-PTLD (BL type) should be treated with chemoimmunotherapy regimens recommended in these guidelines for the treatment of BL in immunocompetent individuals.

M-PTLD (DLBCL or non-BL Type)

RIS with or without surgery and/or systemic therapy (rituximab monotherapy or chemoimmunotherapy) are recommended as first-line therapy options for patients with M-PTLD (DLBCL or non-BL type).[153,155,177]

Surveillance (described for appropriate histologic subtype; PBCL-10 or PMBL-11) or continuation of RIS (as tolerated) with graft function monitoring is recommended for patients achieving CR to first-line therapy.

Second-line therapy options for patients with refractory disease are dependent on initial therapy.

Rituximab or chemoimmunotherapy or chemotherapy are recommended, if RIS with or without surgery was the initial treatment. Chemotherapy or chemoimmunotherapy (not previously used for first-line therapy) are recommended if RIS with or without surgery and rituximab or chemoimmunotherapy was the initial treatment.

M-PTLD (T-Cell/NK-Cell Type or Plasmacytic Type)

One small series (n = 8) reported the efficacy of anthracycline-based chemotherapy regimens (used for acute lymphoblastic lymphoma) for the treatment of PTCL-NOS diagnosed following SOT in children, although the follow-up was relatively short.[161]

The Panel acknowledged that there are no established treatment options (other than RIS) for patients with M-PTLD (T-cell/NK-cell type or plasmacytic type). Treatment for patients with T-cell/NK-cell type M-PTLD should be individualized based on histologic subtype and the nature of the graft organ. Multiple myeloma type treatment can be considered for aggressive/refractory plasmacytic type M-PTLD.

M-PTLD (CHL Type)

In a series of 17 pediatric patients with CHL-type PTLD (onset at a median of 8 years after SOT), treatment with CHL chemotherapy with or without involved field radiotherapy was associated with favorable survival outcomes with an EFS rate of 81% and the OS rate at 2 and 5 years was 86%.[164]

CHL specific chemotherapy (as outlined in the NCCN Guidelines for Pediatric Hodgkin Lymphoma, available at www.NCCN.org) along with RIS is recommended for CHL-type M-PTLD (CHL-type).

Primary CNS PTLD

Favorable survival outcomes have been reported in patients treated with RT or systemic therapy (chemotherapy and/or rituximab) with intrathecal therapy (4-year EFS and OS rates of 50% and 74% in one series of 24 pediatric patients with primary CNS PTLD).[157,158]

High-dose methotrexate with rituximab or systemic chemoimmunotherapy with intrathecal therapy are recommended for patients with primary CNS PTLD.[157,158] RT can be considered in selected cases.[155]

Supportive Care

Supportive care issues that are important in pediatric patients with cancer include management of pain, chemotherapy-induced nausea and vomiting, fatigue, anxiety and depression, fever and neutropenia, neurologic complications, dermatitis, and mucositis.[187-190] In addition, parents and other caregivers of children with cancer frequently experience distress, depression, and even symptoms of post-traumatic stress disorder due to the stress of watching a child suffer and the increased financial burden due to medical costs and disruptions in employment.[188,191-193] The COG and others have published evidence-based guidelines addressing some of these supportive care issues, as well as guidelines on antifungal prophylaxis, fertility preservation, and platelet transfusion.[194-198]

Organ dysfunction and tumor mass effects can cause significant morbidity in pediatric patients. Spinal cord compression, kidney injury and obstructive uropathy, intussusception, bowel obstruction, chest masses with risk of SVC syndrome, and hepatopathy have been described.[199,200] Chemotherapy should be started as soon as possible to preserve organ function and reduce complications for these patients.

The *Principles of Supportive Care* in the algorithm on PBCL-D includes recommendations for infection prophylaxis, TLS prophylaxis, and the management of other treatment-related adverse events (eg, viral reactivation, neutropenia, mucosal and renal toxicity, which are also briefly discussed below).[201-204]

Tumor Lysis Syndrome

TLS is a potentially serious complication characterized by metabolic and electrolyte abnormalities resulting from spontaneous or therapy-induced rapid tumor necrosis and rapid release of intracellular contents of tumor into peripheral blood.[205] TLS can be asymptomatic or can cause major metabolic derangements leading to seizures, cardiac arrhythmias, acute renal failure, neuromuscular abnormalities, hypotension, and death. Risk factors include bulky disease at presentation, elevated LDH, oliguria, preexisting renal impairment, dehydration, and evidence of TLS prior to initiation of therapy.

The prevention and management of TLS is one of the most critical supportive care needs of pediatric patients with aggressive B-cell lymphomas.[205-207] Hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia are the primary electrolyte abnormalities associated with TLS. Hydration along with frequent monitoring and correction of electrolyte abnormalities is essential.

Prophylaxis with allopurinol or rasburicase prior to initiation of systemic therapy is indicated for certain patients.[205,208] Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to an increased risk of methemoglobinemia or hemolysis.[209] G6PD testing should be considered prior to the initiation of rasburicase. However, in patients with TLS at risk for end-organ injury and unknown G6PD status, the benefit of rasburicase may outweigh the risk.

Viral Reactivation

Rituximab is associated with a risk of HBV reactivation and screening for HBV infection should be done prior to initiating treatment with rituximab. Monitoring with HBV PCR and antiviral prophylaxis are recommended for patients with a hepatitis B surface antigen (HBsAg)-positive test, during and after treatment with rituximab.[203] Progressive multifocal leukoencephalopathy (PML) caused by the JCV reactivation has been noted as a rare complication associated with rituximab and there is no known effective treatment.

Infections

Rituximab-related neutropenia may occur weeks to months following last rituximab exposure in some patients. While it can be severe, it is not generally associated with infectious complications. As discussed earlier, hypogammaglobulinemia can also occur during and for months after treatment with rituximab although this is rarely associated with severe infections.[53,54] Baseline Ig panel should be obtained and intravenous IgG replacement therapy should be considered in patients with recurrent infections.[52]

Methotrexate Toxicity

Glucarpidase should be used for patients with significant renal dysfunction receiving high-dose methotrexate and the guidelines recommend the use of a web-based tool to optimize the administration of glucarpidase (based on the plasma concentrations of methotrexate) for patients receiving high-dose methotrexate.[210]

References

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J Clin 2025;75:10-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39817679.

2. Burkhardt B, Zimmermann M, Oschlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol 2005;131:39-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16173961.

3. Hochberg J, Waxman IM, Kelly KM, et al. Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science. Br J Haematol 2009;144:24-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19087093.

4. Sandlund JT, Martin MG. Non-Hodgkin lymphoma across the pediatric and adolescent and young adult age spectrum. Hematology Am Soc Hematol Educ Program 2016;2016:589-597. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27913533.

5. Pfister SM, Reyes-Mugica M, Chan JKC, et al. A summary of the inaugural WHO Classification of Pediatric Tumors: Transitioning from the optical into the molecular era. Cancer Discov 2022;12:331-355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34921008.

6. WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. (WHO classification of tumours series, 5th ed.; vol. 11). Lyon (France): International Agency for Research on Cancer; 2024.

7. Hogfeldt T, Jaing C, Loughlin KM, et al. Differential expression of viral agents in lymphoma tissues of patients with ABC diffuse large B-cell lymphoma from high and low endemic infectious disease regions. Oncol Lett 2016;12:2782-2788. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27698858.

8. Ren W, Ye X, Su H, et al. Genetic landscape of hepatitis B virus-associated diffuse large B-cell lymphoma. Blood 2018;131:2670-2681. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29545328.

9. Lavu E, Morewaya J, Maraka R, et al. Burkitt lymphoma in Papua New Guinea--40 years on. Ann Trop Paediatr 2005;25:191-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16156984.

10. Brady G, MacArthur GJ, Farrell PJ. Epstein-Barr virus and Burkitt lymphoma. J Clin Pathol 2007;60:1397-1402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18042696.

11. Nomura Y, Lavu EK, Muta K, et al. Histological characteristics of 21 Papua New Guinean children with high-grade B-cell lymphoma, which is frequently associated with EBV infection. Pathol Int 2008;58:695-700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18844934.

12. Parkin DM, Sitas F, Chirenje M, et al. Part I: Cancer in indigenous Africans--burden, distribution, and trends. Lancet Oncol 2008;9:683-692. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18598933.

13. Moormann AM, Snider CJ, Chelimo K. The company malaria keeps: how co-infection with Epstein-Barr virus leads to endemic Burkitt lymphoma. Curr Opin Infect Dis 2011;24:435-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21885920.

14. Gouveia MH, Bergen AW, Borda V, et al. Genetic signatures of gene flow and malaria-driven natural selection in sub-Saharan populations of the "endemic Burkitt Lymphoma belt". PLoS Genet 2019;15:e1008027. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30849090.

15. WHO Classification of Tumours Editorial Board. Paediatric tumours. (WHO classification of tumours series, 5th ed.; vol. 7). Lyon (France): International Agency for Research on Cancer; 2022.

16. Yanik EL, Shiels MS, Smith JM, et al. Contribution of solid organ transplant recipients to the pediatric non-Hodgkin lymphoma burden in the United States. Cancer 2017;123:4663-4671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28759103.

17. PubMed Overview. 2023. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed February 19, 2025.

18. Sheikh IN, Elgehiny A, Ragoonanan D, et al. Management of aggressive non-Hodgkin lymphomas in the pediatric, adolescent, and young adult population: An adult vs. pediatric perspective. Cancers (Basel) 2022;14:2912. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35740580.

19. Chung EM, Pavio M. Pediatric extranodal lymphoma. Radiol Clin North Am 2016;54:727-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27265605.

20. Miron I, Miron L, Lupu VV, Ignat A. Silent presentation of multiple metastasis Burkitt lymphoma in a child: A case report and review of the literature. Medicine (Baltimore) 2017;96:e7518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28700504.

21. Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol 2004;22:3046-3052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15284254.

22. Satturwar S, Rekhtman N, Lin O, Pantanowitz L. An update on touch preparations of small biopsies. J Am Soc Cytopathol 2020;9:322-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32417160.

23. Boerma EG, Siebert R, Kluin PM, Baudis M. Translocations involving 8q24 in Burkitt lymphoma and other malignant lymphomas: a historical review of cytogenetics in the light of todays knowledge. Leukemia 2009;23:225-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18923440.

24. Maria Murga Penas E, Schilling G, Behrmann P, et al. Comprehensive cytogenetic and molecular cytogenetic analysis of 44 Burkitt lymphoma cell lines: secondary chromosomal changes characterization, karyotypic evolution, and comparison with primary samples. Genes Chromosomes Cancer 2014;53:497-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24590883.

25. Scholtysik R, Kreuz M, Klapper W, et al. Detection of genomic aberrations in molecularly defined Burkitt's lymphoma by array-based, high resolution, single nucleotide polymorphism analysis. Haematologica 2010;95:2047-2055. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20823134.

26. Toujani S, Dessen P, Ithzar N, et al. High resolution genome-wide analysis of chromosomal alterations in Burkitt's lymphoma. PLoS One 2009;4:e7089. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19759907.

27. Oschlies I, Klapper W, Zimmermann M, et al. Diffuse large B-cell lymphoma in pediatric patients belongs predominantly to the germinal-center type B-cell lymphomas: a clinicopathologic analysis of cases included in the German BFM (Berlin-Frankfurt-Munster) Multicenter Trial. Blood 2006;107:4047-4052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16424389.

28. Miles RR, Raphael M, McCarthy K, et al. Pediatric diffuse large B-cell lymphoma demonstrates a high proliferation index, frequent c-Myc protein expression, and a high incidence of germinal center subtype: Report of the French-American-British (FAB) international study group. Pediatr Blood Cancer 2008;51:369-374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18493992.

29. Akyurek N, Uner A, Benekli M, Barista I. Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. Cancer 2012;118:4173-4183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22213394.

30. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360-3365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20498406.

31. Clipson A, Barrans S, Zeng N, et al. The prognosis of MYC translocation positive diffuse large B-cell lymphoma depends on the second hit. J Pathol Clin Res 2015;1:125-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27347428.

32. Szczepanowski M, Lange J, Kohler CW, et al. Cell-of-origin classification by gene expression and MYC-rearrangements in diffuse large B-cell lymphoma of children and adolescents. Br J Haematol 2017;179:116-119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28643426.

33. Xavier AC, Attarbaschi A, Gratzinger D, Balague O. Dedicated diagnostic approaches for mature B-cell non-Hodgkin lymphomas occurring in children, adolescents, and young adults. Histopathology 2025;86:17-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39564602.

34. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. Blood 2009;114:2273-2279. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19597184.

35. Lu B, Zhou C, Yang W, et al. Morphological, immunophenotypic and molecular characterization of mature aggressive B-cell lymphomas in Chinese pediatric patients. Leuk Lymphoma 2011;52:2356-2364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21740296.

36. Perry AM, Crockett D, Dave BJ, et al. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma: study of 39 cases. Br J Haematol 2013;162:40-49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23600716.

37. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol 2010;34:327-340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20118770.

38. Tomita N, Tokunaka M, Nakamura N, et al. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica 2009;94:935-943. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19535347.

39. Gagnon MF, Bruehl FK, Sill DR, et al. Cytogenetic and pathologic characterization of MYC-rearranged B-cell lymphomas in pediatric and young adult patients. J Hematop 2024;17:51-61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38561469.

40. Burmeister T, Schwartz S, Horst HA, et al. Molecular heterogeneity of sporadic adult Burkitt-type leukemia/lymphoma as revealed by PCR and cytogenetics: correlation with morphology, immunology and clinical features. Leukemia 2005;19:1391-1398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15973450.

41. Woessmann W, Quintanilla-Martinez L. Rare mature B-cell lymphomas in children and adolescents. Hematol Oncol 2019;37 Suppl 1:53-61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31187530.

42. Chisholm KM, Mohlman J, Liew M, et al. IRF4 translocation status in pediatric follicular and diffuse large B-cell lymphoma patients enrolled in Children's Oncology Group trials. Pediatr Blood Cancer 2019;66:e27770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31012208.

43. Berg HE, Peterson JF, Lee HE, McPhail ED. Large B-cell lymphoma with IRF4 gene rearrangements: Differences in clinicopathologic, immunophenotypic and cytogenetic features between pediatric and adult patients. Human Pathology 2023;131:108-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36470475.

44. Hutchison RE, Finch C, Kepner J, et al. Burkitt lymphoma is immunophenotypically different from Burkitt-like lymphoma in young persons. Ann Oncol 2000;11 Suppl 1:35-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10707776.

45. Cairo MS, Sposto R, Perkins SL, et al. Burkitt's and Burkitt-like lymphoma in children and adolescents: a review of the Children's Cancer Group experience. Br J Haematol 2003;120:660-670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12588354.

46. Lones MA, Sanger WG, Le Beau MM, et al. Chromosome abnormalities may correlate with prognosis in Burkitt/Burkitt-like lymphomas of children and adolescents: a report from Children's Cancer

Group Study CCG-E08. J Pediatr Hematol Oncol 2004;26:169-178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15125609.

47. Wagener R, Seufert J, Raimondi F, et al. The mutational landscape of Burkitt-like lymphoma with 11q aberration is distinct from that of Burkitt lymphoma. Blood 2019;133:962-966. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30567752.

48. Nicolae A, Pittaluga S, Abdullah S, et al. EBV-positive large B-cell lymphomas in young patients: a nodal lymphoma with evidence for a tolerogenic immune environment. Blood 2015;126:863-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25999451.

49. Satou A, Asano N, Nakazawa A, et al. Epstein-Barr virus (EBV)-positive sporadic Burkitt lymphoma: an age-related lymphoproliferative disorder? Am J Surg Pathol 2015;39:227-235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25321330.

50. Vaillant V, Reiter A, Zimmermann M, Wagner HJ. Seroepidemiological analysis and literature review of the prevalence of Epstein-Barr virus and herpesvirus infections in pediatric cases with non-Hodgkin lymphoma in Central Europe. Pediatr Blood Cancer 2019;66:e27752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30977593.

51. Richter J, John K, Staiger AM, et al. Epstein-Barr virus status of sporadic Burkitt lymphoma is associated with patient age and mutational features. Br J Haematol 2022;196:681-689. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34617271.

52. Barmettler S, Ong MS, Farmer JR, et al. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Netw Open 2018;1:e184169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30646343.

53. McAtee CL, Lubega J, Underbrink K, et al. Association of Rituximab Use With Adverse Events in Children, Adolescents, and Young Adults. JAMA Netw Open 2021;4:e2036321. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33533931.

54. Alexander S, Auperin A, Bomken S, et al. Effect of rituximab on immune status in children with mature B-cell non-Hodgkin lymphoma: a prespecified secondary analysis of the Inter-B-NHL Ritux 2010 trial. Lancet Haematol 2023;10:e445-e457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37094596.

55. Salzburg J, Burkhardt B, Zimmermann M, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group Report. J Clin Oncol 2007;25:3915-3922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17761975.

56. Cairo MS, Sposto R, Gerrard M, et al. Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (≥ 15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the FAB LMB 96 study. J Clin Oncol 2012;30:387-393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22215753.

57. Mhlanga J, Alazraki A, Cho SY, et al. Imaging recommendations in pediatric lymphoma: A COG Diagnostic Imaging Committee/SPR Oncology Committee White Paper. Pediatr Blood Cancer 2022:e29968. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36114654.

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

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

60. Sandlund JT, Guillerman RP, Perkins SL, et al. International pediatric non-Hodgkin lymphoma response criteria. J Clin Oncol 2015;33:2106-2111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25940725.

61. Meignan M, Gallamini A, Meignan M, et al. Report on the first international workshop on interim-PET-scan in lymphoma. Leuk Lymphoma 2009;50:1257-1260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19544140.

62. Bailly C, Eugene T, Couec ML, et al. Prognostic value and clinical impact of (18)FDG-PET in the management of children with Burkitt lymphoma after induction chemotherapy. Front Med (Lausanne) 2014;1:54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25593926.

63. Abdel Rahman H, Sedky M, Hamoda A, et al. Role of FDG-PET scan in the management of pediatric mature B cell non-Hodgkin's lymphoma. CCHE experience. J Egypt Natl Canc Inst 2016;28:95-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27133974.

64. Bhojwani D, McCarville MB, Choi JK, et al. The role of FDG-PET/CT in the evaluation of residual disease in paediatric non-Hodgkin lymphoma. Br J Haematol 2015;168:845-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25382494.

65. Furth C, Erdrich AS, Steffen IG, et al. Interim PET response criteria in paediatric non-Hodgkin's lymphoma. Results from a retrospective multicenter reading. Nuklearmedizin 2013;52:148-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23928982.

66. Karantanis D, Durski JM, Lowe VJ, et al. 18F-FDG PET and PET/CT in Burkitt's lymphoma. Eur J Radiol 2010;75:e68-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19716248.

67. Riad R, Omar W, Sidhom I, et al. False-positive F-18 FDG uptake in PET/CT studies in pediatric patients with abdominal Burkitt's lymphoma. Nucl Med Commun 2010;31:232-238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20032800.

68. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. Semin Oncol 1980;7:332-339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7414342.

69. Rosolen A, Perkins SL, Pinkerton CR, et al. Revised international pediatric non-Hodgkin lymphoma staging system. J Clin Oncol 2015;33:2112-2118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25940716.

70. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood 2007;109:2736-2743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17138821.

71. Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. N Engl J Med 2020;382:2207-2219. Available at: https://pubmed.ncbi.nlm.nih.gov/32492302/.

72. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage non-Hodgkin's lymphoma. N Engl J Med 1997;337:1259-1266. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9345074.

73. Gerrard M, Cairo MS, Weston C, et al. Excellent survival following two courses of COPAD chemotherapy in children and adolescents with resected localized B-cell non-Hodgkin's lymphoma: results of the FAB/LMB 96 international study. Br J Haematol 2008;141:840-847. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18371107.

74. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the BFM Group Study NHL-BFM95. Blood 2005;105:948-958. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15486066.

75. Goldman S, Smith L, Anderson JR, et al. Rituximab and FAB/LMB 96 chemotherapy in children with Stage III/IV B-cell non-Hodgkin lymphoma: a Children's Oncology Group report. Leukemia 2013;27:1174-1177. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22940833.

76. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood 2007;109:2773-2780. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17132719.

77. Reiter A, Schrappe M, Tiemann M, et al. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. Blood 1999;94:3294-3306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10552938.

78. Meinhardt A, Burkhardt B, Zimmermann M, et al. Phase II window study on rituximab in newly diagnosed pediatric mature B-cell non-Hodgkin's lymphoma and Burkitt leukemia. J Clin Oncol 2010;28:3115-3121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20516455.

79. Goldman S, Smith L, Galardy P, et al. Rituximab with chemotherapy in children and adolescents with central nervous system and/or bone marrow-positive Burkitt lymphoma/leukaemia: a Children's Oncology Group Report. Br J Haematol 2014;167:394-401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25066629.

80. Samochatova EV, Maschan AA, Shelikhova LN, et al. Therapy of advanced-stage mature B-cell lymphoma and leukemia in children and adolescents with rituximab and reduced intensity induction chemotherapy (B-NHL 2004M protocol): the results of a multicenter study. J Pediatr Hematol Oncol 2014;36:395-401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23823112.

81. Frazer JK, Li KJ, Galardy PJ, et al. Excellent outcomes in children and adolescents with CNS(+) Burkitt lymphoma or other mature B-NHL using only intrathecal and systemic chemoimmunotherapy: results from FAB/LMB96 and COG ANHL01P1. Br J Haematol 2019;185:374-377. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30117142.

82. Jourdain A, Auperin A, Minard-Colin V, et al. Outcome of and prognostic factors for relapse in children and adolescents with mature B-cell lymphoma and leukemia treated in three consecutive prospective "Lymphomes Malins B" protocols. A Societe Francaise des Cancers de l'Enfant study. Haematologica 2015;100:810-817. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25724577.

83. Rigaud C, Auperin A, Jourdain A, et al. Outcome of relapse in children and adolescents with B-cell non-Hodgkin lymphoma and mature acute leukemia: A report from the French LMB study. Pediatr Blood Cancer 2019;66:e27873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31207026.

84. Eissa HM, Allen CE, Kamdar K, et al. Pediatric Burkitt's lymphoma and diffuse B-cell lymphoma: are surveillance scans required? Pediatr Hematol Oncol 2014;31:253-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24087880.

85. Brinkman TM, Recklitis CJ, Michel G, et al. Psychological Symptoms, Social Outcomes, Socioeconomic Attainment, and Health Behaviors Among Survivors of Childhood Cancer: Current State of the Literature. J Clin Oncol 2018;36:2190-2197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29874134.

86. McGrady ME, Willard VW, Williams AM, Brinkman TM. Psychological Outcomes in Adolescent and Young Adult Cancer Survivors. J Clin Oncol 2024;42:707-716. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37967297.

87. Fujita N, Mori T, Mitsui T, et al. The role of hematopoietic stem cell transplantation with relapsed or primary refractory childhood B-cell non-Hodgkin lymphoma and mature B-cell leukemia: a retrospective analysis of enrolled cases in Japan. Pediatr Blood Cancer 2008;51:188-192. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18428432.

88. Naik S, Martinez CA, Omer B, et al. Allogeneic hematopoietic stem cell transplant for relapsed and refractory non-Hodgkin lymphoma in pediatric patients. Blood Adv 2019;3:2689-2695. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31511228.

89. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18816698.

90. Anoop P, Sankpal S, Stiller C, et al. Outcome of childhood relapsed or refractory mature B-cell non-Hodgkin lymphoma and acute lymphoblastic leukemia. Leuk Lymphoma 2012;53:1882-1888. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22448922.

91. Osumi T, Mori T, Fujita N, et al. Relapsed/refractory pediatric B-cell non-Hodgkin lymphoma treated with rituximab combination therapy: A report from the Japanese Pediatric Leukemia/Lymphoma Study Group. Pediatr Blood Cancer 2016;63:1794-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27314926.

92. Burkhardt B, Taj M, Garnier N, et al. Treatment and outcome analysis of 639 relapsed non-Hodgkin lymphomas in children and adolescents and resulting treatment recommendations. Cancers (Basel) 2021;13:2075. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33923026.

93. Tiercy JM. How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica 2016;101:680-687. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27252513.

94. Lee CJ, Savani BN, Mohty M, et al. Haploidentical hematopoietic cell transplantation for adult acute myeloid leukemia: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica 2017;102:1810-1822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28883081.

95. Kim H, Park ES, Lee SH, et al. Clinical outcome of relapsed or refractory Burkitt lymphoma and mature B-cell lymphoblastic leukemia in children and adolescents. Cancer Res Treat 2014;46:358-365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25043820.

96. Giulino-Roth L, Ricafort R, Kernan NA, et al. Ten-year follow-up of pediatric patients with non-Hodgkin lymphoma treated with allogeneic or autologous stem cell transplantation. Pediatr Blood Cancer 2013;60:2018-2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24038967.

97. Andion M, Molina B, Gonzalez-Vicent M, et al. High-dose busulfan and cyclophosphamide as a conditioning regimen for autologous peripheral blood stem cell transplantation in childhood non-Hodgkin lymphoma patients: a long-term follow-up study. J Pediatr Hematol Oncol 2011;33:e89-91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21358341.

98. Pasvolsky O, Bassett RL, Ghanem S, et al. Characteristics and outcomes of children, adolescents and young adults with relapsed/refractory non-hodgkin lymphoma undergoing autologous stem cell transplant. BMC Cancer 2023;23:1258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38124057.

99. Gross TG, Hale GA, He W, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. Biol Blood Marrow Transplant 2010;16:223-230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19800015.

100. Westin JR, Kersten MJ, Salles G, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: Observations from the JULIET, ZUMA-1, and TRANSCEND trials. Am J Hematol 2021;96:1295-1312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34310745.

101. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-448. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29385370.

102. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-Cell lymphoma. N Engl J Med 2022;387:2220-2231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36507690.

103. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell-engaging antibody, in relapsed or refractory large B-cell lymphoma: Dose expansion in a phase I/II trial. J Clin Oncol 2023;41:2238-2247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36548927.

104. Liu Y, Deng B, Hu B, et al. Sequential different B-cell antigen-targeted CAR T-cell therapy for pediatric refractory/relapsed Burkitt lymphoma. Blood Adv 2022;6:717-730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34521107.

105. Chu Y, Gardenswartz A, Diorio C, et al. Cellular and humoral immunotherapy in children, adolescents and young adults with non-Hodgkin lymphoma. Best Pract Res Clin Haematol 2023;36:101442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36907635.

106. Cazals-Hatem D, Lepage E, Brice P, et al. Primary mediastinal large B-cell lymphoma. A clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA ("Groupe d'Etude des Lymphomes de l'Adulte") study. Am J Surg Pathol 1996;20:877-888. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8669537.

107. Oschlies I, Burkhardt B, Salaverria I, et al. Clinical, pathological and genetic features of primary mediastinal large B-cell lymphomas and mediastinal gray zone lymphomas in children. Haematologica 2011;96:262-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20971819.

108. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 2003;198:851-862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12975453.

109. Savage KJ, Monti S, Kutok JL, et al. The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood 2003;102:3871-3879. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12933571.

110. Wessendorf S, Barth TF, Viardot A, et al. Further delineation of chromosomal consensus regions in primary mediastinal B-cell lymphomas: an analysis of 37 tumor samples using high-resolution genomic profiling (array-CGH). Leukemia 2007;21:2463-2469. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17728785.

111. Attias D, Hodgson D, Weitzman S. Primary mediastinal B-cell lymphoma in the pediatric patient: Can a rational approach to therapy be based on adult studies? Pediatr Blood Cancer 2009;52:566-570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19058208.

112. Roberts RA, Wright G, Rosenwald AR, et al. Loss of major histocompatibility class II gene and protein expression in primary mediastinal large B-cell lymphoma is highly coordinated and related to poor patient survival. Blood 2006;108:311-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16543468.

113. Mottok A, Woolcock B, Chan FC, et al. Genomic alterations in CIITA are frequent in primary mediastinal large B cell lymphoma and are associated with diminished MHC class II expression. Cell Rep 2015;13:1418-1431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26549456.

114. Joos S, Otano-Joos MI, Ziegler S, et al. Primary mediastinal (thymic) B-cell lymphoma is characterized by gains of chromosomal material including 9p and amplification of the REL gene. Blood 1996;87:1571-1578. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8608249.

115. Bentz M, Barth TF, Bruderlein S, et al. Gain of chromosome arm 9p is characteristic of primary mediastinal B-cell lymphoma (MBL): comprehensive molecular cytogenetic analysis and presentation of a novel MBL cell line. Genes Chromosomes Cancer 2001;30:393-401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11241792.

116. Weniger MA, Pulford K, Gesk S, et al. Gains of the proto-oncogene BCL11A and nuclear accumulation of BCL11A(XL) protein are frequent in primary mediastinal B-cell lymphoma. Leukemia 2006;20:1880-1882. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16871282.

117. Weniger MA, Gesk S, Ehrlich S, et al. Gains of REL in primary mediastinal B-cell lymphoma coincide with nuclear accumulation of REL protein. Genes Chromosomes Cancer 2007;46:406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17243160.

118. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268-3277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20628145.

119. Twa DD, Chan FC, Ben-Neriah S, et al. Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma. Blood 2014;123:2062-2065. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24497532.

120. Seidemann K, Tiemann M, Lauterbach I, et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Munster Group. J Clin Oncol 2003;21:1782-1789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12721255.

121. Gerrard M, Waxman IM, Sposto R, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood 2013;121:278-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23149845.

122. Dourthe ME, Phulpin A, Auperin A, et al. Rituximab in addition to LMB-based chemotherapy regimen in children and adolescents with primary mediastinal large B-cell lymphoma: results of the French LMB2001 prospective study. Haematologica 2022;107:2173-2182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35236054.

123. Dourthe ME, Auperin A, Rigaud C, et al. Excellent outcome of children/adolescents with primary mediastinal large B-cell lymphoma treated with a FAB/ LMB-based chemotherapy regimen with rituximab. Haematologica 2024;109:3790-3794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38988265.

124. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013;368:1408-1416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23574119.

125. Hayden AR, Tonseth P, Lee DG, et al. Outcome of primary mediastinal large B-cell lymphoma using R-CHOP: impact of a PET-adapted approach. Blood 2020;136:2803-2811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32603413.

126. Giulino-Roth L, O'Donohue T, Chen Z, et al. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol 2017;179:739-747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29082519.

127. Knorr F, Zimmermann M, Attarbaschi A, et al. Dose-adjusted EPOCH-rituximab or intensified B-NHL therapy for pediatric primary mediastinal large B-cell lymphoma. Haematologica 2021;106:3232-3235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34498443.

128. Burke GAA, Minard-Colin V, Auperin A, et al. Dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone plus rituximab therapy in children and adolescents with primary mediastinal B-cell lymphoma: A multicenter phase II trial. J Clin Oncol 2021;39:3716-3724. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34570655.

129. Giulino-Roth L. How I treat primary mediastinal B-cell lymphoma. Blood 2018;132:782-790. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29976557.

130. Moleti ML, Testi AM, Foa R. Treatment of relapsed/refractory paediatric aggressive B-cell non-Hodgkin lymphoma. Br J Haematol

2020;189:826-843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32141616.

131. Avivi I, Boumendil A, Finel H, et al. Autologous stem cell transplantation for primary mediastinal B-cell lymphoma: long-term outcome and role of post-transplant radiotherapy. A report of the European Society for Blood and Marrow Transplantation. Bone Marrow Transplant 2018;53:1001-1009. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29463854.

132. Vardhana S, Hamlin PA, Yang J, et al. Outcomes of relapsed and refractory primary mediastinal (thymic) large B cell lymphoma treated with second-line therapy and intent to transplant. Biol Blood Marrow Transplant 2018;24:2133-2138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29909154.

133. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. Blood 2017;129:2328-2330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28264798.

134. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood 2017;130:267-270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28490569.

135. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. J Clin Oncol 2019;37:3291-3299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31609651.

136. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2020;21:541-550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32192573.

137. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for R/R primary mediastinal large B-cell lymphoma: a 3-year follow-up. Blood Adv 2023;7:5272-5280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37352266.

138. Gross TG, Rubinstein JD. Post-transplant lymphoproliferative disease in children, adolescents, and young adults. Hematol Oncol 2023;41 Suppl 1:48-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37294957.

139. Cheng J, Wistinghausen B. Clinicopathologic Spectrum of Pediatric Posttransplant Lymphoproliferative Diseases Following Solid Organ Transplant. Arch Pathol Lab Med 2024;148:1052-1062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38051286.

140. Schober T, Framke T, Kreipe H, et al. Characteristics of early and late PTLD development in pediatric solid organ transplant recipients. Transplantation 2013;95:240-246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23222898.

141. Afify ZAM, Taj MM, Orjuela-Grimm M, et al. Multicenter study of pediatric Epstein-Barr virus-negative monomorphic post solid organ transplant lymphoproliferative disorders. Cancer 2023;129:780-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36571557.

142. Ferreiro JF, Morscio J, Dierickx D, et al. EBV-Positive and EBV-Negative Posttransplant Diffuse Large B Cell Lymphomas Have Distinct Genomic and Transcriptomic Features. Am J Transplant 2016;16:414-425. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26780579.

143. Menter T, Juskevicius D, Alikian M, et al. Mutational landscape of B-cell post-transplant lymphoproliferative disorders. Br J Haematol 2017;178:48-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28419429.

144. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. Am J Transplant 2004;4:222-230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14974943.

145. Allen UD, Farkas G, Hebert D, et al. Risk factors for post-transplant lymphoproliferative disorder in pediatric patients: a case-control study.

Pediatr Transplant 2005;9:450-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16048596.

146. Dharnidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU. Associations between EBV serostatus and organ transplant type in PTLD risk: an analysis of the SRTR National Registry Data in the United States. Am J Transplant 2012;12:976-983. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22226225.

147. Weintraub L, Weiner C, Miloh T, et al. Identifying predictive factors for posttransplant lymphoproliferative disease in pediatric solid organ transplant recipients with Epstein-Barr virus viremia. J Pediatr Hematol Oncol 2014;36:e481-486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24878618.

148. West SC, Friedland-Little JM, Schowengerdt KO, Jr., et al. Characteristics, risks, and outcomes of post-transplant lymphoproliferative disease >3 years after pediatric heart transplant: A multicenter analysis. Clin Transplant 2019;33:e13521. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30861200.

149. Allen UD, Preiksaitis JK. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019;33:e13652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31230381.

150. Tajima T, Martinez OM, Bernstein D, et al. Epstein-Barr virus-associated post-transplant lymphoproliferative disorders in pediatric transplantation: A prospective multicenter study in the United States. Pediatr Transplant 2024;28:e14763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38682750.

151. Martinez OM, Krams SM, Robien MA, et al. Mutations in latent membrane protein 1 of Epstein-Barr virus are associated with increased risk of posttransplant lymphoproliferative disorder in children. Am J Transplant 2023;23:611-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36796762.

152. Maecker B, Jack T, Zimmermann M, et al. CNS or bone marrow involvement as risk factors for poor survival in post-transplantation lymphoproliferative disorders in children after solid organ transplantation. J Clin Oncol 2007;25:4902-4908. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17971586.

153. Webber SA, Naftel DC, Fricker FJ, et al. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. Lancet 2006;367:233-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16427492.

154. Ullah A, Lee KT, Malham K, et al. Post-transplant Lymphoproliferative Disorder (PTLD) in the US Population: Demographics, Treatment Characteristics, and Survival Analysis. Cureus 2023;15:e39777. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37398803.

155. Allen UD, L'Huillier AG, Bollard CM, et al. The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: IV-consensus guidelines for the management of post-transplant lymphoproliferative disorders in children and adolescents. Pediatr Transplant 2024;28:e14781. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38808744.

156. Picarsic J, Jaffe R, Mazariegos G, et al. Post-transplant Burkitt lymphoma is a more aggressive and distinct form of post-transplant lymphoproliferative disorder. Cancer 2011;117:4540-4550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21446044.

157. Cavaliere R, Petroni G, Lopes MB, et al. Primary central nervous system post-transplantation lymphoproliferative disorder: an International Primary Central Nervous System Lymphoma Collaborative Group Report. Cancer 2010;116:863-870. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20052713.

158. Taj MM, Maecker-Kolhoff B, Ling R, et al. Primary post-transplant lymphoproliferative disorder of the central nervous system: characteristics, management and outcome in 25 paediatric patients. Br J Haematol 2021;193:1178-1184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33764500.

159. Tiede C, Maecker-Kolhoff B, Klein C, et al. Risk factors and prognosis in T-cell posttransplantation lymphoproliferative diseases: reevaluation of 163 cases. Transplantation 2013;95:479-488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23296147.

160. Herreman A, Dierickx D, Morscio J, et al. Clinicopathological characteristics of posttransplant lymphoproliferative disorders of T-cell origin: single-center series of nine cases and meta-analysis of 147 reported cases. Leuk Lymphoma 2013;54:2190-2199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23402267.

161. Cheng J, Mariani R, Punia JN, et al. Clinical and pathological features of pediatric peripheral T-cell lymphoma after solid organ transplantation. Blood Neoplasia 2024;1. Available at: https://doi.org/10.1016/j.bneo.2024.100039.

162. Perry AM, Aoun P, Coulter DW, et al. Early onset, EBV(-) PTLD in pediatric liver-small bowel transplantation recipients: a spectrum of plasma cell neoplasms with favorable prognosis. Blood 2013;121:1377-1383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23255556.

163. Plant AS, Venick RS, Farmer DG, et al. Plasmacytoma-like post-transplant lymphoproliferative disorder seen in pediatric combined liver and intestinal transplant recipients. Pediatr Blood Cancer 2013;60:E137-139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23813867.

164. Kampers J, Orjuela-Grimm M, Schober T, et al. Classical Hodgkin lymphoma-type PTLD after solid organ transplantation in children: a report on 17 patients treated according to subsequent GPOH-HD treatment schedules. Leuk Lymphoma 2017;58:633-638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27685149.

165. Swerdlow SH, Harris NL, Jaffe ES, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC; 2017.

166. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood 2022;140:1229-1253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35653592.

167. Matsumura M, Miyagi S, Tokodai K, et al. Probable posttransplant lymphoproliferative disorder after pediatric living donor liver transplantation: Is a biopsy still needed? Clin Case Rep 2022;10:e6454. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36348984.

168. Orjuela MA, Alobeid B, Liu X, et al. CD20 expression predicts survival in paediatric post-transplant lymphoproliferative disease (PTLD) following solid organ transplantation. Br J Haematol 2011;152:733-742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21275950.

169. Salmeron-Villalobos J, Castrejon-de-Anta N, Guerra-Garcia P, et al. Decoding the molecular heterogeneity of pediatric monomorphic post-solid organ transplant lymphoproliferative disorders. Blood 2023;142:434-445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37053555.

170. Preiksaitis J, Allen U, Bollard CM, et al. The IPTA Nashville Consensus Conference on Post-Transplant lymphoproliferative disorders after solid organ transplantation in children: III - Consensus guidelines for Epstein-Barr virus load and other biomarker monitoring. Pediatr Transplant 2024;28:e14471. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37294621.

171. Nouwen J, Smets F, Rombaux P, et al. Acute tonsillitis as the first manifestation of post-transplant lymphoproliferative disorder. Ann Otol Rhinol Laryngol 2002;111:165-168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11860070.

172. Webber S, Harmon W, Faro A, et al. Anti-CD20 Monoclonal Antibody (rituximab) for Refractory PTLD after Pediatric Solid Organ Transplantation: Multicenter Experience from a Registry and from a Prospective Clinical Trial [abstract]. Blood 2004;104:Abstract 746. Available at: https://doi.org/10.1182/blood.V104.11.746.746.

173. Oertel SH, Verschuuren E, Reinke P, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative

disorder (PTLD). Am J Transplant 2005;5:2901-2906. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16303003.

174. Gross TG, Bucuvalas JC, Park JR, et al. Low-dose chemotherapy for Epstein-Barr virus-positive post-transplantation lymphoproliferative disease in children after solid organ transplantation. J Clin Oncol 2005;23:6481-6488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16170157.

175. Schubert S, Abdul-Khaliq H, Lehmkuhl HB, et al. Diagnosis and treatment of post-transplantation lymphoproliferative disorder in pediatric heart transplant patients. Pediatr Transplant 2009;13:54-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18518912.

176. Gross TG, Orjuela MA, Perkins SL, et al. Low-dose chemotherapy and rituximab for posttransplant lymphoproliferative disease (PTLD): a Children's Oncology Group Report. Am J Transplant 2012;12:3069-3075. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22883417.

177. Mark C, Martin G, Baadjes B, et al. Treatment of Monomorphic Posttransplant Lymphoproliferative Disorder in Pediatric Solid Organ Transplant: A Multicenter Review. J Pediatr Hematol Oncol 2024;46:e127-e130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38145403.

178. Guerra-Garcia P, Bomken S, Ling R, et al. Management of paediatric monomorphic post-transplant lymphoproliferative disorders with low-intensity treatment: A multicentre international experience. Pediatr Blood Cancer 2024;71:e31053. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38757407.

179. Maecker-Kolhoff B, Beier R, Zimmermann M, et al. Response-Adapted Sequential Immuno-Chemotherapy of Post-Transplant Lymphoproliferative Disorders in Pediatric Solid Organ Transplant Recipients: Results from the Prospective Ped-PTLD 2005 Trial [abstract]. Blood 2014;124:Abstract 4468. Available at: https://doi.org/10.1182/blood.V124.21.4468.4468.

180. Savoldo B, Goss JA, Hammer MM, et al. Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). Blood 2006;108:2942-2949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16835376.

181. Haque T, Wilkie GM, Jones MM, et al. Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. Blood 2007;110:1123-1131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17468341.

182. Heslop HE, Slobod KS, Pule MA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. Blood 2010;115:925-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19880495.

183. Prockop S, Doubrovina E, Suser S, et al. Off-the-shelf EBV-specific T cell immunotherapy for rituximab-refractory EBV-associated lymphoma following transplantation. J Clin Invest 2020;130:733-747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31689242.

184. Mahadeo KM, Baiocchi R, Beitinjaneh A, et al. Tabelecleucel for allogeneic haematopoietic stem-cell or solid organ transplant recipients with Epstein-Barr virus-positive post-transplant lymphoproliferative disease after failure of rituximab or rituximab and chemotherapy (ALLELE): a phase 3, multicentre, open-label trial. Lancet Oncol 2024;25:376-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38309282.

185. Ghobadi A, Baiocchi R, Beitinjaneh AM, et al. Updated Clinical Results: A Multicenter, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Hematopoietic Cell Transplant Recipients with Epstein-Barr Virus-Driven Post Transplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab Plus Chemotherapy [abstract]. Blood 2024;144:Abstract 70. Available at: https://doi.org/10.1182/blood-2024-198159.

186. Afify Z, Orjuela-Grimm M, Smith CM, et al. Burkitt lymphoma after solid-organ transplant: Treatment and outcomes in the paediatric PTLD collaborative. Br J Haematol 2023;200:297-305. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36454546.

187. Levine DR, Mandrell BN, Sykes A, et al. Patients' and parents' needs, attitudes, and perceptions about early palliative care integration in pediatric oncology. JAMA Oncol 2017;3:1214-1220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28278329.

188. Olagunju AT, Sarimiye FO, Olagunju TO, et al. Child's symptom burden and depressive symptoms among caregivers of children with cancers: an argument for early integration of pediatric palliative care. Ann Palliat Med 2016;5:157-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27199271.

189. Sung L, Zaoutis T, Ullrich NJ, et al. Children's Oncology Group's 2013 blueprint for research: cancer control and supportive care. Pediatr Blood Cancer 2013;60:1027-1030. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23255159.

190. Anghelescu DL, Faughnan LG, Jeha S, et al. Neuropathic pain during treatment for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2011;57:1147-1153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21319291.

191. Kearney JA, Salley CG, Muriel AC. Standards of psychosocial care for parents of children with cancer. Pediatr Blood Cancer 2015;62 Suppl 5:S632-683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26700921.

192. Choi EK, Yoon SJ, Kim JH, et al. Depression and distress in caregivers of children with brain tumors undergoing treatment: psychosocial factors as moderators. Psychooncology 2016;25:544-550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26426911.

193. Warner EL, Kirchhoff AC, Nam GE, Fluchel M. Financial burden of pediatric cancer for patients and their families. J Oncol Pract 2015;11:12-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25316026.

194. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol 2017;35:2082-2094. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28459614.

195. Patel P, Robinson PD, Thackray J, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update. Pediatr Blood Cancer 2017;64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28453189.

196. Robinson PD, Oberoi S, Tomlinson D, et al. Management of fatigue in children and adolescents with cancer and in paediatric recipients of haemopoietic stem-cell transplants: a clinical practice guideline. Lancet Child Adolesc Health 2018;2:371-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30169270.

197. Diorio C, Robinson PD, Ammann RA, et al. Guideline for the management of clostridium difficile infection in children and adolescents with cancer and pediatric hematopoietic stem-cell transplantation recipients. J Clin Oncol 2018:JCO1800407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30216124.

198. Flank J, Robinson PD, Holdsworth M, et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. Pediatr Blood Cancer 2016;63:1144-1151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26960036.

199. Derinkuyu BE, Boyunaga O, Oztunali C, et al. Imaging features of Burkitt lymphoma in pediatric patients. Diagn Interv Radiol 2016;22:95-100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26611257.

200. Fallon SC, Redell MS, El-Bietar J, et al. Intestinal perforation after treatment of Burkitt's lymphoma: case report and review of the literature. J Pediatr Surg 2013;48:436-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23414881.

201. Righini-Grunder F, Hurni M, Warschkow R, Rischewski J. Frequency of oral mucositis and local virus reactivation in herpes simplex virus seropositive children with myelosuppressive therapy. Klin Padiatr 2015;227:335-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26502184.

202. Mikulska M, Lanini S, Gudiol C, et al. ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: An infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect 2018;24 Suppl 2:S71-S82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29447988.

203. Cao X, Wang Y, Li P, et al. HBV reactivation during the treatment of non-Hodgkin lymphoma and management strategies. Front Oncol 2021;11:685706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34277431.

204. Bernhardt MB, Brown AL, Grim AT, et al. Safety analysis of high-dose methotrexate in pediatric non-Hodgkin lymphomas. Pediatr Blood Cancer 2022;69:e29940. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36069680.

205. Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol 2010;149:578-586. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20331465.

206. Pession A, Masetti R, Gaidano G, et al. Risk evaluation, prophylaxis, and treatment of tumor lysis syndrome: consensus of an Italian expert panel. Adv Ther 2011;28:684-697. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21779956.

207. Perissinotti AJ, Bishop MR, Bubalo J, et al. Expert consensus guidelines for the prophylaxis and management of tumor lysis syndrome in the United States: Results of a modified Delphi panel. Cancer Treat Rev 2023;120:102603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37579533.

208. Galardy PJ, Hochberg J, Perkins SL, et al. Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: a Children's Oncology Group Report. Br J Haematol 2013;163:365-372. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24032600.

209. Gammal RS, Pirmohamed M, Somogyi AA, et al. Expanded clinical pharmacogenetics implementation consortium guideline for medication use in the context of G6PD genotype. Clin Pharmacol Ther 2023;113:973-985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36049896.

210. Taylor ZL, Mizuno T, Punt NC, et al. MTXPK.org: A clinical decision support tool evaluating high-dose methotrexate pharmacokinetics to inform post-infusion care and use of glucarpidase. Clin Pharmacol Ther 2020;108:635-643. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32558929.