National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Aggressive Mature B-Cell Lymphomas

Version 2.2024 — September 3, 2024

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.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
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 ¥
Patient Advocate

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 €
UC San Diego Moores Cancer Center | Rady Children's Hospital-San Diego

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

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

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

Paul L. Martin, MD, PhD € ξ
Duke Cancer Institute | Duke Children's Hospital & Health 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

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

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
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.

NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

NCCN Categories of Preference.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Pediatric Aggressive Mature B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates to Version 2.2024 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 1.2024 include:

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

Updates to Version 1.2024 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 1.2023 include:

PBCL-2
- Additional Diagnostic Testing
  - Essential
    - ◊ Bullet 1, sub-bullet 1 revised: IHC panel for BL and DLBCL: Ki-67, BCL2, BCL6, CD3, CD10, CD20, *IRF4*/MUM1
    - ◊ Bullet 1, sub-bullet 2 revised: IHC panel for PMBL: CD10, CD19, CD20, PAX5, CD23, CD30, BCL2, BCL6, *IRF4/*MUM1, and Ki-67; EBV is absent
    - ◊ Bullet 2 revised: *Karyotype or* FISH: MYC rearrangement
  - Useful Under Certain Circumstances
    - ◊ Bullet 3 revised: Epstein-Barr *virus-encoded RNA* ~~encoding region~~ in-situ hybridization (EBER-ISH)
    - ◊ Bullet 4 revised: IHC/*ISH* Panel: MYC and Kappa/Lambda ISH ~~IRF4/MUM1~~
    - ◊ Bullet 5 added: IHC for CD56 in absence of CD38 bright by flow cytometry (for HGBL with 11q aberrations)
    - ◊ Bullet 6 revised: Karyotype or FISH for IRF4/MUM1, *BCL2, and BCL6* rearrangements
    - ◊ Bullet incorporated into bullet 6: FISH for BCL2 and BCL6 rearrangements

PBCL-3
- Workup
  - Useful Under Certain Circumstances
    - ◊ Last bullet revised: ~~Consider~~ *Obtain* baseline immunoglobulin panel, ~~if use of~~ *prior to using* rituximab ~~is contemplated~~

PBCL-4
- The order of the Staging and Risk Group Definitions pages was switched.

Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma

PBCL-9
- Response
  - Revised after Response assessment after COP reduction phase: Continue *same* chemotherapy regimen ~~as at induction~~. If <20% reduction following COP, can consider changing to regimen C3

PBCL-10
- H&P
  - BL
    - ◊ Sub-bullet 1 revised: Every *1–3* month*s* for 1 year
- Bullet 3 revised: Routine surveillance imaging is not recommended. ~~Consider only if clinical suspicion of relapse:~~ *Reassess sites of original disease with imaging studies as indicated (PBCL-3), only if clinical suspicion of relapse.*
  - Sub-bullet removed: CT chest with IV contrast and CT abdomen/pelvis with IV and oral contrast. Consider FDG-PET/CT or FDG-PET/MRI if relapse is suspected based on CT scan findings.
- Footnote jj added : More frequent follow-up may be needed if the patient is symptomatic.
- Bullet removed: Abdominal ultrasound
  - Sub-bullet removed: 3 months after therapy, if clinical concern

PBCL-11
- CR, Consolidation/additional therapy
  - Donor options for allogeneic HCT moved to footnote pp: 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).*

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Pediatric Aggressive Mature B-Cell Lymphomas

NCCN Guidelines Index
Table of Contents
Discussion

Updates to Version 1.2024 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 1.2023 include:

Primary Mediastinal Large B-Cell Lymphoma

PMBL-1
- Response
  - <CR: New node added.
  - Follow-up (CR): Deauville 5-point scale criteria moved to Response column.
    - Bullet 1, sub-bullet 1 revised: Every *1–3* month*s* for 1 year
    - Bullet 3, sub-bullet 3, sub-sub-bullet moved to <CR.
- Footnote h revised: *PET/CT scan is essential at EOT.* Residual mediastinal masses are common. Biopsy of PET-positive mass *should be considered* ~~is recommended~~ if additional systemic treatment is contemplated.

PBCL-A 1 of 3
- Principles of Diagnostic Pathology
  - Immunophenotyping
    - Bullet 7 added: PMBL expresses CD23, CD30, and MUM1 in most of the cases, in addition to pan T-cell markers. BCL2 and BCL6 are variable. At least one of the biomarkers should be expressed: CD200, MAL, PD-L1, and PD-L2.

PBCL-B 2 of 15
- Principles of Systemic Therapy
  - COG ANHL1131 (based on FAB/LMB96) Regimen B
    - Sub-bullet 1
      - Sub-sub-bullet 2 revised: 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*.
      - Sub-sub-bullet 3 added: 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.
  - Bottom table
    - Row 1, column 2 revised: 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 (Also for PBCL-B 4 of 15)

PBCL-B 4 of 15
- Principles of Systemic Therapy
  - Regimen C1/Induction 1 & 2 R-COPADM
    - Sub-bullet 1,
      - Sub-sub-bullet 2 revised: 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*.

PBCL-B 6 of 15
- Principles of Systemic Therapy
  - Top table
    - Row 1, column 2 revised: *250* ~~500~~ mg/m²/~~day~~ *dose every 12 hours* on days 2–3 (~~2~~ *4* doses *total*)

PBCL-B 8 of 15
- Principles of Systemic Therapy
  - Top table
    - Row 1, Column 4 revised: 1 to <2 ~~3~~ years old
    - Row 1, column 5 revised: ≥*2 to* <3 ~~to <9~~ years old
    - Row 1, column 6 revised: ≥*3* ~~9~~ years old

PBCL-D 3 of 4
- Principles of Supportive Care
  - Supportive Care Related to Systemic Therapy
    - Bullet 3, sub-bullet 2 revised: Optimal administration of glucarpidase is within 48 to 60 hours from the start of methotrexate infusion. ~~Leucovorin should be continued for at least 2 days following glucarpidase administration and should be administered at least 2 hours before or 2 hours after glucarpidase.~~ *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.*

DIAGNOSIS[a,b]

- **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.**

→

SUBTYPES[c,d,e]

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

→ **Additional Diagnostic Testing (PBCL-2)**

[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).

[d] 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.

[e] 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.

[f] 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). Optimum management of this rare subtype is undefined, although it is most often treated like typical BL.

[g] Double- and triple-hit lymphomas 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.

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

ADDITIONAL DIAGNOSTIC TESTING[c]

ESSENTIAL

- **Adequate immunophenotyping to establish diagnosis[h,i,j]**
  - **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[k]**

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)[l]**
- **IHC/ISH Panel: MYC 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[g]**
- **TdT IHC or flow cytometry**
- **Clonality testing by polymerase chain reaction (PCR) for immunoglobulin gene rearrangement**

→ **Workup (PBCL-3)**

[c] Principles of Diagnostic Pathology (PBCL-A).
[g] Double- and triple-hit lymphomas 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.
[h] 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.
[i] 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.
[j] If flow cytometry is initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the flow results.
[k] On formalin-fixed, paraffin-embedded tissue, *MYC* rearrangement is best assessed by *MYC* break apart probe to capture any partner gene.
[l] EBER-ISH is most applicable in endemic BL or immunocompromised clinical settings for either BL or DLBCL.

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
- Evaluation for signs or symptoms of 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 transaminase (AST), alanine transaminase (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
  - Cell count and differential
  - Cytology, including total nucleated cell count and morphologic review of cytospin

ESSENTIAL (continued)

- 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, if clinically indicated
- MRI of the spine, if clinically indicated
- Flow cytometry of cerebrospinal fluid (CSF)[p]
- Flow cytometry, FISH for *MYC* rearrangement, and IHC of bone marrow[q]
- Obtain baseline immunoglobulin panel prior to using rituximab

BL or DLBCL[r] (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	**A single tumor not in the 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.

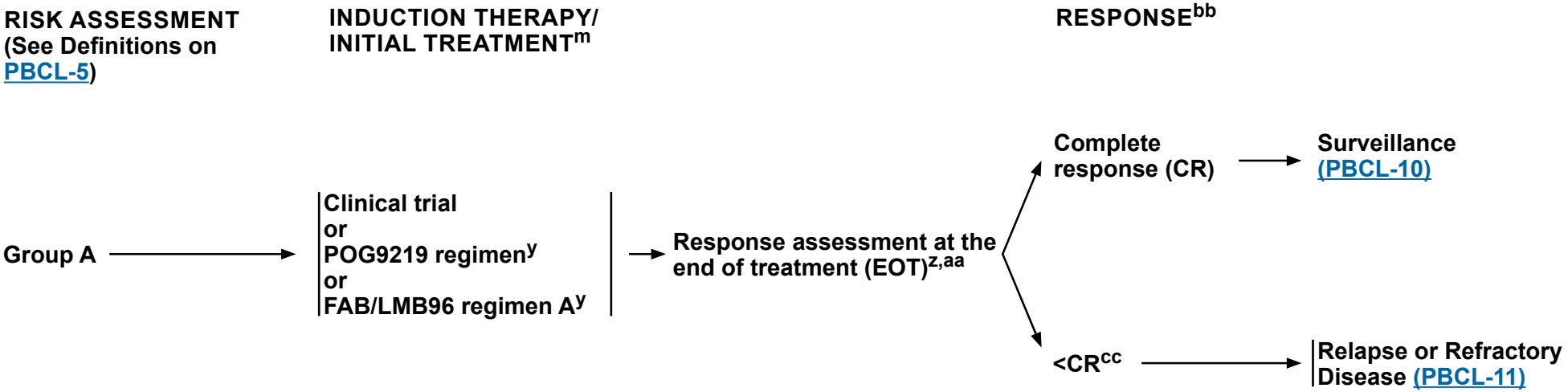
RISK GROUP DEFINITIONS

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

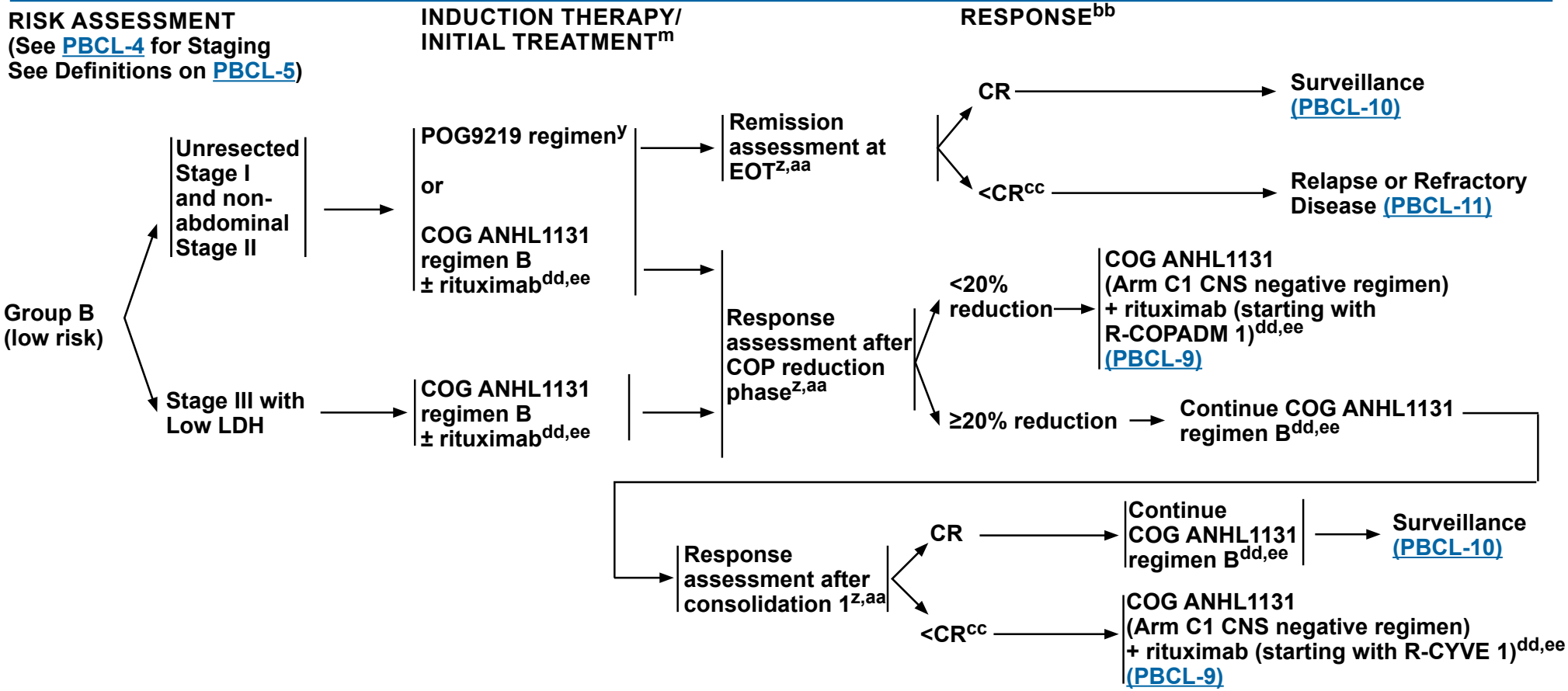
[w] Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. N Engl J Med 2020;382:2207-2219.
[x] Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma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

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



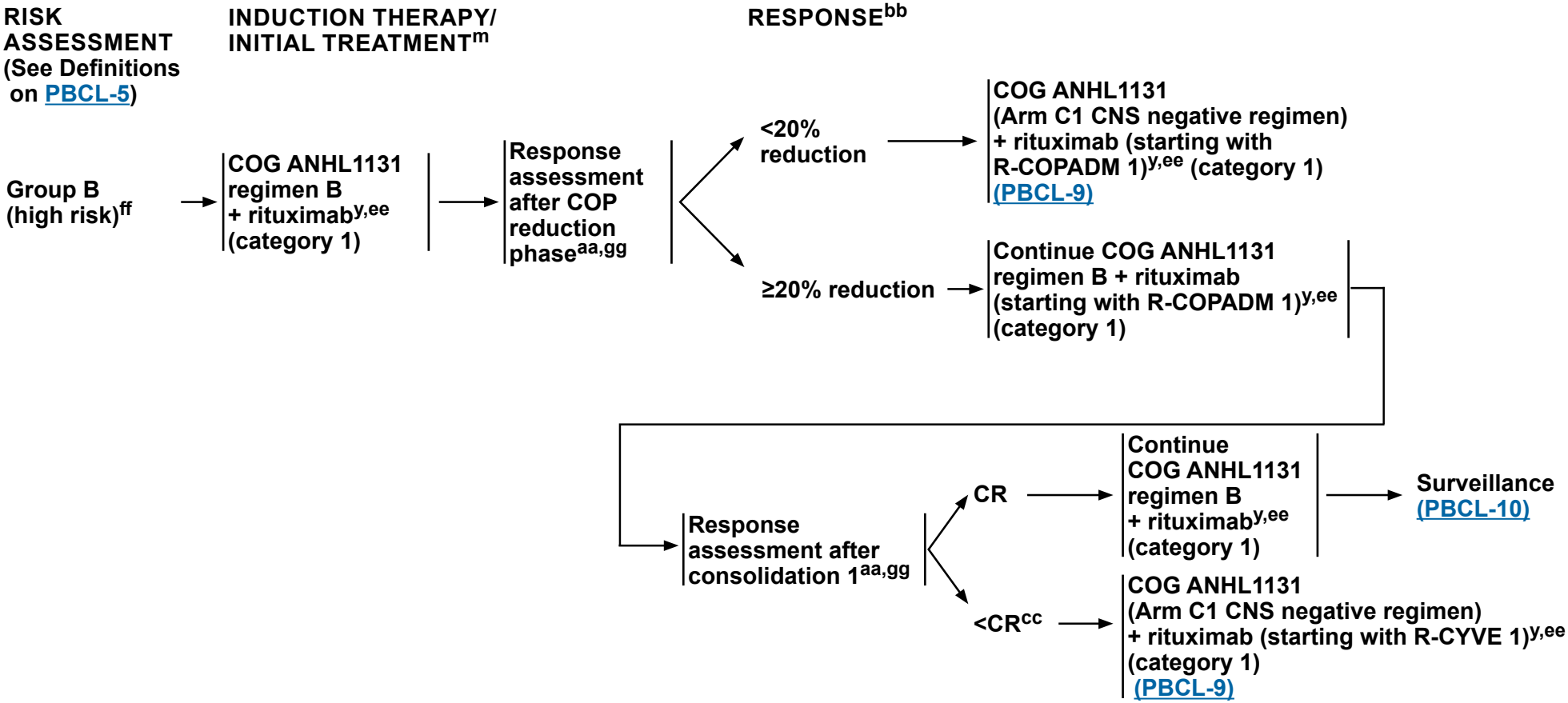
[m] Principles of Supportive Care (PBCL-D).
[y] Principles of Systemic Therapy (PBCL-B).
[z] Reassess sites of original disease with imaging studies as indicated (PBCL-3).
[aa] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging 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 rituximab.

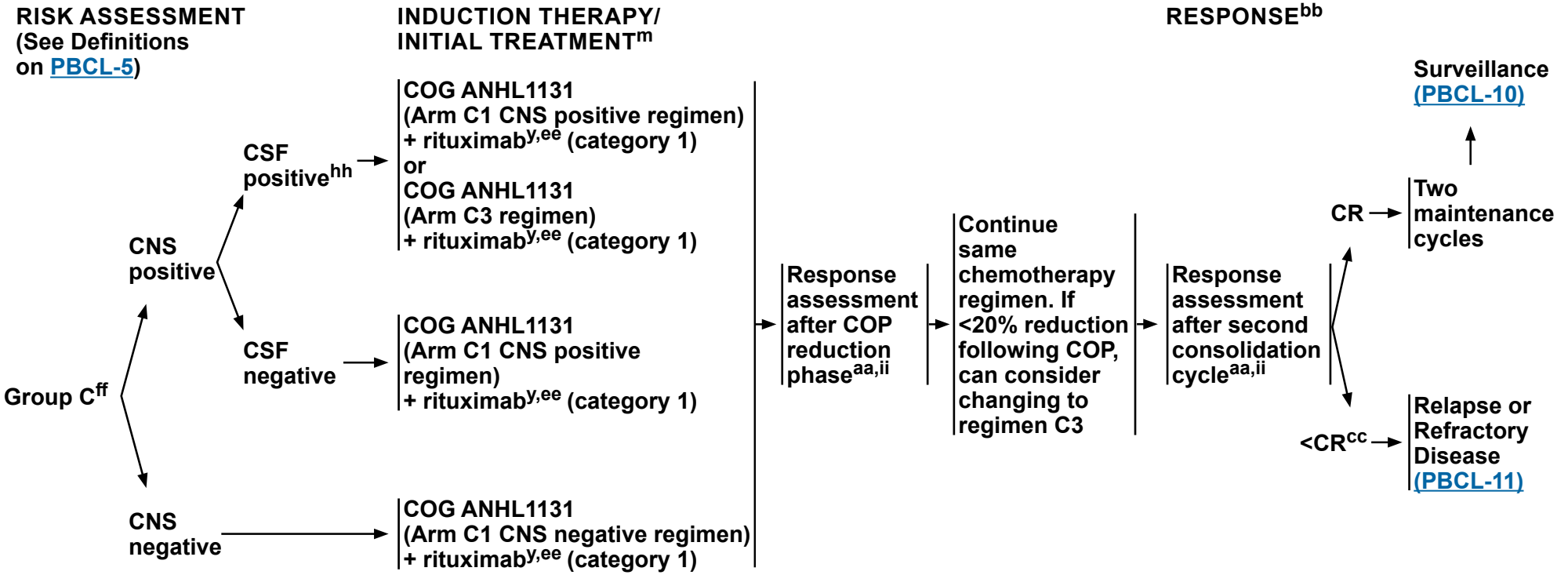
Note: All recommendations are category 2A unless otherwise indicated.



[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 rituximab.
[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 were 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 rituximab.
[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.**

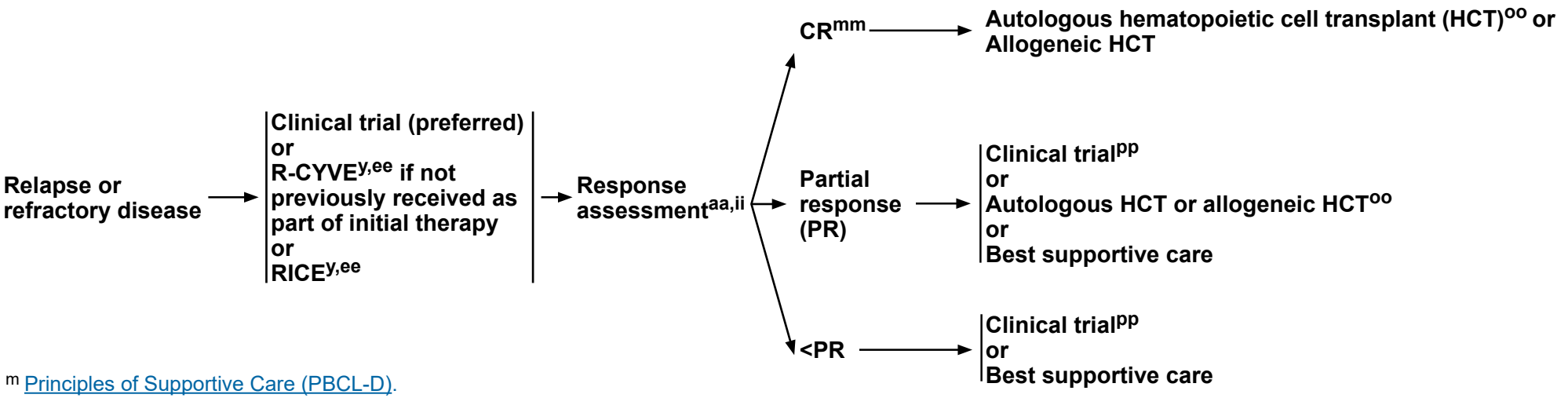
→ **Relapse[kk]** → **Relapse or Refractory Disease (PBCL-11)**

LATE EFFECTS MONITORING

- **Attention to cardiac, gonadal, and neurocognitive function, bone health, and risk of secondary leukemia.**
  (See Children's Oncology Group Survivorship Guidelines)

[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.



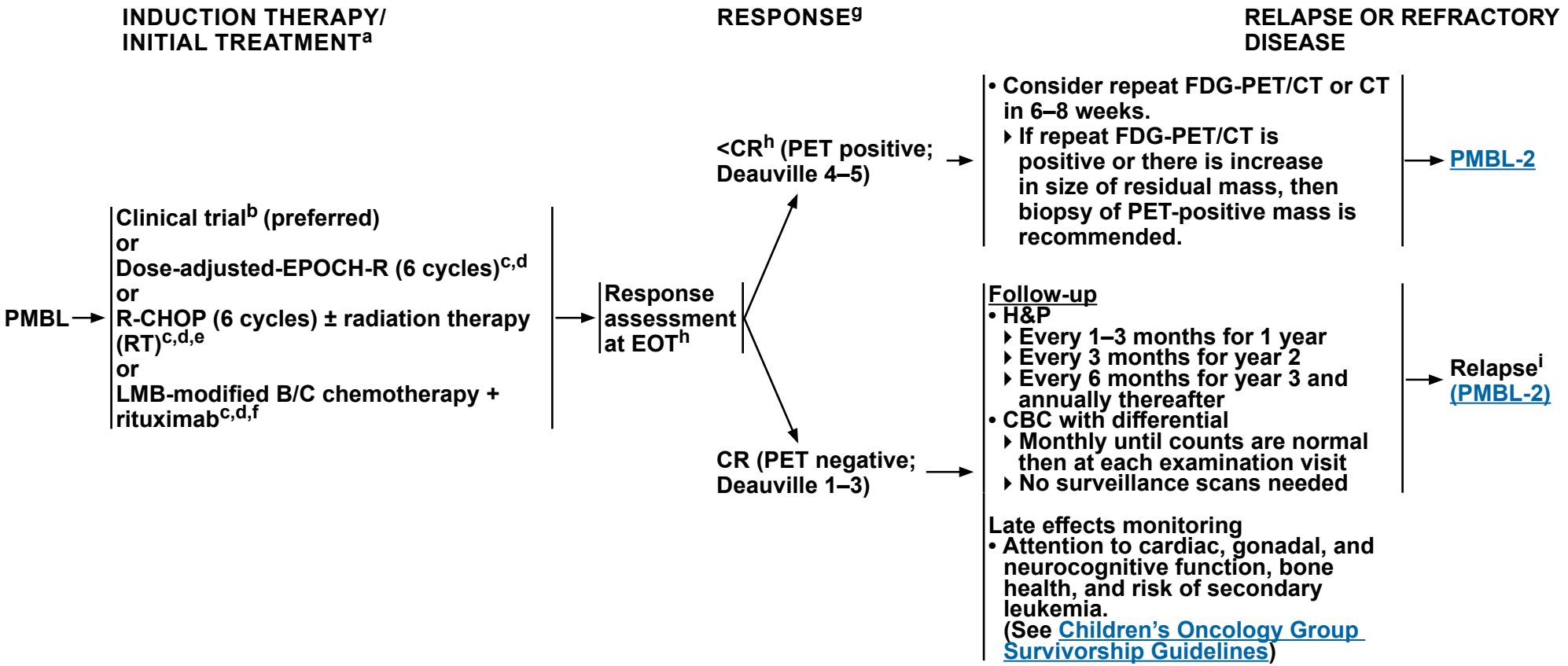
[m] Principles of Supportive Care (PBCL-D).
[y] Principles of Systemic Therapy (PBCL-B).
[aa] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not replace imaging with contrast-enhanced diagnostic-quality CT or MRI. A patient's therapy should 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 rituximab.
[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.

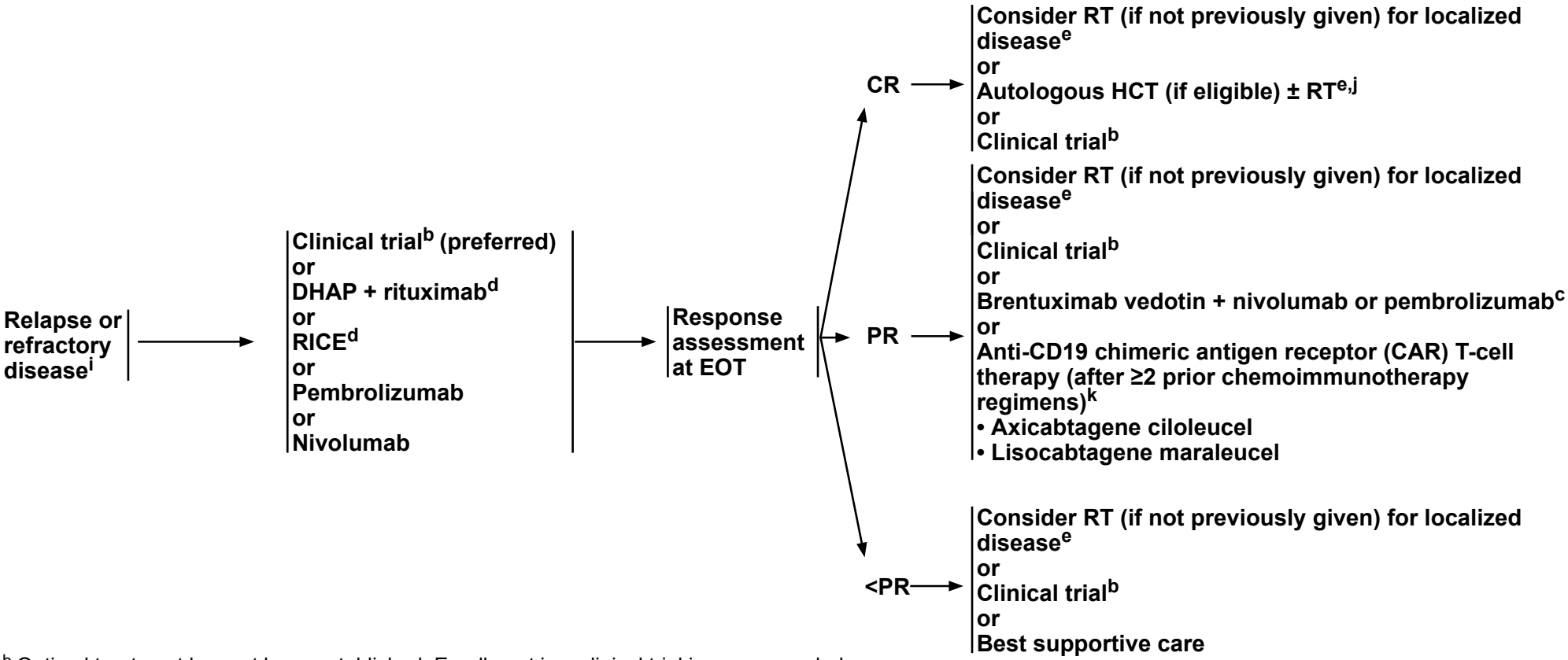
NCCN Guidelines Version 2.2024
Primary Mediastinal Large B-Cell Lymphoma

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).
[d] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[e] There are not enough data on the use of RT in pediatric patients.
[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).
[d] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[e] There are not enough data on the use of RT in pediatric patients.
[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 and/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 regimen 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%–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

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

PRINCIPLES OF SYSTEMIC THERAPY[a]
(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[b] 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[c] 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]
(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[b] 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[d,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[a] 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]
(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[d,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[b] on day 2
IT cytarabine and hydrocortisone	Age-based dosing[b] on day 7

Useful in Certain Circumstances[c] 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]
(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[b] 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[d,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[b] 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]
(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[d,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[b] 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]
(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 to 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[b] 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[c] for Group C

- **Equivalent BFM Regimen**

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

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

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

Preferred Regimens for Relapsed/Refractory Disease

• R-CYVE[6]

Drug	Dose and schedule
Rituximab[e]	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[b] on day 1 at least 6 hours before cytarabine

• RICE (Rituximab, ifosfamide, carboplatin, etoposide)[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[g]
IT methotrexate and cytarabine	Age-based dosing[b]: • 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]
(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**

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

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

PRINCIPLES OF SYSTEMIC THERAPY[a]
(PMBL)

Preferred Regimens for Induction Therapy

- **Dose Adjusted-EPOCH-R (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab)[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[e]	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[e]	375 mg/m²/day on day 1

- **LMB-Modified B/C Chemotherapy + Rituximab[e,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]
(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 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) 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/m²/day)			10	12	14.4	17.3	20.7	24.8
Etoposide (mg/m²/day)			50	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m²/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]
(PMBL)

Preferred Regimens for Induction Therapy

- **LMB-Modified B/C Chemotherapy + Rituximab[e,10] (based on FAB/LMB96)**
  - **Pre-phase COP**
    - ◊ **COP pre-phase is not mandatory but may be required one week prior to commencement of course 1 for patients requiring urgent treatment whilst 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[b] 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[b] 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]
(PMBL)

Preferred 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]
(PMBL)

Preferred 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] For age-based dosing for IT therapy, see PBCL-B 8 of 15.
[c] 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.
[d] Rituximab is optional for patients with low-risk Group B disease. See PBCL-6. 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.
[e] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[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] There are not enough data on the use of RT in pediatric patients.

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

PRINCIPLES OF SYSTEMIC THERAPY
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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.
- 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 infectious disease specialist and monitor for reactivation during and after treatment with rituximab.
- 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.
- 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 the John Cunningham (JC) virus 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.
- 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.

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.
- 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

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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
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
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
HSV	herpes simplex virus
ICC	International Consensus Classification
IHC	immunohistochemistry
IT	intrathecal
JC	John Cunningham
LBCL	large B-cell lymphoma
LDH	lactate dehydrogenase
LMB	Lymphome Malin de Burkitt
MCL	mantle cell lymphoma
MHC	major histocompatibility complex
MR	minor response
MUGA	multigated acquisition
NOS	not otherwise specified
NR	no response
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
SNP	single nucleotide polymorphism
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.

This discussion corresponds to the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas. Last updated: September 3, 2024

Discussion

Table of Contents

Overview

An estimated 9620 children (≤14 years of age) and 5290 adolescents (aged 15–19 years) will be diagnosed with cancer in the United States in 2024, and 1040 children and 550 adolescents will die from the disease.[1] The SEER Program reports that in 2024, an estimated 84,100 adolescents and young adults (AYAs; 15–39 years of age) will be diagnosed with cancer and 8890 AYAs will die from the disease.[2]

Non-Hodgkin lymphomas (NHLs) account for 6% and 7% of all cancers, respectively, in children and adolescents. The 5-year relative survival rates are 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.[3-6] BL and DLBCL account for about 38% and 20% of NHLs, respectively, in children aged 0 to 14 years, whereas 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.[4] 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.[7]

Endemic, sporadic, and immunodeficiency-associated BL are the three clinical variants of BL described in the updated 2022 World Health Organization (WHO) classification (WHO5).[8] The endemic variant is associated with Epstein-Barr virus (EBV) and malaria infections.[9-11] It is prevalent in equatorial Africa, South America, and Papua New Guinea.[12-14] The endemic variant is the most common form of childhood cancer occurring in equatorial Africa, where malaria is highly prevalent and intense.[14] The sporadic variant mainly occurs in North America and Europe and can be associated with EBV infection in about 15% of cases.[9] The endemic variant most commonly presents in the jaw, orbit, mesentery, and central nervous system (CNS), whereas 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 primary immune deficiency and dysregulation (ID/D), and in some patients following hematopoietic cell transplant (HCT). Up to 70% of these patients test positive for EBV. 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.[13,15,16]

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Aggressive Mature B-Cell Lymphomas provide recommendations for the diagnosis and management of pediatric patients with PMBL and sporadic variants of BL and DLBCL. 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. These guidelines do not address the management of endemic or immunodeficiency-associated BL or DLBCL. In addition, rare clinical scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines.

The NCCN Pediatric Aggressive Mature B-Cell Lymphoma 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. NCCN Guidelines® for Pediatric Aggressive Mature B-Cell Lymphomas are intended to apply to all pediatric patients and AYA patients with good organ function treated in a pediatric oncology setting. AYA patients treated in an adult oncology setting and those without good

organ function should be treated as per the adult NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org).

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, and pediatric primary mediastinal large B-cell lymphoma. 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.

Clinical Presentation

Patients with DLBCL and BL 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] 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] 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.

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.[7,21,22] 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), and those with abdominal disease may present with abdominal distention and nausea/vomiting.[7,22]

Diagnosis

Biopsy

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.[23]

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.[24]

BL, DLBCL, and PMBL have distinctive morphologic and pathologic characteristics. 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.[7] 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.

DLBCL is characterized by large cells with variable nuclear contours, condensed to vesicular chromatin, single or multiple nucleoli, and scant to moderately abundant cytoplasm.[7] Cytoplasmic vacuoles are not typically present. 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” appearance is generally not prominent.

PMBL has variable morphologic features, and typical findings include diffuse sheets of atypical lymphocytes in a background of compartmentalizing fibrosis.[7,21,22,25] The atypical lymphocytes are medium to large in size, with round to lobulated or irregular nuclei, dispersed chromatin, prominent nucleoli, and abundant pale to clear cytoplasm. Occasionally, atypical lymphocytes are more pleomorphic and may even resemble Reed-Sternberg cells.[7,22]

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.

BL and DLBCL express surface immunoglobulin (sIg) and B-cell antigens. BL is CD10+, CD20+, BCL2-, BCL6+, and Ki-67+ (≥95%), whereas DLBCL is CD20+ with variable expression of CD10, BCL2, BCL6, MUM1, and Ki-67. BL and DLBCL are both typically negative for terminal deoxynucleotidyl transferase (TdT), a marker of cellular immaturity, and negative for CD3, a T-cell marker. Pediatric DLBCLs are predominantly of

germinal center B-cell (GCB) subtype (CD10+; or BCL6+ and MUM1-), and the t(14;18) translocation that results in the overexpression of BCL2 is also absent in pediatric DLBCL.[26,27]

BLs generally exhibit 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].[28-31] Aggressive mature B-cell lymphomas without *MYC* rearrangement that are morphologically similar to BL with a more complex karyotype than BL have bee described.[32,33] These have been renamed as high-grade B-cell lymphomas (HGBL) with 11q aberration in the updated 2022 WHO Classification (WHO5).[8] The epidemiology and natural history of this entity are yet to be defined, but pediatric cases have been described.[34-36] The diagnosis of HGBL with 11q aberration may be pursued in the absence of an *MYC* rearrangement.[8,37-39] Optimum management is not defined although it is most often treated like typical sporadic BL.

DLBCL has a variable karyotype and may include rearrangements of *MYC, BCL6, BCL2*, and/or other *IGH* rearrangements.[40-43] HGBL with *MYC* and *BCL2 or BCL6* rearrangements are not well described in the pediatric population, but may be more common in AYA patients.[44-49] The treatment recommendations included in these guidelines also apply to HGBL with *MYC* and *BCL2 or BCL6* rearrangements. The diagnosis of LBCL with *IRF4* rearrangement may be pursued in the absence of *MYC* or *BCL2* rearrangements and by the strong expression of IRF4/MUM1.[50-52] Optimum management is not defined though it is most often treated like typical DLBCL.

Fluorescence in situ hybridization (FISH) using a break-apart probe is more reliable for the detection of t(8;14) and its variants, and is often utilized to detect any partner gene involved in *MYC* rearrangement.[53] Karyotype or FISH for *MYC* rearrangement is essential for diagnosis of BL and DLBCL whereas FISH for *BCL2* and *BCL6* rearrangements may be considered for AYA patients.[49] Cytogenetic analysis for detection of t(8;14) or variants [t(2;8) or t(8;22)] may be useful under certain circumstances. 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.

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.[22] 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.[54-57] Genetic alterations involving the major histocompatibility complex (MHC) class II transactivator (*CIITA*) gene at chromosome 16p are highly recurrent in PMBL.[58,59] Gains or amplifications in chromosome 9p24 (including *JAK2, PD1*, *and PD2*) and chromosome 2p16 (including *REL* and *BCL11A*) have also been detected in PMBL.[60-65]

Epstein-Barr encoding region in situ hybridization (EBER-ISH) may be useful to demonstrate EBV association, if indicated by a history or suspicion of immunodeficiency. EBV expression is predominantly seen in the endemic form of BL. However, EBV-positive DLBCL and BL can be

seen in pediatric patients without recognized primary ID/D, 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 similar to EBV-positive endemic BL.[66-69] EBER-ISH is most applicable for endemic variant of BL or in immunocompromised clinical settings for either BL or DLBCL. 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 BL or DLBCL or PMBL (as outlined on PBCL-3) includes history and physical examination, laboratory analysis, bilateral bone marrow aspirate and biopsy, lumbar puncture, and imaging. Baseline immunoglobulin panel should be obtained prior to using rituximab.

Imaging should include cross-sectional scans of the neck, chest, abdomen, and pelvis. Fluorodeoxyglucose ((FDG))-PET/CT or (FDG)-PET/MRI is recommended if available.[70] 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. Information regarding bone marrow and CNS involvement and distant spread is important for staging (see *Staging and Risk Group Classification*, below). In addition, a baseline echocardiogram (ECHO) or multigated acquisition (MUGA) scan, and electrocardiogram (ECG) is recommended.

Pediatric and AYA patients treated with cytotoxic 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.[71,72]

Response Criteria

The Panel recommends use of the International Pediatric NHL Response Criteria.[73] 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.[74] 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 a residual lesion is (FDG)-PET negative (Deauville 1–3), biopsy is not necessary because of the high negative predictive value of (FDG)-PET.[75-79] 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.[80]

False-positive findings may include inflammation, necrotic tumor, reactive lymphadenitis, brown fat, thymic rebound, and secondary malignancy.

Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma

Pediatric BL and DLBCL 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. All recommendations are classified as category 2A if not otherwise noted.

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.[81] 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.[82] The NCCN Pediatric Aggressive Mature B-Cell Lymphoma panel supports use of the revised IPNHLSS.

Bone marrow involvement is defined by morphologic evidence of lymphoma cells in a bone marrow aspirate.[82] Patients with bone marrow involvement have stage IV disease. CNS involvement is found in approximately 9% and 3% of pediatric patients with BL and DLBCL, respectively.[83,84] Patients with 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 pediatric patients with BL and DLBCL are based on the risk group classification used in the French-American-British/Lymphoma Malignancy B group FAB/LMB96 trial[85,86]:

- 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 DLBCL (based on many clinical trials, including those discussed below) and is highly effective for most patients. For example, in the FAB/LMB96 study (see below), only 2.5% of patients had refractory disease and 7% experienced disease relapse after CR to initial therapy.[87] 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 Children's Cancer Group, 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 NHL, 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.[86]

Group A

POG 9219 regimen or the FAB/LMB96 regimen A are included as preferred regimens if they are not enrolled in a clinical trial.[88,89]

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.[88] Chemotherapy consisted of induction/-consolidation chemotherapy (vincristine, doxorubicin, cyclophosphamide, and prednisone) 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 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.[89] All patients with resected stage I or completely resected abdominal stage II disease received two courses of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin) 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.[90] 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.

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 less than 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 greater than or equal to 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).

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.[86,91]

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%).[91] The COG ANHL1131 regimen B used in the Inter-B-NHL-Ritux-2010 study[86] is based on the chemotherapy regimen used for Group B patients in the FAB/LMB96 trial.[92] 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.[92] 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.[86] 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.[86] 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 less than 500 U/L received five cycles of therapy, including a cytoreductive pre-phase.[90] Failure-free survival 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.[93] 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.[86] Other studies have also demonstrated high cure rates with the use of rituximab in patients with Group C disease.[94-96] 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% .[95]. 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.[97]

The treatment 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.[90,93]

Surveillance

As few as 5% of patients treated for BL or DLBCL experience a relapse and the majority of these relapses occur in the first 6 months after completion of treatment, with fewer than 10% of relapses occurring after 15 months.[98,99] 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.[100]

In addition, patients should be monitored for late effects of treatment as per the COG Survivorship Guidelines. Particular attention should be paid to cardiac, gonadal, and neurocognitive function; bone health; and the risk for secondary leukemia.

Treatment for Relapsed or Refractory Disease

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. Clinical trial is the preferred option for patients with relapsed/refractory disease.

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).

Treatment of relapsed disease can lead to sustained complete second remissions in some patients.[98,99,101-103] CYVE and ICE (ifosfamide, carboplatin, and etoposide) have been evaluated for relapsed/refractory disease in the LMB89, LMB96, and LMB2001 studies resulting in a 30% 5-year survival rate with manageable toxicity in patients with relapsed disease.[98] 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.[98,99] The addition of rituximab to chemotherapy in the relapsed/refractory setting has also been evaluated in other small studies.[104-106] 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.[104] A multicenter case series in the United Kingdom also demonstrated an association between rituximab and survival in the relapse/refractory setting.[105] In addition, a Japanese study reported a 73% response rate for 223 patients treated with R-ICE in the relapsed/refractory setting.[106]

In another report that analyzed the outcomes of 639 children and adolescents with relapsed/refractory NHL, the estimated 8-year probability of OS was 34 ± 2% for the entire study population with significant differences between the NHL subtypes.[107] 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. The survival rates were in the range of 50% for patients who underwent HCT compared to <10% in patients who did not receive HCT.

In the multicenter case series in the United Kingdom mentioned above, 9 of 16 patients who received HCT survived for >6 years; no patient who did not receive HCT survived.[105] In another case series, OS was better for patients who received HCT compared with patients who did not (P < .01).[102] Other studies have also shown comparable survival rates for patients who undergo HCT in this setting.[101,103,108,109] 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.[110]

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).

R-CYVE (if not previously received as part of initial therapy) or R-ICE are included as options for second-line therapy.[98,99,104,106] Most patients with relapsed/refractory disease achieving a CR to second-line therapy should receive an autologous or allogeneic HCT. Patients with a PR to second-line therapy can also receive an autologous or allogeneic HCT. 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/refractory DLBCL. Best supportive care is another option.

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.[108,111] Donor options

include human leukocyte antigen (HLA)-matched related donor; HLA-matched unrelated donor, cord blood or a haploidentical donor.[112,113]

CD19-directed chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies have demonstrated significant efficacy for the treatment of relapsed/refractory DLBCL in adult patients after ≥2 prior systemic therapy regimens. Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel are the 3 anti-CD19 CAR T-cell therapies that are approved for relapsed/refractory DLBCL in adults.[114] Tisagenlecleucel is also approved for relapsed/refractory ALL in pediatric and young adult patients.[115] Epcoritamab and glofitamab are the two bispecific antibodies that are approved for the treatment of relapsed/refractory DLBCL in adults.[116,117] The feasibility of CD19-directed CAR T-cell therapy in pediatric patients with relapsed/refractory BL has been demonstrated only in a small cohort of patients.[118] Several 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.[119]

CAR T-cell therapy is currently not recommended in the guidelines for the treatment of patients with relapsed/refractory BL or DLBCL.

Primary Mediastinal Large B-Cell Lymphoma

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 DLBCL (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] ± 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.[57]

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).[100]

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. Particular attention should be paid to cardiac, gonadal, and neurocognitive function; bone health; and the risk for secondary leukemia.

Treatment for Relapsed/Refractory Disease

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

There are very limited data for the outcome of patients with relapsed/refractory PMBL in pediatric patients.[132] Enrollment in clinical trials is recommended for all patients. R-ICE (rituximab, ifosfamide, carboplatin, and etoposide), R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), pembrolizumab, and nivolumab are included as options for second-line therapy for relapsed/refractory PMBL.

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

Targeted therapies such as programmed cell death inhibitors (pembrolizumab and nivolumab) and anti-CD30 antibody drug conjugate (brentuximab vedotin, single agent or in combination with nivolumab) have demonstrated activity in relapsed/refractory PMBL.[133-137] Brentuximab vedotin in combination with nivolumab or pembrolizumab are included as options for patients with a PR to second-line therapy based.[135,138] 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/refractory PMBL (ZUMA-1 [axicabtagene ciloleucel] and TRANSCEND-NHL-001 trials [lisocabtagene maraleucel]).[114]

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, although there are not enough data on the use of RT in pediatric patients. RT alone could be considered an option for local recurrence with disease restricted to the mediastinum.[129]

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.[139-142] 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 suffering and endangered and the increased financial burden due to medical costs and disruptions in employment.[140,143-145] 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.[146-150]

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.[151,152] Chemotherapy should be started as soon as possible to preserve organ function and reduce complications for these patients.

Many of the chemotherapy regimens are associated with serious infections, viral reactivation, profound neutropenia, severe mucosal toxicity and renal toxicity.[153-157] 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 (which are also briefly discussed below).

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.[158] 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.[159-161] 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.[159,162] Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to an increased risk of methemoglobinemia or hemolysis.[163] 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.

Rituximab is associated with a risk of HBV reactivation and hypogammaglobulinemia. Screening for HBV infection should be done prior to initiating treatment rituximab. Monitoring with HBV polymerase chain reaction (PCR) and antiviral prophylaxis are recommended for patients with a HBsAg-positive test, during and after treatment with

rituximab.[156] Intravenous immunoglobulin G replacement therapy should be considered in patients with recurrent infections.[155]

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.[164]

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