National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pediatric Aggressive Mature B-Cell Lymphomas

Version 2.2021 — June 7, 2021

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NCCN Guidelines Version 2.2021
Pediatric Aggressive Mature B-Cell Lymphomas

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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NCCN Guidelines Version 2.2021
Pediatric Aggressive Mature B-Cell Lymphomas

Updates to Version 2.2021 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 1.2021 include:

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

Updates to Version 1.2021 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 2.2020 include:

PBCL-1
- **Diagnosis: Under Biopsy;**
  - **Sub-bullet 2 added: 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).**
  - **Sub-bullet 3 added: 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.**
  - **Sub-bullet 4 added: Cores must be of sufficient size and number to allow for evaluation of morphology, tumor architecture, and all necessary ancillary studies (immunohistochemistry [IHC], flow cytometry, karyotype, and FISH for major translocations, as applicable).**
  - **Sub-bullet removed: 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. If core biopsies are to be used for diagnosis, the cores must be of sufficient size and number to allow for evaluation of morphology, tumor architecture, and all necessary ancillary studies (immunohistochemistry [IHC], flow cytometry, karyotype, and FISH for major translocations as applicable)**

PBCL-3
- **Workup: Essential**
  - **Bullet 3 revised: Evaluation for signs or symptoms of ureteral *or bowel* obstruction.**
  - **Imaging**
    - ◊ **Bullet removed: CT chest/abdomen/pelvis contrast or CT chest/MRI abdomen and pelvis.**
    - ◊ **Bullet 1 added: Cross-sectional scans of the neck, chest, abdomen and pelvis.**
      - – **Sub-bullet 1 new: Neck CT with IV contrast or MRI with and without contrast (moved from Useful Under Certain Circumstances and edited)**
      - – **Sub-bullet 2 new: Chest CT with IV contrast**
      - – **Sub-bullet 3 new: Abdomen and pelvis CT with oral and IV contrast or MRI with and without contrast**
  - **Echocardiogram (ECHO) or multigated acquisition (MUGA) scan *and ECG***
- **Workup: Useful under Certain Circumstances**
  - **Bullet removed: MRI or CT of the neck, if evidence of neck disease**

Continued

Updates to Version 1.2021 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 2.2020 include:

PBCL-5
- Footnote w revised: Reassess sites of original disease with radiologic studies as indicated ~~(abdominal ultrasound, chest/ abdominal/pelvic CT with intravenous and oral contrast, and/or MRI of the head, neck, abdomen, and/or pelvis~~). (See PBCL-3) (Also PBCL-6).

PBCL-6
- Footnote cc revised and added biosimilar statement: ...population is deemed appropriate. *An FDA-approved biosimilar is an appropriate substitute for rituximab*.

PBCL-7
- Category 1 added after each mention of rituximab. (Also on PBCL-8)
- Footnote ff added: 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. An FDA-approved biosimilar is an appropriate substitute for rituximab. (Also PBCL-8)

PBCL-7 (continued)
- Footnote gg revised: Reassess sites of original disease with radiologic studies as indicated [~~abdominal ultrasound, chest/ abdominal/pelvic CT with intravenous and oral contrast, and/or MRI of the head, neck, abdomen, and/or pelvis~~] (See PCBL-3). Bone marrow and CSF studies should also be performed if bone marrow or CSF were initially involved. (Also on PBCL-8, PBCL-10)

PBCL-9
- Disease Surveillance/Follow-up
  - Bullet 4 revised: Routine surveillance imaging is not recommended. *Consider only if clinical suspicion of relapse:* FDG-PET/CT or FDG-PET/MRI or *CT* chest *with IV contrast and CT* abdominal/pelvis with *IV and oral* contrast.

PBCL-A
- Diagnosis-Morphology
  - Bullet 1 revised: Touch preparations of fresh lesional tissue *should be* ~~are~~ encouraged ~~scenarios where rapid preliminary diagnosis is indicated~~ *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*).
  - Sub-bullet 1 revised: "...and have round nuclei, relatively coarse chromatin *that is finely dispersed* with multiple small nucleoli, and ~~scant~~ *moderate amounts of densely basophilic* cytoplasm..."
  - Sub-bullet 2 removed: Cytoplasmic vacuoles are not typically present.
- Tissue section of BL and DLBCL are also distinctive.
  - Bullet 1 revised: "...starry sky" appearance indicative of high cell turnover. *Mitoses and apoptotic bodies are often numerous*. While a morphologic spectrum is..."
  - Bullet 2 revised: "...nuclear pleomorphism and ~~scant to~~ *more* abundant..."
- Diagnosis - Immunophenotyping
  - Bullet 1 revised: "...express *TdT and do not express CD34* ~~markers associated with cell immaturity (TdT, CD34).~~"
  - Bullet 2 revised: "...by surface *or cytoplasmic* immunoglobulin..."
  - Bullet 4 new: Strong expression of MUM1/IRF4, often with BCL6 and CD10 positivity, should raise consideration of the diagnosis of large B-cell lymphoma (LBCL) with IRF4 rearrangement.

Continued

Updates to Version 1.2021 of the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas from Version 2.2020 include:

PBCL-B (1 of 9)
- **Preferred Treatment Regimens for Group A**
  - **Doxorubicin: Under dose and schedule added: May administer dexrazoxane. Dexrazoxane dosing as 10:1 ratio of dexrazoxane:doxorubicin. (Also for PBCL-B, 2 of 9, 4 of 9, and 6 of 9).**
  - **~~Triple IT~~ revised to IT methotrexate, cytarabine, hydrocortisone..**

PBCL-B (2 of 9)
- **Table 2**
  - **Doxorubicin: Under dose and schedule removed, "as a one-hour infusion." (Also on PBCL-B, 4 of 9, PBCL-B, 6 of 9, PBCL-7 of 9)**

**Footnote c revised: 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. An FDA-approved biosimilar is an appropriate substitute for rituximab. (Also PBCL-3 of 9, 4 of 9, 5 of 9)*

PBCL-B (7 of 9)
- **Preferred Treatment Regimens for Relapsed/Refractory Disease**
  - **New row added: IT methotrexate and cytarabine. Added dose and schedule: Age-based dosing.**
    - **◊ 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.**
- **Footnote f new: An FDA-approved biosimilar is an appropriate substitute for rituximab.**

PBCL-B (8 of 9)
- **Table heading revised: Age-Based Dosing for IT Methotrexate, Cytarabine, Hydrocortisone for Therapies Other than RICE.**
- **New table added*: Age-Based Dosing for IT Methotrexate, Cytarabine for RICE.***

PBCL-B (9 of 9)
- **References**
  - **Reference 6 updated: Minard-Colin V, Auperin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in Children. N Engl J Med 2020;382:2207-2219.**

PBCL-D (2 of 5) Principles of Supportive Care
- **Tumor Lysis Syndrome**
  - **Sub-bullet 2, 6th bullet revised: ~~Allopurinol and rasburicase are generally not given concurrently.~~ For ongoing control of TLS, consider restarting allopurinol after rasburicase therapy is completed.**

PBCL-D (3 of 5)
- **Risk of Infection**
  - **Bullet 2 revised: *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 patient is positive for hepatitis B, consult with infectious disease specialist and monitor for reactivation during and after treatment with rituximab.***
  - **Bullet 3 revised: ~~There may be a risk of hepatitis B reactivation during treatment with rituximab~~. *Antiviral prophylaxis is recommended.***

PEDIATRIC AGGRESSIVE MATURE B-CELL LYMPHOMA[a] DIAGNOSIS[e]

Pediatric Burkitt lymphoma and Pediatric diffuse large B-cell lymphoma (DLBCL) including adolescent and young adult (AYA) patients treated in the pediatric oncology setting[b,c,d]

→

- **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 evaluation of morphology, tumor architecture, and all necessary ancillary studies (immunohistochemistry [IHC], flow cytometry, karyotype, and 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[f]**
  - **Morphologic and immunohistochemistry review as clinically indicated.**
  - **Touch preparation for cytologic examination is recommended.**

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

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

[b]Recommendations for the management of primary mediastinal B-cell lymphoma (PMBL) are not included in these guidelines. For PMBL first-line therapy recommendations, see the adult NCCN Guidelines for B-Cell Lymphomas (BCEL-B, page 1 of 3).

[c]The Pediatric Aggressive Mature B-Cell Lymphomas panel considers “pediatric” to include any patient aged 18 years and younger, and AYA patients older than 18 years of age, 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 (defined by the National Cancer Institute as <39 years of age) 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.

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

[e]Definitive diagnosis may not be feasible before beginning treatment. If the patient is very sick, morphology and flow cytometry are the minimum methodologies from which to yield diagnostic information to begin treatment. Malignant fluid cytology and flow cytometry may suffice.

[f]See Principles of Pathology (PBCL-A).

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

ADDITIONAL DIAGNOSTIC TESTING[f]

ESSENTIAL

- **Adequate immunophenotyping to establish diagnosis[g,h,i]**
  - **Immunohistochemistry panel: Ki-67, BCL-2, BCL-6, CD3, CD10, CD20, MUM1**
  - **Flow cytometry: Surface kappa/lambda, CD3, CD5, CD10, CD19, CD20, CD45**
  - **Fluorescence in situ hybridization (FISH): C-MYC rearrangement[j]**

USEFUL UNDER CERTAIN CIRCUMSTANCES

- **Karyotype: t(8;14) or variants t(2;8) or t(8;22) and to identify additional chromosomal abnormalities**
- **FISH for BCL-2 and BCL-6 rearrangements[k]**
- **FISH or single nucleotide polymorphism (SNP) array for 11q aberration**
- **EBER-ISH[l]**
- **C-MYC immunohistochemistry**
- **TdT immunohistochemistry or flow cytometry**
- **Clonality testing by polymerase chain reaction (PCR) for immunoglobulin gene rearrangement**

→ **Workup (See PBCL-3)**

[f] See Principles of Pathology (PBCL-A).
[g] Typical immunophenotype of Burkitt lymphoma: 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 C-MYC, BCL6, BCL2, and/or other IgH rearrangements.
[h] 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.
[i] If flow cytometry is initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the flow results.
[j] On formalin-fixed, paraffin-embedded tissue, MYC rearrangement is best assessed by MYC break apart probe to capture any partner gene.
[k] Double- and triple-hit lymphomas are currently not well described or studied in the pediatric population but FISH for BCL-2 and BCL-6 rearrangements may be considered in the AYA population.
[l] EBER-ISH is most applicable in endemic Burkitt lymphoma or immunocompromised clinical settings for either Burkitt lymphoma or DLBCL.

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WORKUP

ESSENTIAL

- History, including personal and family history of immunodeficiency
- Physical exam, 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
  - 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 G6PD testing for male patients[m]
  - Pregnancy test for females of childbearing age
- Bilateral bone marrow aspirate and biopsy
- Lumbar puncture
  - Cell count & 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 ECG
- Fertility counseling recommended; fertility preservation 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)[o]
- Flow cytometry, FISH for MYC rearrangement, and immunohistochemistry of bone marrow[p]

See Risk Group Definitions (PBCL-4)

[m] See 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] Flow cytometry of CSF samples is not routinely recommended, but may be useful at the pathologist's discretion.
[p] For low-level or morphologically indeterminate involvement.

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RISK GROUP DEFINITIONS[q]

Group Classification[r]		Initial Therapy
Group A	**Completely resected stage I or Completely resected abdominal stage II**	**See PBCL-5**
Group B	**All cases not eligible for Group A or Group C (unresected stage I and non-abdominal stage II, stage III, and non-CNS stage IV with <25% bone marrow involvement)**	**See PBCL-6 and PBCL-7**
Group C	**Any CNS involvement[s] and/or Bone marrow involvement (≥25% lymphoma cells)**	**See PBCL-8**

[q]Adapted with permission from 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.

[r]For Staging, see ST-1.
[s]The central nervous system (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

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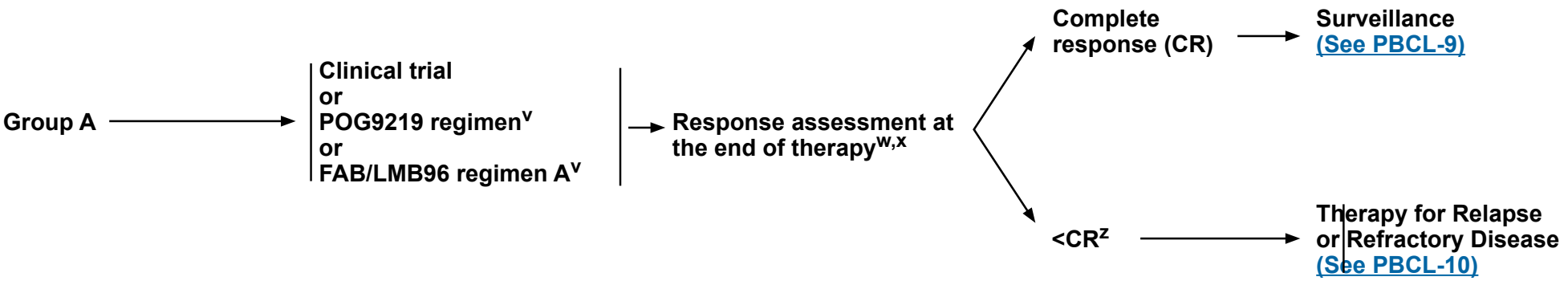
RISK ASSESSMENT (See Definitions on PBCL-4)

INDUCTION THERAPY/ INITIAL TREATMENT[m,t,u]

RESPONSE[y]



[m] See Principles of Supportive Care (PBCL-D).
[t] The Berlin-Frankfurt-Münster (BFM) group has equivalent regimens that are not standardly used in North America.
[u] Radiation therapy rarely has a role in pediatric aggressive mature B-cell lymphomas due to the rapid lysis of tumor to chemotherapy and the avoidance of long-term side effects in children.
[v] See Principles of Systemic Therapy (PBCL-B).
[w] Reassess sites of original disease with radiologic studies as indicated (See PBCL-3).
[x] 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; See 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.
[y] See Response Criteria (PBCL-C).
[z] Residual mass should be biopsied prior to categorizing it as residual disease.

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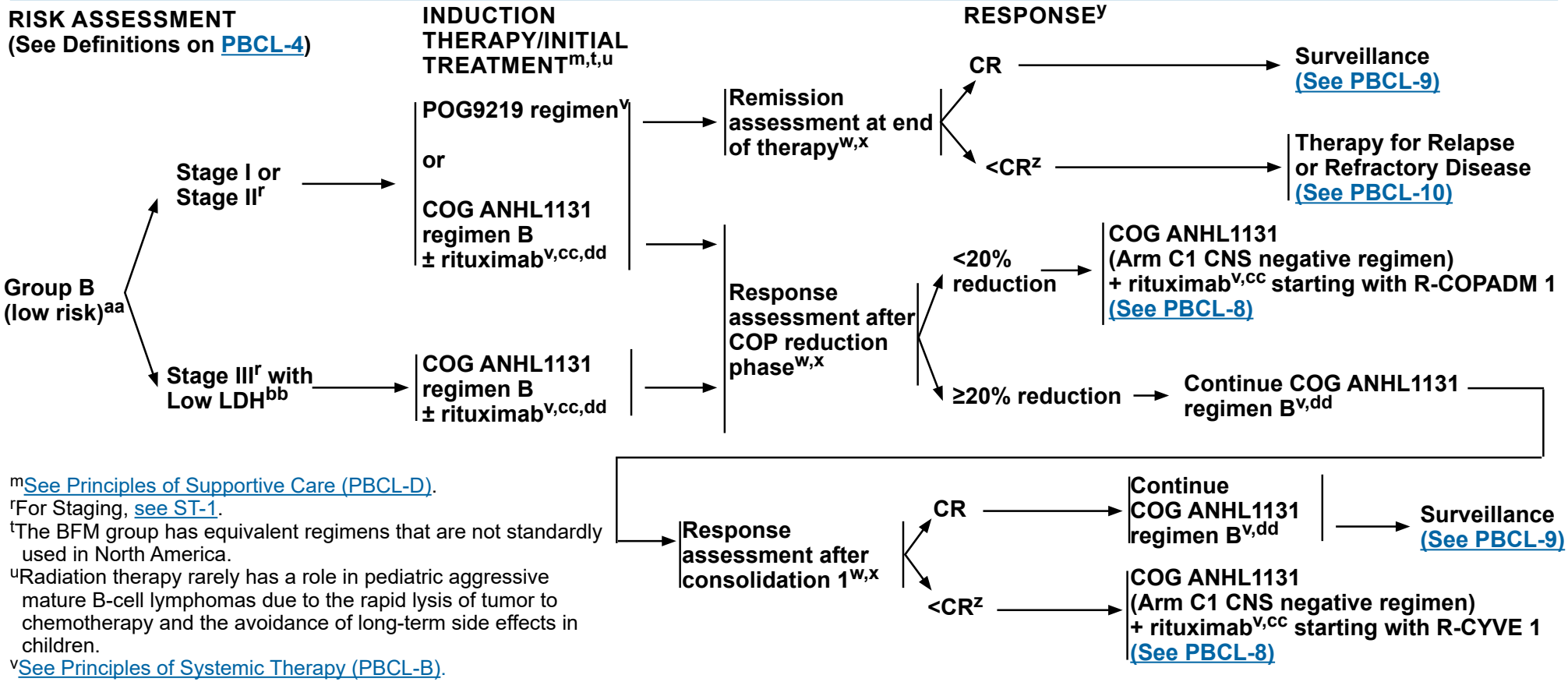

[m] See Principles of Supportive Care (PBCL-D).
[r] For Staging, see ST-1.
[t] The BFM group has equivalent regimens that are not standardly used in North America.
[u] Radiation therapy rarely has a role in pediatric aggressive mature B-cell lymphomas due to the rapid lysis of tumor to chemotherapy and the avoidance of long-term side effects in children.
[v] See Principles of Systemic Therapy (PBCL-B).
[w] Reassess sites of original disease with radiologic studies as indicated (See PBCL-3).
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[y] See Response Criteria (PBCL-C).
[z] Residual mass should be biopsied prior to categorizing it as residual disease.
[aa] Any Stage III patient with LDH ≤2 times the upper limit of normal (ULN), and all Stage I or II patients who are not fully resected Group A.
[bb] High LDH: >2 times the ULN. Low LDH: ≤2 times the ULN.
[cc] 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 high-risk patients, inclusion of rituximab in treatment of this patient population is deemed appropriate. An FDA-approved biosimilar is an appropriate substitute for rituximab.
[dd] If Rituximab is included in induction/initial treatment, it should be continued throughout therapy. See Principles of Systemic Therapy (PBCL-B).

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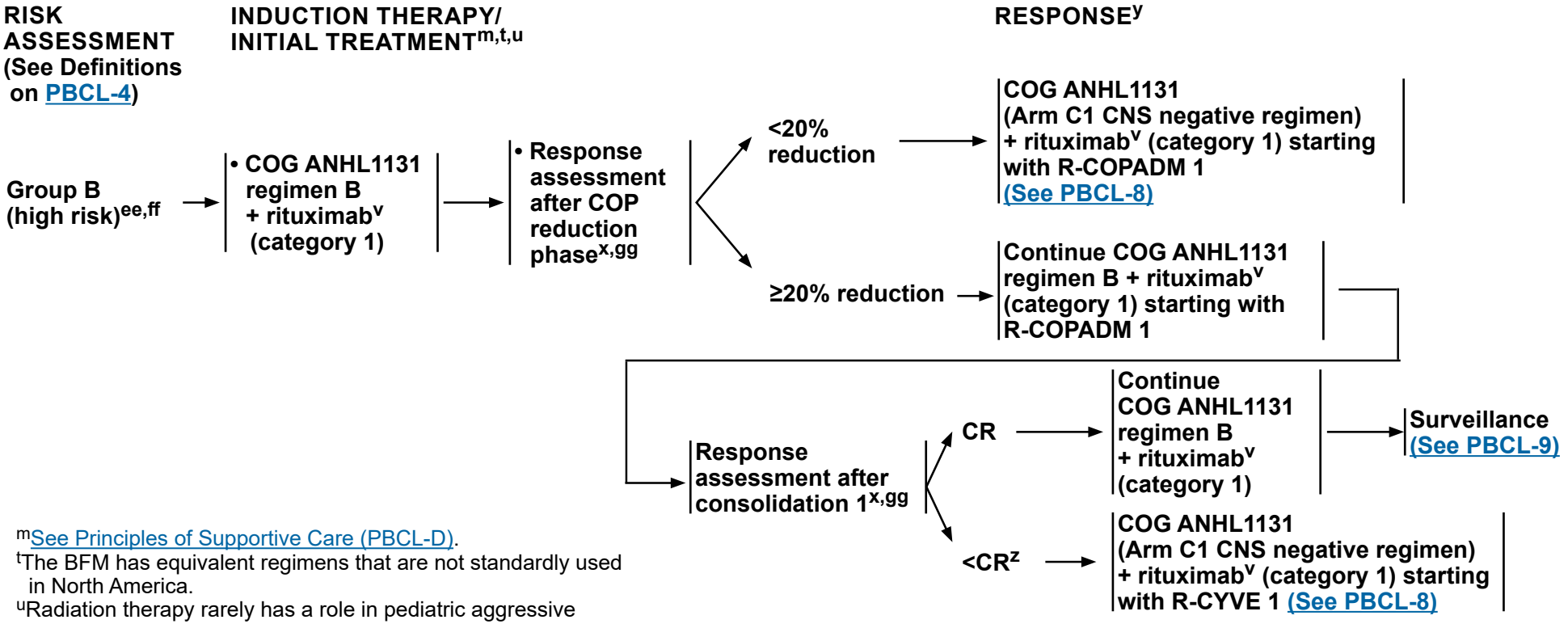

[m] See Principles of Supportive Care (PBCL-D).

[t] The BFM has equivalent regimens that are not standardly used in North America.

[u] Radiation therapy rarely has a role in pediatric aggressive mature B-cell lymphomas due to the rapid lysis of tumor to chemotherapy and the avoidance of long-term side effects in children.

[v] See Principles of Systemic Therapy (PBCL-B).

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[y] See Response Criteria (PBCL-C).

[z] Residual mass should be biopsied prior to categorizing it as residual disease.

[ee] Any Stage III patient with LDH > 2 times ULN, and all non-CNS Stage IV patients with <25% bone marrow involvement.

[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. An FDA-approved biosimilar is an appropriate substitute for rituximab.

[gg] Reassess sites of original disease with radiologic studies as indicated (See PCBL-3). Bone marrow and CSF studies should also be performed if bone marrow or CSF were initially involved.

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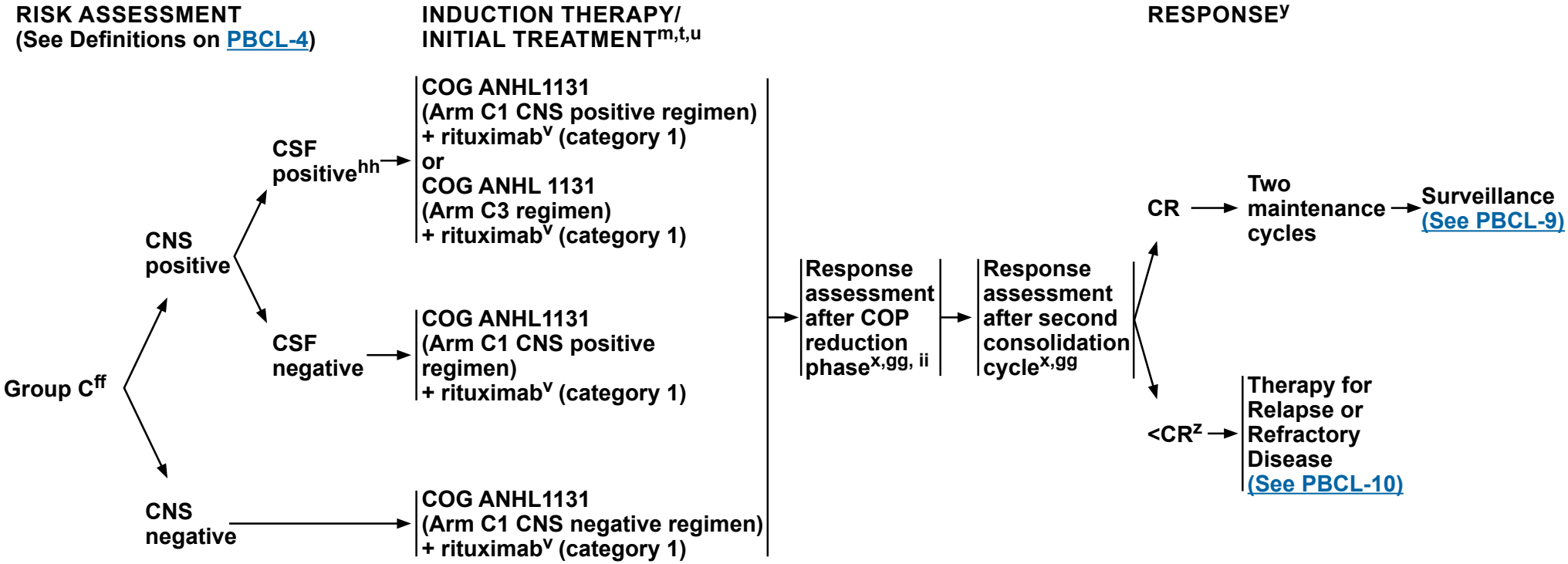

[m] See Principles of Supportive Care (PBCL-D).
[t] The BFM has equivalent regimens that are not standardly used in North America.
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[x] FDG-PET/CT or FDG-PET/MRI may be considered, if not obtained as part of diagnostic evaluation. FDG-PET should not 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; See 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.
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[z] Residual mass should be biopsied prior to categorizing it as residual disease.
[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. An FDA-approved biosimilar is an appropriate substitute for rituximab.
[gg] Reassess sites of original disease with radiologic studies as indicated (See PBCL-3). Bone marrow and CSF studies should also be performed if bone marrow or CSF were initially involved.
[hh] COG protocol ANHL1131 distinguished between lymphomatous CNS or parameningeal disease (CNS+) and lymphoma cells in the CSF (CSF+). CSF+ patients 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 CSF+ patients.
[ii] For patients on regimen C1 therapy with less than 20% response to the reduction phase, continue regimen C1 therapy or change to regimen C3 therapy.

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DISEASE SURVEILLANCE/FOLLOW-UP

- **H&P**
  - **Burkitt lymphoma**
    - ◊ **Every month for one 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 exam visit**
- **Ultrasound of abdominal tumors**
  - **3 months after therapy, if clinical concern**
- **Routine surveillance imaging is not recommended. Consider only if clinical suspicion of relapse:**
  - **FDG-PET/CT or FDG-PET/MRI**
    or
  - **CT chest with IV contrast and CT abdominal/pelvis with IV and oral contrast**

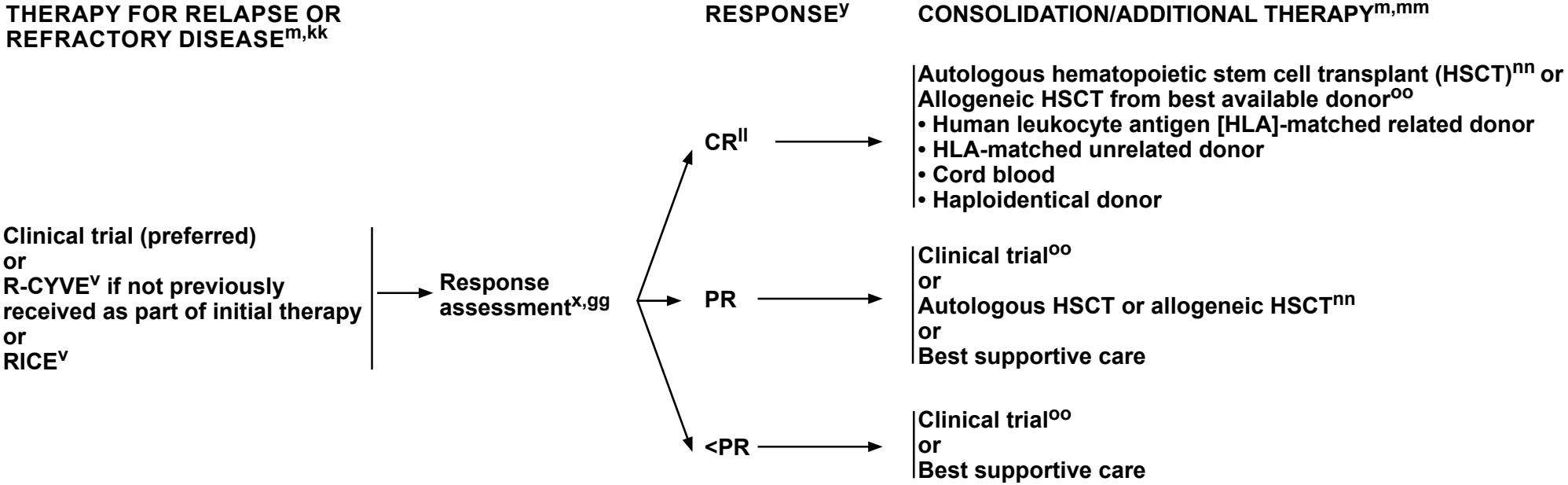
→ **Relapse[jj]** → **See Therapy for Relapsed or Refractory Disease (PBCL-10)**

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]Pathologic confirmation of relapse is recommended before starting relapse therapy, and restaging workup should be completed as for initial diagnosis.

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



[m] See Principles of Supportive Care (PBCL-D).

[v] See Principles of Systemic Therapy (PBCL-B).

[x] 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; See 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.

[y] See Response Criteria (PBCL-C).

[gg] Reassess sites of original disease with radiologic studies as indicated (See PBCL-3). Bone marrow and CSF studies should also be performed if bone marrow or CSF were initially involved.

[kk] It is rare for patients who are risk group A at initial diagnosis to relapse. There are little data and no proven standard of care for these patients, and transplant is usually not 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 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.

[ll] Patients with late relapse from early-stage disease after a complete response to relapse-refractory therapy may not require consolidation with transplant.

[mm] 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]).

[nn] There are no data to support autologous versus allogeneic HSCT; therefore, the decision regarding transplant should be based on physician preference.

[oo] Second-line therapy for relapsed/refractory disease should be in a clinical trial with incorporation of investigational agent. Regimens and agents used for adults with relapsed/refractory DLBCL can also be considered. See BCEL-C 2 of 4 from the NCCN Guidelines for B-Cell Lymphomas.

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PRINCIPLES OF PATHOLOGY

Diagnosis - 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 Burkitt lymphoma (BL) is distinctive.[2] Cytologically, the lymphoid cells are intermediate in size (similar in size to a histiocyte nucleus) and have round nuclei, relatively coarse chromatin that is finely dispersed with multiple small nucleoli, and moderate amounts of densely basophilic cytoplasm. Clear cytoplasmic vacuoles may be seen on Wright Giemsa-stained touch preparations.
  - The cells of DLBCL are large with variable nuclear contours, condensed to vesicular chromatin, single or multiple nucleoli, and scant to moderately abundant cytoplasm.

- Tissue sections of BL and DLBCL 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.

Diagnosis - Immunophenotyping

- As lymphomas of mature B-cell origin, BL and DLBCL express pan-B-cell markers (CD20, CD19, CD79a, CD22, PAX5) and do not generally express TdT and do not express CD34.
- Clonality may be inferred by surface or cytoplasmic immunoglobulin (Ig) light chain (kappa or lambda) restriction, most reliably by flow cytometry.
- All BL and a majority of DLBCL express markers of germinal center follicular B cells (CD10, BCL6). Although an earlier study using immunohistochemistry 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 large B-cell lymphoma (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 EBV-encoded RNA by in situ hybridization (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. The 2017 revised WHO entity of EBV-positive DLBCL, not otherwise specified (NOS) 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.

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

Continued

PRINCIPLES OF PATHOLOGY

Diagnosis - Cytogenetic and Molecular Studies

- BL is defined by a simple karyotype including rearrangement of the *C-MYC* gene located on the long arm of chromosome 8 (8q24).[8] The most common translocation partner is the Ig heavy (*IGH)* chain (chromosome 14) followed by Ig kappa and lambda light chains on chromosomes 2 and 22, respectively.
  - Because of heterogeneity in translocation partners, FISH using a *C-MYC* break-apart probe is the recommended test for detection of *C-MYC* rearrangement.
  - Conventional karyotype analysis may also be of use to demonstrate a translocation involving *C-MYC* rearrangement and other karyotypic abnormalities.
  - In the absence of a *C-MYC* rearrangement, the diagnosis of Burkitt-like lymphoma with 11q aberration 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. The recommended treatment for Burkitt-like lymphoma is the same for BL.
  - The karyotype of BL is simpler than that of Burkitt-like lymphoma with 11q aberration. 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 *C-MYC* rearrangement, when morphologic and/or immunophenotypic features raise consideration for a differential diagnosis of high-grade B-cell lymphoma ("double" or "triple hit"), *IGH/BCL2* and *BCL6* rearrangement status may be interrogated by FISH. At present, high-grade B-cell lymphoma is thought to be uncommon in children,[14-17] although cases have been reported. Pediatric high-grade B-cell lymphoma is treated with the same regimen as pediatric BL[18] See the NCCN Guidelines for B-Cell Lymphomas for a full discussion on high-grade B-cell lymphomas.

- DLBCL may show rearrangements of *C-MYC*, *BCL2*, and/or *BCL6* as well as aneuploidy of these and other loci.
  - Isolated C-MYC rearrangement is seen in up to 8%–14% of DLCBL cases.[19-21] The *C-MYC* rearrangement is seen with similar frequency in children and adult patients.[6]
  - Although FISH studies for *C-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 does not occur in children; therefore CCND1 interrogation for pleomorphic mantle cell lymphoma is not needed in pediatric DLBCL.

- The molecular genetic bases 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.

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Continued

PRINCIPLES OF PATHOLOGY - REFERENCES

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PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for 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)
IT methotrexate, cytarabine, hydrocortisone	Age-based dosing[a] on days 1, 8, 22, 43, and 64 for Head and Neck primary tumors only

OR

- **FAB/LMB96 Regimen A (COPAD)**[2]
  - **Treatment Details: Two 21-day cycles. No intrathecal 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[b] **for Group A**

- **Equivalent BFM Regimen**

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.
[b]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 standardly used in North America.

POG: Pediatric Oncology Group
FAB: The French-American-British
LMB: Lymphomes Maline B

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for Group B

- **POG9219 Regimen (as for Group A on PBCL-B 1 of 9) – Only for Stage I or II, normal LDH**

OR

- **COG ANHL1131 (based on FAB/LMB96) Regimen B[3-6]**
  - **Regimen B/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 and hydrocortisone	Age-based dosing[a] on day 1

If less than 20% size reduction after COP, proceed to Regimen C1, CNS-negative, starting with R-COPADM1.

- **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.**
  - ◊ **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[c]	375 mg/m²/day on day minus 2 (day 6 of COP pre-phase for R-COPADM1) 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

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.
[c]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. An FDA-approved biosimilar is an appropriate substitute for rituximab.

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for Group B – (continued)

- **COG ANHL1131 (based on FAB/LMB96) Regimen B continued**
  - **Regimen B/Consolidation 1 & 2 R-CYM**
    - **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.**

Drug	Dose and schedule
Rituximab[c]	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[a] on day 2
IT cytarabine and hydrocortisone	Age-based dosing[a] on day 7

Useful in Certain Circumstances[b] for Group B

- **Equivalent BFM Regimen**

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.
[b]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 standardly used in North America.
[c]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. An FDA-approved biosimilar is an appropriate substitute for rituximab.

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for Group C

- **COG ANHL1131 (based on FAB/LMB96 with omission of M3 and M4 cycles) Regimen C1[d,3-6]**
  - **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[a] on days 1, 3, and 5
Leucovorin	15 mg/m² every 12 hours for two doses on day 2 and again on day 4

  - **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.**
    - ◊ **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[c]	375 mg/m² on day minus 2 (day 6 of COP pre-phase for R-COPADM1) 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[a] on day 2 (prior to start of leucovorin), day 4, and day 6

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.

[c]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. An FDA-approved biosimilar is an appropriate substitute for rituximab.

[d]COG protocol ANHL1131 distinguished between lymphomatous central nervous system or parameningeal disease (CNS+) and lymphoma cells in the CSF (CSF+). CSF+ patients 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 CSF patients.

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for 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[c]	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)
Cytarabine – high dose	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 INTRATHECAL AFTER R-CYVE 1 ONLY, AS BELOW:	
Methotrexate	8 g/m²/day over 4 hours on day ~18, when ANC is over 500 and platelets over 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[a] on day after high-dose methotrexate (prior to start of leucovorin)

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.
[c]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. An FDA-approved biosimilar is an appropriate substitute for rituximab.

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

PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for 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	500 mg/m²/day on days 2–3 (2 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 adminster 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[a] 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)

OR

- **COG ANHL1131 Regimen C3[d,3-6]**
  - **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[b] for Group C

- **Equivalent BFM Regimen**

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.
[b]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 standardly used in North America.
[d]COG protocol ANHL1131 distinguished between lymphomatous CNS or parameningeal disease (CNS+) and lymphoma cells in the CSF (CSF+). CSF+ patients 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 CSF+ patients.

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

Continued

PRINCIPLES OF SYSTEMIC THERAPY

Preferred Treatment Regimens for Relapsed/Refractory Disease

- **R-CYVE: Rituximab[f], cytarabine, etoposide[7]**

Drug	Dose and schedule
Rituximab[f]	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
HD 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[a] on day 1 at least 6 hours before cytarabine

- **RICE: Rituximab[f], ifosfamide, carboplatin, etoposide[8]**

Drug	Dose and schedule
Rituximab[f]	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	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[e]
IT methotrexate and cytarabine	Age-based dosing:[a] • 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

[a]For age-based dosing for intrathecal therapy, see PBCL-B 8 of 9.
[e]Consider changing mesna to 3 g/m^2 continuous IV infusion over 24 hours if microscopic or gross hematuria occurs.
[f]An FDA-approved biosimilar is an appropriate substitute for rituximab.

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Continued

PRINCIPLES OF SYSTEMIC THERAPY

• Age-Based Dosing for IT Methotrexate, Cytarabine, Hydrocortisone for Therapies Other than RICE[g] (see PBCL-B 1–7 of 9)

Age-Based Intrathecal Therapy[g]					
Drug		**<1 year old**	**1 to <3 years old**	**3 to <9 years old**	**≥9 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[g] (see PBCL-B 7 of 7)

Age-Based Intrathecal Therapy[g]					
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**

[g]For full details on all phases of therapy, see References.

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

PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES

Preferred Treatment Regimens for Initial Therapy

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Preferred Treatment Regimens for Relapsed/Refractory Disease

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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 [See 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 [See Table 2] on FDG-PET with increase in lesional uptake from baseline; or new morphologic disease in BM or CSF**

Abbreviations	
BM	Bone marrow
CR	Complete response
CRb	Complete response biopsy negative
CRu	Complete response unconfirmed
MR	Minor response
NR	No response
PD	Progressive disease
PR	Partial response
SPD	Sum of product of greatest perpendicular diameters

[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.

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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.

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PRINCIPLES OF SUPPORTIVE CARE

Tumor Lysis Syndrome[1-6]

- **Laboratory tumor lysis syndrome (TLS) signs**
  - **High uric acid (> upper limit of normal [ULN] for children)**
  - **High phosphorus (>6.5 mg/dL in children)**
  - **High potassium (>6.0 mmol/L)**
  - **Low calcium (corrected calcium <7.0 mg/dL)**
  - **Need 2 or more metabolic abnormalities in the same 24-hour period**
- **TLS can be asymptomatic but can cause seizures, cardiac arrhythmias, acute renal failure, neuromuscular abnormalities, hypotension, and death**
- **TLS risk factors**
  - **Burkitt lymphoma and leukemia**
  - **Elevated LDH (>2X ULN)**
  - **Bulky disease**
  - **Evidence of TLS prior to initiation of therapy**
  - **Oliguria**
  - **Preexisting renal impairment**
  - **Dehydration**

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Continued

PRINCIPLES OF SUPPORTIVE CARE

Tumor Lysis Syndrome[1-6] (continued)

- **Prophylaxis/treatment 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**
  - **Management of 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.**
    - ◊ **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.**
    - ◊ **For ongoing control of TLS, consider restarting allopurinol after rasburicase therapy is completed.**
  - **Hyperkalemia: Treat per standard hyperkalemia algorithms, such as in Pediatric Advanced Life Support (PALS). Ensure that all exogenous sources of potassium, such as in IV fluids, have been removed. Frequent measurement of potassium levels (every 4–6 hours), continuous cardiac monitoring, and the administration of oral sodium polystyrene sulfonate are recommended. Glucose plus insulin or beta agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of dysrhythmia while awaiting hemodialysis and/or hemofiltration, which most effectively remove potassium.**
  - **Hyperphosphatemia: Treat with phosphorous-restricted diet; consider phosphate binder such as sevelamer. Do not use calcium carbonate in patients at risk for TLS as this may prompt formation of calcium phosphate crystals and worsen renal and other organ function, especially if the calcium phosphate product is >60 mg^2/dL^2.**
  - **Hypocalcemia: Correct hyperphosphatemia; calcium supplementation should not be used unless patient is symptomatic with tetany, muscle spasm, Trousseau/Chvostek signs, etc.**
  - **Consider hemodialysis/continuous renal replacement therapies (CRRT) in patients with worsening renal function whose electrolyte abnormalities do not correct with medical management.**

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Continued

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 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 HBsAg-positive patients.
- Patients on treatment should be on pneumocystis 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 replacement.
- Screen for herpes simplex virus (HSV) if 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 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.

Following Initiation of Chemotherapy[12]

- 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.

Mass Lesions at Presentation[13]

- 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.

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Continued

PRINCIPLES OF SUPPORTIVE CARE

Supportive Care Related to the Chemotherapy

- **Growth factors**
  - **There is a high incidence of fever and 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]**
  - **Consider use of glucarpidase in patients with significant renal dysfunction and toxic plasma methotrexate (MTX) concentrations with delayed MTX clearance (plasma MTX concentrations >2 standard deviations of the mean MTX excretion curve specific for the dose of MTX administered). Leucovorin remains a component in the treatment of MTX toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within 2 hours prior to or following glucarpidase clearance.**
  - **MTX neurotoxicity can occur following high-dose or intrathecal (IT) MTX. MRI may allow for discrimination between MTX 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 MTX 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 (non-alcoholic and unsweetened) may be used twice daily and after meals.**
  - **Management**
    - **Supportive care measures: Maintain hydration, provide adequate nutrition with enteral or parenteral sources, control bleeding, treat viral (HSV) or fungal (candida) mouth infections, and manage pain with topical anesthetics and oral or IV analgesics.**

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Continued

PRINCIPLES OF SUPPORTIVE CARE – REFERENCES

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

STAGING

International Pediatric Non-Hodgkin Lymphoma Staging System[a,b]	
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,[c] bone marrow,[d] or both.**

[a]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.

[b]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.

[c]CNS is considered involved if one or more of the following apply:
- 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

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

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

NCCN Guidelines Version 2.2021
Pediatric Aggressive Mature B-Cell Lymphomas

Discussion

This discussion corresponds to the NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas. Last updated on 06/04/2021.

Table of Contents

Overview

An estimated 15,590 children and adolescents aged 19 years or younger will be diagnosed with cancer in the United States in 2021, and 1,780 will die of the disease.[1] In those aged 14 years or younger, non-Hodgkin lymphoma (NHL) accounts for 6% of cancers, whereas in adolescents aged 15 to 19 years, NHL accounts for 7%.[1] The 5-year relative survival rates for patients with NHL in these age groups are 90% and 89%, respectively.[2] Pediatric aggressive mature B-cell lymphomas are the most common NHL types in children, and they include Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL).[3]

Three epidemiologic variants of BL exist: endemic, immunodeficiency-associated, and sporadic.[4] The endemic form of BL is associated with Epstein-Barr virus (EBV) infection in approximately 95% of cases and occurs mainly in equatorial Africa, South America, Turkey, and Papua New Guinea, with presentation most commonly in the jaw, orbit, mesentery, and central nervous system (CNS). It is also often associated with malaria infection.[5,6] In fact, endemic BL accounts for as many as 70% of childhood cancers in equatorial Africa, where malaria is highly prevalent and intense.[7] Immunodeficiency-associated disease occurs primarily in people living with HIV (PLWH), in whom it may be the initial AIDS-defining condition. Up to 70% of these patients test positive for EBV. Sporadic cases, about 15% of which are EBV+, mainly occur in North America and Europe and commonly present in the abdomen, lymph nodes, bone marrow, or cerebrospinal fluid (CSF). Endemic DLBCL has also been described and may be associated with EBV, hepatitis B virus (HBV), and/or John Cunningham virus (JCV) infection.[8-10] These guidelines do not address endemic or immunodeficiency-associated BL or DLBCL at this time.

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Aggressive Mature B-Cell Lymphomas. These guidelines are intended to provide guidance regarding pathology and diagnosis, staging, initial treatment, disease reassessment, surveillance, therapy for relapsed/refractory disease, and supportive care for clinicians who treat sporadic pediatric BL and DLBCL. These guidelines do not include recommendations for the management of patients with primary mediastinal B-cell lymphoma (PMBL), who should be treated as per the adult NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org). 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.

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

Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines and that all recommendations are classified as category 2A if not otherwise noted. 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.

Literature Search Criteria and Guidelines Update Methodology

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 and pediatric diffuse large B-cell lymphoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[11] The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Practice Guideline; Meta-Analysis; Randomized Controlled Trials; Systematic Reviews; and Validation Studies.

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.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Initial Presentation

Patients with DLBCL and BL may present with fever, chills, night sweats, unexplained/unintentional weight loss, painless regional or diffuse lymphadenopathy, fatigue, bone pain, and/or irritability. Extranodal involvement on presentation is common.[12] Oncologic emergencies may also be the reason for initial presentation, because of the potential for complications of rapid tumor growth (ie, tumor lysis syndrome, superior vena cava [SVC] syndrome, respiratory compromise, spinal cord compression). In addition, patients with abdominal tumors may have a history of abdominal pain/swelling, poor appetite/early satiety, constipation, and/or nausea/emesis.[13] Intrathoracic masses can cause coughing, 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.

Pathology and Diagnosis

Excisional or incisional biopsy of the most accessible site is preferred, with fresh biopsy tissue sent to pathology in saline to ensure viable diagnostic tissue. Touch preparation for cytologic examination is recommended, and morphologic and immunohistochemistry (IHC) review should be performed as clinically indicated.[14] Immunophenotyping and cytogenetics are essential to establish a diagnosis of BL or DLBCL. However, definitive diagnosis may not be feasible before beginning treatment. Morphology and flow cytometry are the minimum methodologies from which to yield diagnostic information to begin treatment, especially if the patient is very sick. Malignant fluid cytology and flow cytometry may suffice.

Morphology

BL and DLBCL are morphologically distinct.[15,16] Cytologically, BL lymphoid cells are intermediate in size (similar in size to a histiocyte nucleus) and have round nuclei, relatively coarse chromatin that is finely dispersed with multiple small nucleoli, and moderate amounts of densely basophilic cytoplasm. Clear cytoplasmic vacuoles may be seen on Wright Giemsa-stained touch preparations. The cells of DLBCL are large with variable nuclear contours, condensed to vesicular chromatin, single or multiple nucleoli, and scant to moderately abundant cytoplasm. Cytoplasmic vacuoles are not typically present.

Tissue sections of BL and DLBCL are also distinctive.[15-17] 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 (tangible body macrophages) confer the so-called “starry sky” appearance indicative of high cell turnover. Mitosis and apoptotic bodies are often numerous. Pediatric BL tends to show little morphologic variation. 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.

Immunophenotyping

Immunophenotyping to establish a diagnosis of BL or DLBCL is performed by IHC and flow cytometry.[15,16] As mature B-cell lymphomas, BLs and DLBCLs express surface immunoglobulin (sIg) and the surface B-cell marker CD20. All BLs and most DLBCLs also express CD10, a germinal center B-cell marker. They are both typically negative for terminal deoxynucleotidyl transferase (TdT), a marker of cellular immaturity, and negative for CD3, a T-cell marker. BLs are negative for BCL2 and positive for BCL6. Greater than or equal to 95% of BLs are Ki-67–positive. For DLBCL, expression of Ki-67, BCL2, and BCL6 is variable.

Cytogenetics

Fluorescence in situ hybridization (FISH) for *C-MYC* rearrangement is also recommended for diagnosis of BL and DLBCL. BLs generally exhibit a simple karyotype, with *MYC* translocation involving an immunoglobulin gene as their sole abnormality.[18-21] The karyotype of DLBCL is variable and may include rearrangements of *MYC, BCL6, BCL2*, and/or other *IgH* rearrangements.[22-25] Double- and triple-hit lymphomas (ie, those with *MYC* rearrangement that also have *BCL2* and/or *BCL6* rearrangements) are rare in the pediatric BL and DLBCL populations, but may be more common in AYA patients.[26-30] The recommended treatment for double- and triple-hit lymphomas in the pediatric patient population is the same as for other BLs and DLBCLs in the pediatric age group. Therefore, the treatment recommendations in these guidelines apply to double- and triple-hit lymphomas.

Demonstration of EBV association using EBV-encoded RNA by in situ hybridization (EBER-ISH) may be performed in BL and DLBCL, if indicated by a history or suspicion of immunodeficiency. Historically, EBV expression was predominantly seen in the endemic form of BL. However, EBV-positive DLBCL and BL can be seen in pediatric patients without recognized immunodeficiency.[16,31,32] Some evidence suggests that EBV positivity in sporadic BL may be associated with older age at diagnosis and higher incidence of nodal involvement.[33]

Burkitt-Like Lymphoma

In the absence of a *C-MYC* rearrangement, the diagnosis of Burkitt-like lymphoma with 11q aberration may be pursued.[34,35] Burkitt-like lymphomas have a more complex karyotype than BL, and are sometimes seen in the post-transplant setting.[36,37] The epidemiology and natural history of this recently recognized entity has yet to be defined, but pediatric cases have been described.[38-40] The recommended treatment for Burkitt-like lymphoma is the same as for BL.

Workup

Workup for patients with a diagnosis of BL or DLBCL is delineated in the Guidelines. It includes history and physical exam, laboratory analysis, bilateral bone marrow aspirate and biopsy, lumbar puncture, and imaging. Imaging should include cross-sectional scans of the neck, chest, abdomen, and pelvis. FDG-PET/CT or FDG-PET/MRI is recommended if available.[41] 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 (also see *Response Assessment*,

below). Information regarding bone marrow and CNS involvement and distant spread is important for staging (see *Staging and Risk Group Classification*, below). CNS positivity is found in approximately 9% and 3% of pediatric patients with BL and DLBCL, respectively.[42,43]

In addition, a baseline echocardiogram (ECHO) or multigated acquisition (MUGA) scan, and electrocardiogram (ECG) is recommended, and fertility counseling should be offered with fertility preservation as clinically appropriate.

Staging and Risk Group Classification

Historically, the Murphy/St. Jude Childhood NHL staging classification, published in 1980, was used for staging of pediatric BL and DLBCL.[44] A revised system, the International Pediatric NHL Staging System (IPNHLSS), was published in 2015.[45] It addresses 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. The panel supports use of the revised IPNHLSS, as detailed in the Guidelines above.

CNS Positivity

Patients with CNS involvement have stage IV disease. 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

Bone Marrow Positivity

Bone marrow involvement is defined by morphologic evidence of greater than or equal to 5% lymphoma cells in a bone marrow aspirate.[45] Patients with bone marrow involvement have stage IV disease. However, patients with any detectable bone marrow involvement should not be considered for Group A or POG 9219 therapy.

Risk Groups

The panel's 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.[46]

- Group A includes patients with completely resected stage I or completely resected abdominal stage II disease.
- Group C includes patients with CNS involvement and/or with greater than or equal to 25% lymphoma cells in the bone marrow.
- Group B includes all patients not eligible for Group A or C.
- Group B is further divided into low risk and high risk:
  - To qualify as low-risk Group B, the patient must have incompletely resected stage I or II disease or stage III disease if lactate dehydrogenase (LDH) is less than or equal to 2 times the upper limit of normal (ULN).
  - High-risk Group B includes patients with CNS-negative stage IV disease and bone marrow involvement of less than 25% and includes patients with stage III disease and LDH greater than 2 times the ULN.

Initial Treatment

Systemic therapy is the mainstay of initial treatment for patients with BL or DLBCL based on many clinical trials, including those discussed below. Several cooperative groups have been instrumental in establishing the

standard regimens for these patients, including the Children's Oncology Group (COG), the Pediatric Oncology Group (POG), the French Society of Pediatric Oncology, the Children's Cancer Group, the United Kingdom Children's Cancer Study Group, and the German Berlin-Frankfurt-Münster (BFM) group.

The intensive, multiagent regimens used as initial therapy are highly effective for most patients. For example, in the FAB/LMB96 study (see below), only 2.5% of patients had refractory disease and 6.8% experienced disease relapse after complete response (CR) to initial therapy.[47]

Rituximab, a CD20-directed monoclonal antibody with indications in certain adults with NHL,[48] may be included for low-risk Group B patients (see below), and is recommended for patients with high-risk Group B and Group C disease.

Group A

Group A patients should receive the POG9219 regimen or the FAB/LMB96 regimen A if they are not enrolled in a clinical trial, with the exception of Group A patients with any detectable bone marrow disease who should be treated as Group B.

The POG9219 regimen is based on two trials with a total of 340 pediatric patients with stage I or II NHL, resected or not (ie, Group A and low-risk Group B), conducted by the POG between 1983 and 1991.[49] In the first trial, patients were randomized to receive induction and consolidation chemotherapy with or without radiation therapy (RT). In the second trial, all patients received induction and consolidation chemotherapy without RT, and those with complete remission after 9 weeks were randomized to continuation of therapy or no continuation. The chemotherapy regimen included vincristine, doxorubicin, cyclophosphamide, and prednisone. The 5-year rates of continuous complete remission 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 chemotherapy is sufficient in this group of patients.

The FAB/LMB96 international study included pediatric patients with all stages of NHL.[50] All patients with resected stage I or completely resected abdominal stage II disease received 2 courses of COPAD without intrathecal therapy after surgery (Regimen A; cyclophosphamide, vincristine, prednisone, and doxorubicin). After a median follow-up of 50.5 months, the 4-year event-free survival (EFS; with events defined as treatment failure for any reason) was 98.3% and overall survival (OS) was 99.2%.

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.[51] 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-hours 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.

Group B

Low-risk Group B patients with stage I or II disease can be treated with the POG9219 regimen as for patients with Group A disease (discussed above), or with the COG ANHL1131 regimen B with or without rituximab. The latter regimen is the only recommended option for low-risk Group B patients with stage III disease and normal LDH levels (with or without rituximab) and for patients with high-risk Group B disease (with rituximab). Rituximab has not been tested in clinical trials for patients with low-risk

Group B. However, in keeping with adult practice and data on efficacy and toxicity in high-risk patients (see below), the panel deems the inclusion of rituximab in the treatment of this patient population to be appropriate.

COG ANHL1131 regimen B is based on that used for Group B patients in the FAB/LMB96 trial.[52] In that trial, patients with Group B disease received COP reduction, followed by induction with two courses of COPADM with either full-dose or half-dose cyclophosphamide for those with good response, followed by consolidation with two courses of CYM, and then followed by maintenance or no maintenance for those with continued response. Intrathecal therapy was included. The results showed that treatment reductions did not have significant effects on EFS. Therefore, COG ANHL1131, a trial comparing EFS in pediatric patients with high-risk Group B or Group C NHL treated with and without rituximab, used the lower-intensity chemotherapy as its backbone.[53]

The use of rituximab in high-risk Group B patients is supported by the COG ANHL01P1 trial.[54] In this international study of patients younger than 30 years of age 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%). Likewise, results of the COG ANHL1131 trial support the improved efficacy of rituximab in addition to standard LMB therapy in children and adolescents with high-risk BL and DLBCL.[55] The results of the COG ANHL1131 trial demonstrated a 3-year EFS of 93.9% in the rituximab plus chemotherapy group versus 82.3% in the chemotherapy alone group (95% CI, 89.1–96.7; 75.7–87.5, respectively).[55] The 3-year OS was 95.1% for the rituximab/chemotherapy group versus 87.3% in the chemotherapy alone group (95% CI, 90.5–97.5; 82.1–91.6, respectively). Complete remission 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 or without rituximab for patients in low-risk Group B and with rituximab for those in high-risk Group B. Those with less than 20% tumor reduction after COP start induction with R-COPADM1 of COG ANHL1131 regimen C1 CNS-negative with rituximab, even if rituximab was not included initially (see *Group* C, below). Those with greater than or equal to 20% tumor reduction after COP reduction 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 change to COG ANHL1131 regimen C1 CNS-negative with rituximab, starting with R-CYVE1 (see *Group* C, below).

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 500U/L received five cycles of therapy, including a cytoreductive prephase.[51] 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 prephase, followed by six courses of chemotherapy with intrathecal therapy for patients with high-risk Group B and Group C disease.[56] The 6-year pEFS was 78% +/- 3% in this group of patients.

Group C

The recommended treatment regimens for patients in Group C are those being used in COG ANHL1131 (see above) and are dependent on CNS and CSF involvement.[53] These regimens are based on those used in the FAB/LMB96 trial, with omission of two maintenance cycles.[46,52] The COG

ANHL1131 Arm C1 CNS-positive regimen is an option for patients with CNS-positive disease, regardless of CSF positivity. Patients with CNS and CSF involvement can alternatively be treated according to the Arm C3 regimen. The relative efficacy of the C3 versus the C1 regimen for CSF-positive patients has not been established. Patients without CNS involvement should receive the Arm C1 CNS-negative regimen.

Rituximab is a category 1 recommendation for all patients in Group C. The small COG ANHL01P1 study in pediatric patients with CNS and/or bone marrow-positive BL evaluated FAB/LMB96 chemotherapy with rituximab.[57] The 3-year EFS/OS was 90% (95% CI, 76%–96%) in the 40 evaluable patients, and the regimen was well tolerated. In addition, a combined analysis of results from the inclusion of rituximab for patients with CNS involvement in the FAB/LMB96 C1 arm and COG ANHL01P1 showed that EFS and OS were improved with rituximab compared with historic LMB89 results.[58] Other studies have also seen high cure rates with the use of rituximab in these patients.[55,59,60] See *Group B* (above) for the recent results of the randomized comparison of chemotherapy with and without rituximab in the COG ANHL1131 trial. [55]

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 prephase and 6 courses of chemotherapy.[51,56]

Response Assessment

Response assessment is critical during therapy for patients with pediatric aggressive mature B-cell lymphomas, especially for Group B patients on COG ANHL1131 regimen B, because their treatment depends on the level of response to early rounds of therapy.

Sites of original disease should be reassessed with radiologic studies as indicated (abdominal ultrasound, chest/abdominal/pelvic 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. 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[61]), biopsy is not necessary because of the high negative predictive value of FDG-PET.[62-66] In the absence of clinical concern, FDG-PET does not need to be repeated once it is negative. It is important to note, however, that the positive predictive value of FDG-PET is fairly low.[67] False-positive findings may include inflammation, necrotic tumor, reactive lymphadenitis, brown fat, thymic rebound, and secondary malignancy.

The panel recommends use of the International Pediatric NHL Response Criteria, as adapted in the Guidelines above.[68] In the response criteria system, disease is classified as progressive disease (PD), no response (NR), minimal response (MR), partial response (PR), and CR. For patients with less than CR by these criteria at the end of therapy, the residual mass should be biopsied to confirm the presence or absence of residual disease. The majority of residual masses at the end of therapy are necrotic tumor.

Surveillance

As few as 5% of patients treated for BL or DLBCL experience a relapse.[69,70] A majority of these relapses occur in the first 6 months post treatment, with fewer than 10% of relapses occurring after 15 months.[69,70] DLBCL relapses tend to occur later than BL relapses and may be seen up to 3 years post treatment. Treatment of relapsed disease can lead to sustained complete second remissions in some patients.[69-74] Therefore,

patients with a CR to initial treatment should undergo routine clinical surveillance.

A history and physical exam are recommended more frequently in the first 3 years, and then annually. A CBC with differential is recommended monthly until counts are normal, and then at each exam visit. Routine surveillance imaging is not recommended. FDG-PET/CT or FDG-PET/MRI or CT chest with IV contrast/abdominal/pelvis with IV and oral contrast should only be considered if there is a clinical suspicion of relapse.[75] Ultrasound of abdominal tumors is indicated 3 months after therapy if there is clinical concern.

In addition, patients should be monitored for late effects of treatment as per the COG (Children's Oncology Group) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers (available at www.survivorshipguidelines.org). In particular, attention should be paid to cardiac, gonadal, and neurocognitive function; bone health; and the risk for secondary leukemia.

Subsequent Therapy for Relapsed or Refractory Disease

Treatment for patients with relapsed or refractory disease is systemic therapy, with clinical trial participation preferred. Systemic therapy options for most patients are R-CYVE (if not previously received as part of initial therapy) or R-ICE. Consolidation therapy is recommended based on response (see below).

It is rare for patients who had Group A disease at initial diagnosis to relapse, and there are little data and no proven standard of care for these patients. 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), 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.

CYVE and ICE were used in the relapse/refractory setting in the LMB89, LBM96, and LBM2001 studies with 29.9% 5-year survival rate for patients with relapses.[69] After 1996, 16 relapsed/refractory patients received rituximab with CYVE or ICE. Six of them were in complete remission after relapse/refractory treatment, but there was no difference in survival rates between those that did and did not receive rituximab.[69,70] A multicenter case series in the United Kingdom, however, demonstrated an association between rituximab and survival in the relapse/refractory setting.[76] In a small COG study, patients with relapsed/refractory NHL received rituximab with ICE (ie, R-ICE).[77] Toxicities were manageable. The CR/PR rate was 60% in 20 evaluable patients, with 30% able to complete consolidation therapy. In addition, a Japanese study reported a 73% response rate from 223 patients treated with R-ICE in this setting.[78]

Consolidation Therapy

Most relapsed/refractory patients with a CR to systemic therapy should receive an autologous or allogeneic hematopoietic stem cell transplant (HSCT). The exception is for patients with Group A or stage I/II Group B disease at diagnosis (see *Subsequent Therapy for Relapsed or Refractory Disease,* above). In the multicenter case series in the United Kingdom mentioned above, 9 of 16 patients who received HSCT survived for more than 6 years; no patient who did not receive transplant survived.[76] In another case series, OS was better for patients who received HSCT transplanted compared with patients who did not ($P < .01$).[72] Other studies have also shown comparable survival rates for patients who undergo HSCT in this setting.[71,74,79,80]

No data support autologous versus allogeneic HSCT; therefore, the decision regarding type of transplant should be based on physician preference.[79,81] For an allogeneic transplant, the best available donor should be used: generally, a human leukocyte antigen [HLA]-matched

related donor is the best option, followed by an HLA-matched unrelated donor, then cord blood or a haploidentical donor.[82,83]

Patients with a PR to initial therapy for relapsed/refractory disease can also receive an autologous or allogeneic HSCT. For patients with PR or less than a partial response, a clinical trial of second-line systemic 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.

Supportive Care

Supportive care issues that are important in pediatric patients with cancer during treatment include management of pain, chemotherapy-induced nausea and vomiting, fatigue, anxiety and depression, fever and neutropenia, neurologic complications, dermatitis, and mucositis.[84-87] The COG and others have evidence-based guidelines addressing some of these supportive care issues, as well as guidelines on antifungal prophylaxis, fertility preservation, and platelet transfusion.[88-91 92,93] 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.[85,94-96]

Specific to the treatment regimens recommended for pediatric patients with BL or DLBCL, there is a high risk of serious infections associated with profound neutropenia and severe mucosal toxicity.[97] Rituximab is associated with hepatitis B reactivation, and HBV polymerase chain reaction (PCR) monitoring and antiviral prophylaxis is recommended for HBsAg-positive patients.[98] The *Principles of Supportive Care* in the algorithm on PBCL-D above list other recommendations for infection prophylaxis and treatment for these patients.

Organ dysfunction and tumor mass effects can affect pediatric patients with BL and DLBCL, causing significant morbidity. Spinal cord compression, kidney injury and obstructive uropathy, intussusception, bowel obstruction, chest masses with risk of SVC syndrome, and hepatopathy have been described.[99,100] Chemotherapy should be started as soon as possible to preserve organ function and reduce complications for these patients.

Tumor Lysis Syndrome

One of the most critical supportive care needs of pediatric patients with BL and DLBCL is the prevention and management of tumor lysis syndrome (TLS). TLS results from spontaneous or therapy-induced rapid tumor necrosis and release of tumor cell contents into the blood stream.[101,102] It 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.

Prophylaxis with allopurinol or rasburicase prior to initiation of systemic therapy is indicated for certain patients as described in the *Principles of Supportive Care* in the algorithm on PBCL-D above.[103] Management of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia associated with TLS is also described in that section of the algorithm.[101,102,104,105]

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