Pediatric Aggressive Mature B-Cell Lymphomas, Version 2.2020

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ABSTRACT

Pediatric aggressive mature B-cell lymphomas are the most common types of non-Hodgkin lymphoma in children, and they include Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). These diseases are highly aggressive but curable, the treatment is complex, and patients may have many complicated supportive care issues. The NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas 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.

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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 noted.

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.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

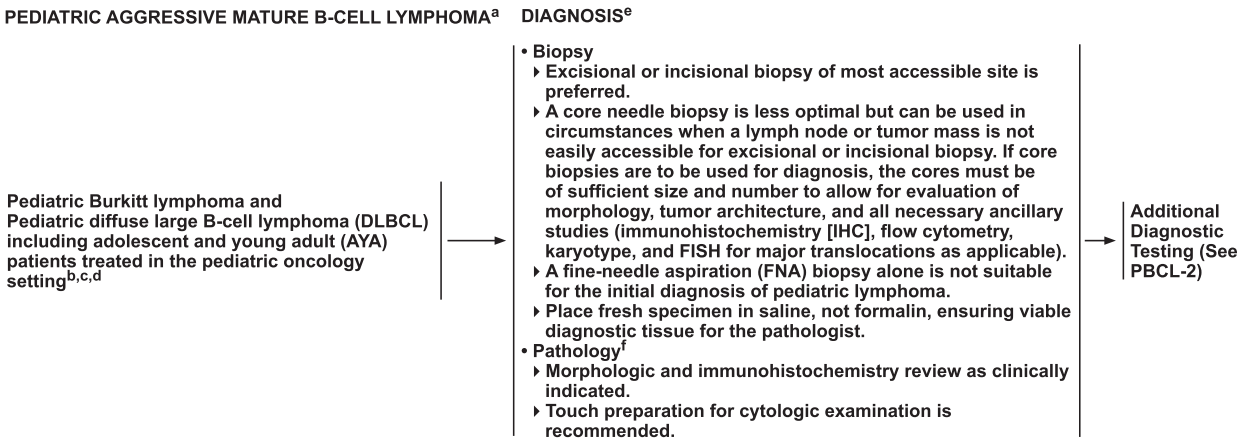
The complete NCCN Guidelines for Pediatric Aggressive Mature B-Cell Lymphomas are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Pediatric Aggressive Mature B-Cell Lymphomas Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Pediatric Aggressive Mature B-Cell Lymphomas Panel members can be found on page 1123. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[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*).

†To view the most recent version of these guidelines, visit NCCN.org.
*Available in the supplemental online content at JNCCN.org.

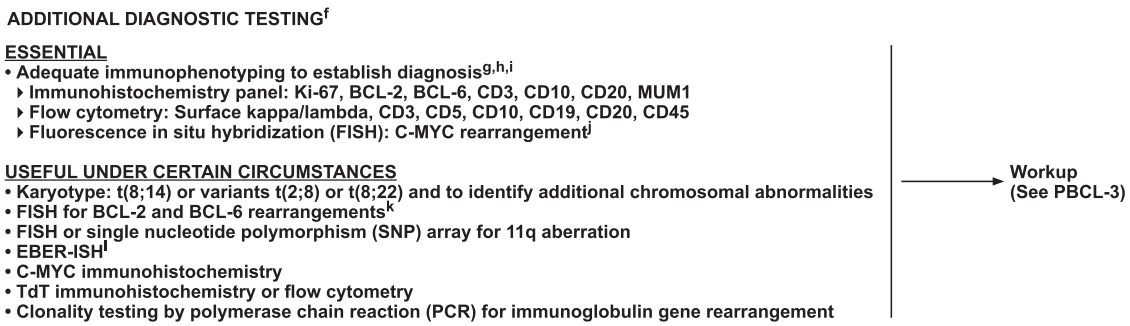
PBCL-1

Overview

An estimated 16,850 children and adolescents aged 19 years or younger will be diagnosed with cancer in the United States in 2020, and 1,730 will die of the disease.[1] In those aged 14 or younger, non-Hodgkin lymphoma (NHL) accounts for 5% 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 91% and 88%, respectively.[1] 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).[2]

Three epidemiologic variants of BL exist: endemic, immunodeficiency-associated, and sporadic.[3] 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.[4,5] In fact, endemic BL accounts for as many as 70% of childhood cancers in equatorial Africa, where malaria is highly prevalent and intense.[6] Immunodeficiency-associated disease occurs primarily in people living with HIV, 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 infection.[7–9] 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, who should be treated as per the adult NCCN Guidelines



[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.

†To view the most recent version of these guidelines, visit NCCN.org.
*Available in the supplemental online content at JNCCN.org.

for B-Cell Lymphomas (available at 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.

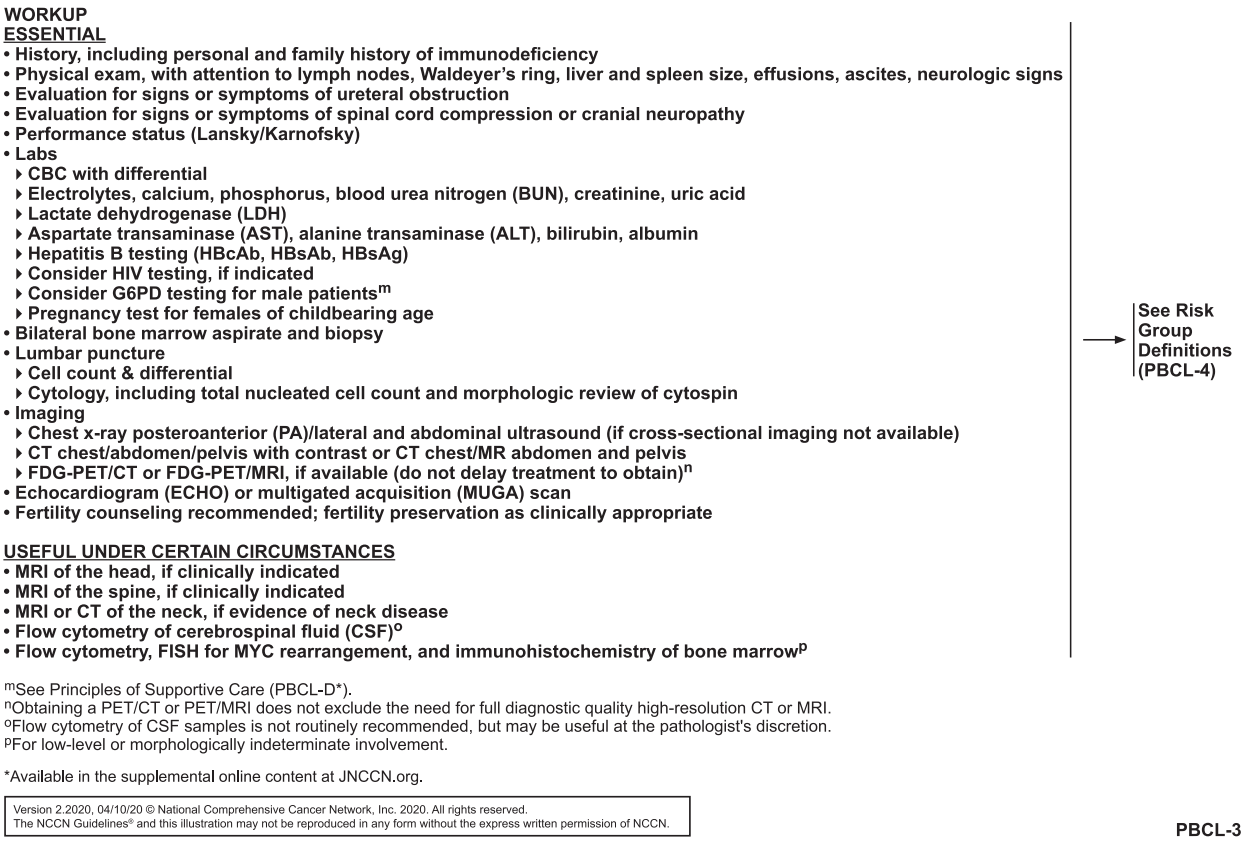
The Pediatric Aggressive Mature B-Cell Lymphoma Panel considers *pediatric* to include any patient aged 18 years and younger, and adolescent and young adult (AYA) patients older than age 18 years who are treated in a pediatric oncology setting. Practice patterns vary from center to center in terms of 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 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

Before initial development of these NCCN Guidelines, 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 lymphoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[10] The search results were narrowed by selecting studies in humans published in English.

The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations



for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available on the NCCN website (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.[11] 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 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.[12] 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 review should be performed as clinically indicated.[13] 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.[14,15] Cytologically, BL lymphoid cells are intermediate in size (similar in size to a histiocyte nucleus) and have round

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 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

nuclei, relatively coarse chromatin with multiple small nucleoli, and scant 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.

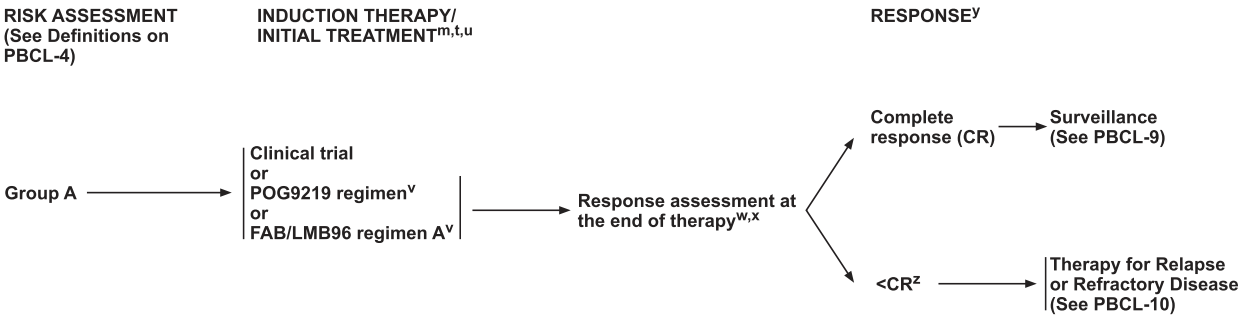
Tissue sections of BL and DLBCL are also distinctive.[14–16] BL is composed of patternless sheets of lymphoid cells that appear to mold to one another (pseudo-cohesion). Scattered histiocytes with apoptotic debris in the cytoplasm (tingible-body macrophages) confer the so-called "starry sky" appearance indicative of high cell turnover. Pediatric BL tends to show little morphologic variation. The architecture of DLBCL also shows sheet-like growth, but the significant nuclear pleomorphism and scant to 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 immunohistochemistry and flow cytometry.[14,15] As mature B-cell lymphomas, BLs and DLBCLs express surface immunoglobulin 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, 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 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.[17–20] The karyotype of DLBCL is variable and may include rearrangements of *MYC, BCL6, BCL2*, and/or other *IgH* rearrangements.[21–24] 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.[25–29]



[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 (abdominal ultrasound, chest/abdominal/pelvic CT with contrast, and/or MRI of the head, neck, abdomen, and/or pelvis).
[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.

*Available in the supplemental online content at JNCCN.org.

PBCL-5

The recommended treatment of 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 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.[15,30,31] Some evidence suggests that EBV positivity in sporadic BL may be associated with older age at diagnosis and higher incidence of nodal involvement.[32]

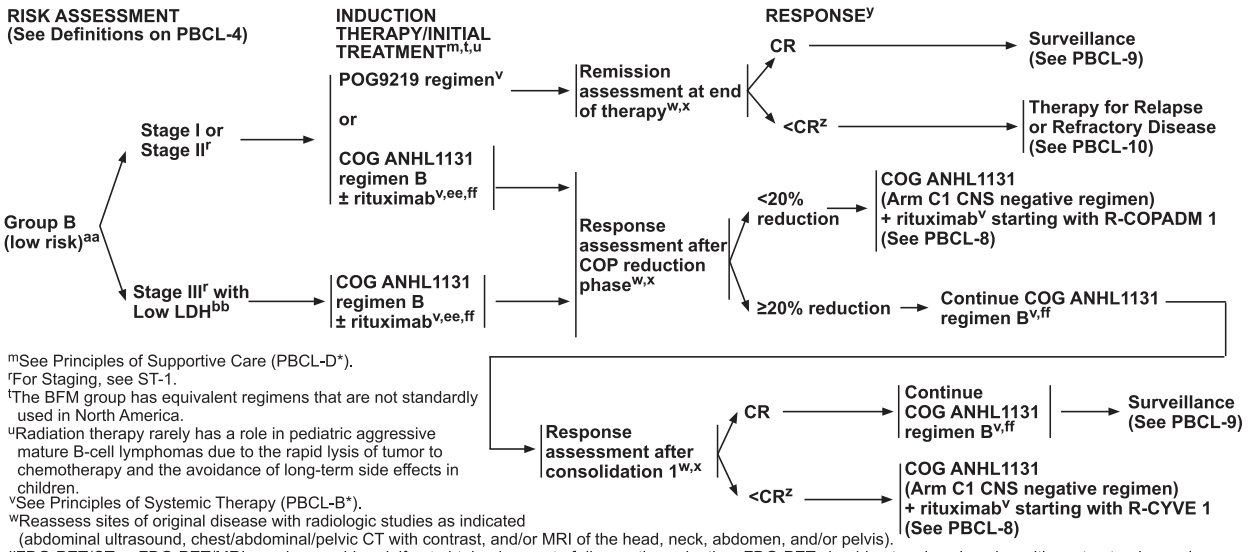
Burkitt-Like Lymphoma

In the absence of a *C-MYC* rearrangement, the diagnosis of Burkitt-like lymphoma with 11q aberration may be pursued.[33,34] Burkitt-like lymphomas have a more complex karyotype than BL and are sometimes seen in the posttransplant setting.[35,36] The epidemiology and natural history of this recently recognized entity has yet to be defined, but pediatric cases have been described.[37–39] The recommended treatment of 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. FDG-PET/CT or FDG-PET/MRI is recommended if available.[40] However, treatment should not be delayed 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," page 1116). Information regarding bone marrow and CNS involvement and distant spread is important for staging (see "Staging and Risk Group Classification," next section). CNS positivity is found in approximately 9% and 3% of pediatric patients with BL and DLBCL, respectively.[41,42]

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



[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 (abdominal ultrasound, chest/abdominal/pelvic CT with contrast, and/or MRI of the head, neck, abdomen, and/or pelvis).
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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 upper limit of normal (ULN). Low LDH: ≤2 times the ULN.
[ee]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.
[ff]If rituximab is included in induction/initial treatment, it should be continued throughout therapy. See Principles of Systemic Therapy (PBCL-B*).

*Available in the supplemental online content at JNCCN.org.

PBCL-6

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.[43] A revised system, the international pediatric NHL staging system (IPNHLSS), was published in 2015.[44] 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 algorithm.

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

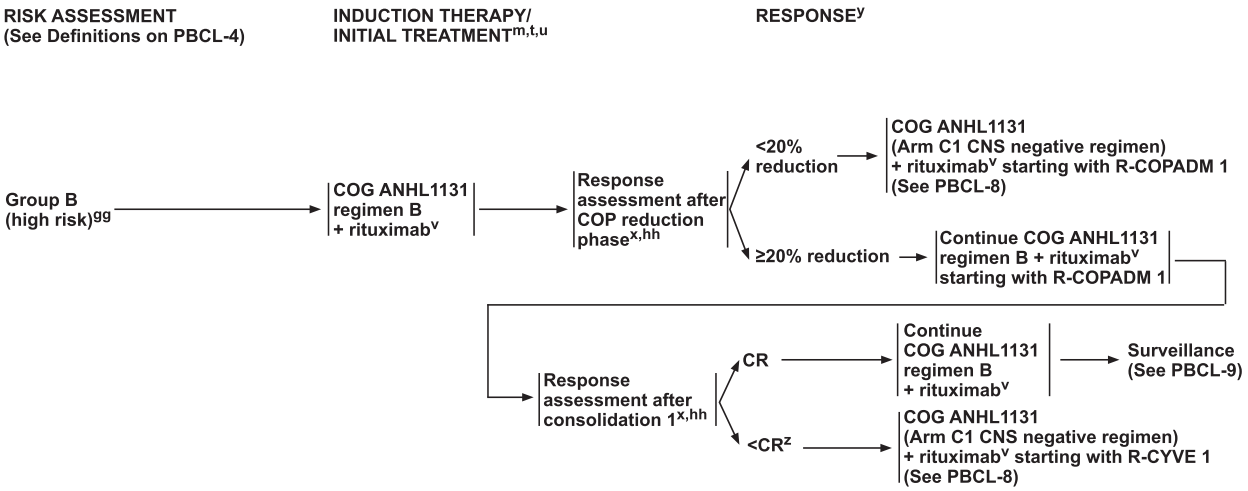
Bone Marrow Positivity

Bone marrow involvement is defined by morphologic evidence of ≥5% lymphoma cells in a bone marrow aspirate.[44] 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 Pediatric Oncology Group (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.[45]

- 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 ≥25% lymphoma cells in the bone marrow.
- Group B includes all patients not eligible for Group A or C.



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[y]See Response Criteria (PBCL-C).
[z]Residual mass should be biopsied prior to categorizing it as residual disease.
[gg]Any Stage III patient with LDH > 2 times ULN, and all non-CNS Stage IV patients with <25% bone marrow involvement.
[hh]Reassess sites of original disease 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 bone marrow or CSF were initially involved.

*Available in the supplemental online content at JNCCN.org.

PBCL-7

- 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 ≤2 times the upper limit of normal.
- High-risk Group B includes patients with CNS-negative stage IV disease and bone marrow involvement of <25% and includes patients with stage III disease and LDH >2 times the upper limit of normal.

Initial Treatment

Systemic therapy is the mainstay of initial treatment of patients with BL or DLBCL based on many clinical trials, including those discussed subsequently. Several cooperative groups have been instrumental in establishing the standard regimens for these patients, including the Children's Oncology Group (COG), the 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.

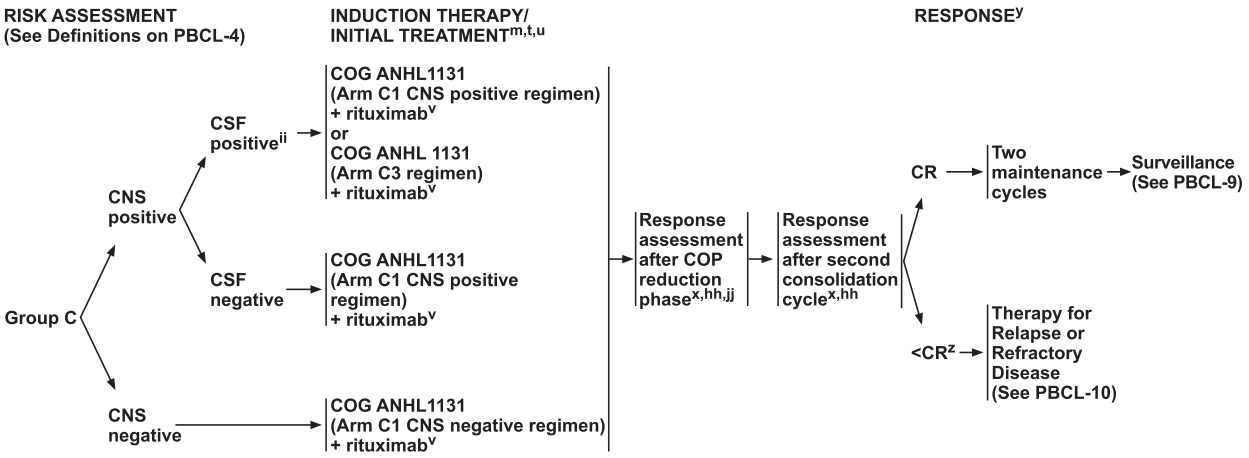
The intensive, multiagent regimens used as initial therapy are highly effective for most patients. For example, in the FAB/LMB96 study (see next section), only 2.5% of patients had refractory disease and 6.8% experienced disease relapse after complete response (CR) to initial therapy.[46]

Rituximab, a CD20-directed monoclonal antibody with indications in certain adults with NHL,[47] may be included for low-risk Group B patients (see "Group B," page 1113), 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 2 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.[48] 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



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[y]See Response Criteria (PBCL-C).
[z]Residual mass should be biopsied prior to categorizing it as residual disease.
[hh]Reassess sites of original disease 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 bone marrow or CSF were initially involved.
[ii]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.
[jj]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.

*Available in the supplemental online content at JNCCN.org.

PBCL-8

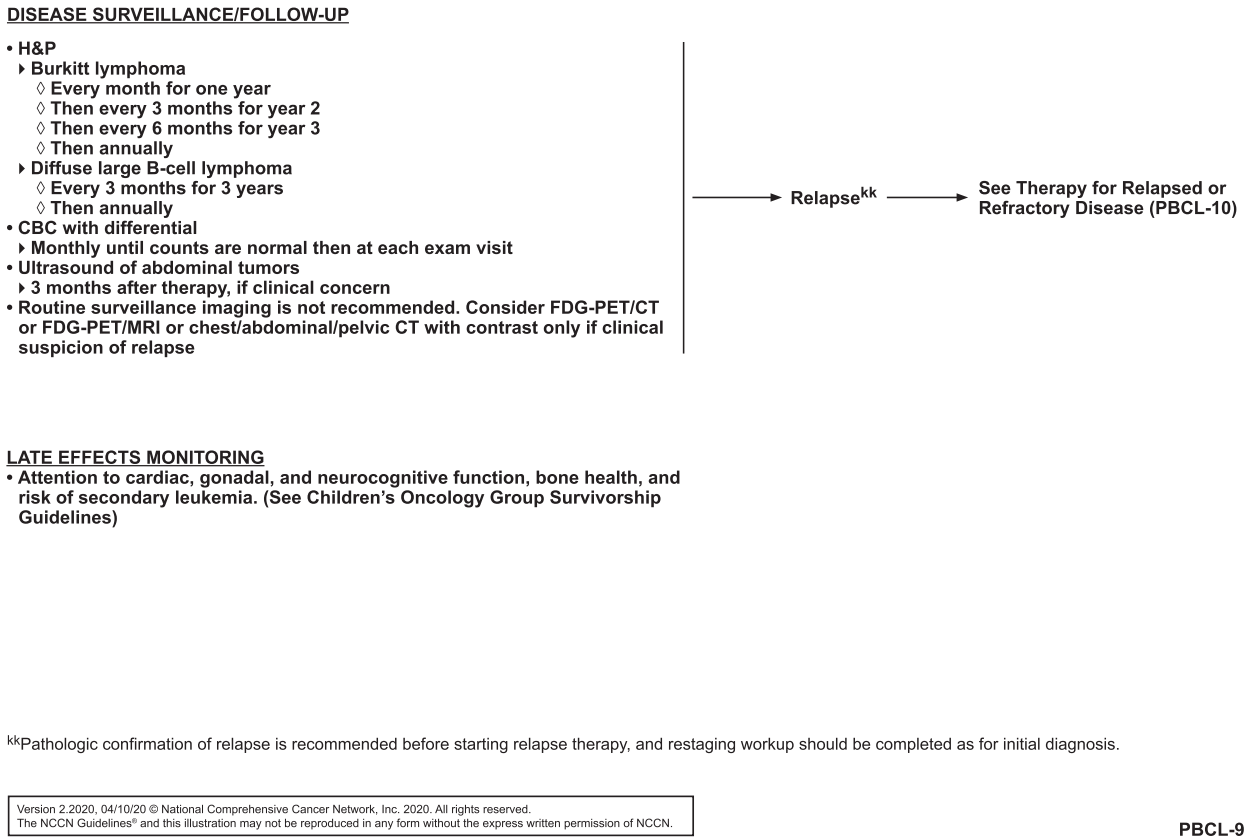
induction and consolidation chemotherapy without RT, and those with complete remission after 9 weeks were randomized to continuation of therapy or no continuation. The chemotherapy regimen included vincristine, doxorubicin, cyclophosphamide, and prednisone. The 5-year rates of continuous complete remission 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.[49] All patients with resected stage I or completely resected abdominal stage II disease received 2 courses of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin) without intrathecal therapy after surgery (Regimen A). 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 noninferiority 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.[50] Patients in Group A received 2 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 noninferiority 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 previously), 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



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

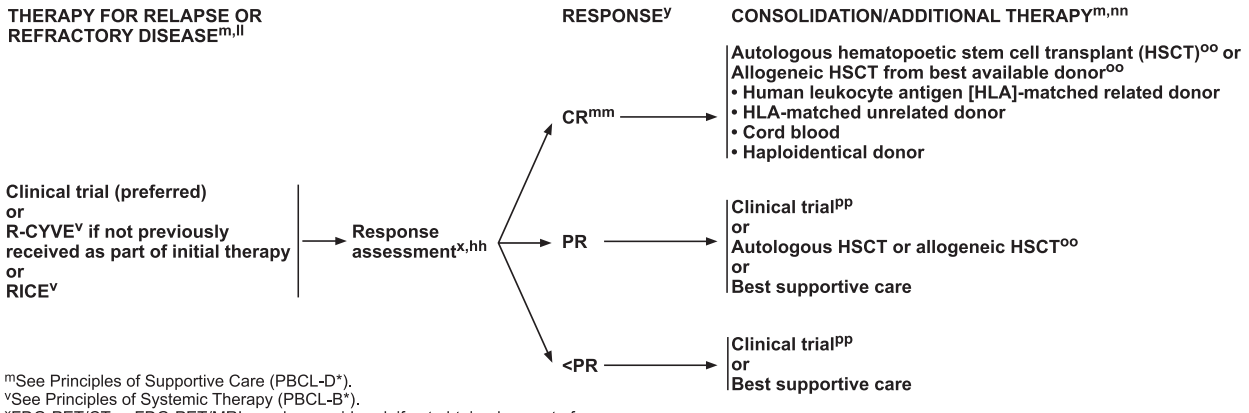
PBCL-9

high-risk patients (see following paragraphs), 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.[51] 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.[52]

The use of rituximab in high-risk Group B patients is supported by the COG ANHL01P1 trial.[53] In this international study of patients <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, initial 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.[54] This trial, which randomized 310 patients with high-risk mature B-cell lymphomas between standard LMB chemotherapy and the same chemotherapy with the addition of rituximab, demonstrated a 1-year EFS of 95% in the rituximab group versus 81.5% in the chemotherapy only group, a statistically significant difference.

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 <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," next page). Those with ≥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



[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).
[hh]Reassess sites of original disease 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 bone marrow or CSF were initially involved.
[ll]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.
[mm]Patients with late relapse from early-stage disease after a complete response to relapse-refractory therapy may not require consolidation with transplant.
[nn]For conditioning therapy used in transplant, institutions can use their center's choice of myeloablative regimen. Retrospective studies showed efficacy of many regimens (eg, busulfan-cyclophosphamide-etoposide, BEAM [carmustine-etoposide-cytarabine-melphalan], CBV[low] [low-dose cyclophosphamide-carmustine-etoposide]).
[oo]There are no data to support autologous versus allogeneic HSCT; therefore, the decision regarding transplant should be based on physician preference.
[pp]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[†].

[†]To view the most recent version of these guidelines, visit NCCN.org.
*Available in the supplemental online content at JNCCN.org.

PBCL-10

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," page 1112), patients with nonresected stage I or stage II disease and those with stage III disease and LDH <500 U/L received 5 cycles of therapy, including a cytoreductive prephase.[50] 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 6 courses of chemotherapy with intrathecal therapy for patients with high-risk Group B and Group C disease.[55] 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 previous sections) and are dependent on CNS and CSF involvement.[52] These regimens are based on those used in the FAB/LMB96 trial, with omission of 2 maintenance cycles.[45,51] 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 should be included 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.[56] 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.[57] Other studies have also seen high cure rates with the use of rituximab in these patients.[58,59] The randomized comparison of

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 et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 2015; 33(18):2106-2111.

chemotherapy with and without rituximab in the COG ANHL1131 has been published only in abstract form to date.[52]

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.[50,55]

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[60]), biopsy is not necessary because of the high negative predictive value of FDG-PET.[61–65] 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.[66] 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 these guidelines.[67] In the response criteria system, disease is classified as progressive disease, no response, minimal response, partial response, 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.[68,69] Most of these relapses occur in

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 Aug;50(8):1257-1260.

the first 6 months after treatment, with fewer than 10% of relapses occurring after 15 months.[68,69] DLBCL relapses tend to occur later than BL relapses and may be seen up to 3 years after treatment. Treatment of relapsed disease can lead to sustained complete second remissions in some patients.[68–73] Therefore, patients with a CR to initial treatment should undergo routine clinical surveillance.

A history and physical exam is 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 and chest/abdominal/pelvic CT with contrast should only be considered if there is a clinical suspicion of relapse.[74] 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 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 of 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 later sections).

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.[68]

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(18):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.

ST-1

After 1996, 16 relapsed/refractory patients received rituximab with CYVE or ICE. Six patients 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.[68,69] A multicenter case series in the United Kingdom, however, demonstrated an association between rituximab and survival in the relapse/refractory setting.[75] In a small COG study, patients with relapsed/refractory NHL received rituximab with ICE (ie, *R*-ICE).[76] 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.[77]

Consolidation Therapy

Most patients with relapsed/refractory disease 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," page 1117). In the multicenter case series in the United Kingdom mentioned previously, 9 of 16 patients who received HSCT survived >6 years; no patient who did not receive transplant survived.[75] In another case series, OS was better for patients who received transplant compared with patients who did not ($P<.01$).[71] Other studies have also shown comparable survival rates for patients who undergo HSCT in this setting.[70,73,78,79]

No data support autologous versus allogeneic HSCT; therefore, the decision regarding type of transplant should be based on physician preference.[78,80] For an allogeneic transplant, the best available donor should be used: generally, a human leukocyte antigen–matched related donor is the best option, followed by a human leukocyte antigen–matched unrelated donor, then cord blood or a haploidentical donor.[81,82]

Patients with a partial response to initial therapy for relapsed/refractory disease can also receive an autologous or allogeneic HSCT. For patients with partial response 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.[83–86] 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.[87–92] In addition, parents and other caregivers of children with cancer frequently experience distress, depression, and even symptoms of posttraumatic 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.[84,93–95]

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.[96] Rituximab is associated with hepatitis B reactivation, and hepatitis B virus polymerase chain reaction monitoring and antiviral prophylaxis is recommended for HBsAg-positive patients.[97] The "Principles of Supportive Care" in the algorithm (see supplemental online content at JNCCN.org) list other recommendations for infection prophylaxis and treatment of 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 superior vena cava syndrome, and hepatopathy have been described.[98,99] 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.[100,101] 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 before start of therapy.

Prophylaxis with allopurinol or rasburicase before start of systemic therapy is indicated for certain patients as described in the "Principles of Supportive Care" in the algorithm (see supplemental online content at JNCCN.org).[102] Management of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia associated with TLS is also described in that section of the algorithm.[100,101,103,104]

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Individual Disclosures for the NCCN Pediatric Aggressive Mature B-Cell Lymphomas Panel

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[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Paul J. Galardy: Abbott Laboratories, and AbbVie, Inc.