# Management of Adults With Burkitt Lymphoma

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**Abstract**: Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma characterized by marked tumor proliferation resulting from translocation of the *MYC* oncogene. Distinct clinical variants include endemic, sporadic, and immunodeficiency-associated cases. All variants are characterized by rapidly dividing tumor masses that quickly disseminate to extranodal sites, including the bone marrow and central nervous system (CNS). Although common in children, BL is rare in adults, mandating a high index of clinical suspicion for timely diagnosis. Prompt recognition and initiation of comprehensive supportive care are essential for prevention of early complications, such as tumor lysis syndrome and multisystem organ dysfunction. BL is highly sensitive to chemotherapy, and patients who tolerate highly intensive combination chemotherapy regimens are frequently cured. Most regimens were developed in children and young adults, however, and the treatment-related toxicities remain a major barrier for those with advanced age and/or comorbid conditions. Younger patients are less susceptible to acute toxicities but are more likely to experience long-term sequelae of treatment, including infertility and secondary malignancies. The infusional regimen of dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and regular- or double-dose rituximab (DA-EPOCH-R or -RR) is less toxic than standard BL regimens, yet maintains high rates of cure across a diverse range of patients, including those with disseminated disease, advanced age, and HIV infection. Patients with low-risk BL can be cured with just 3 cycles of DA-EPOCH-RR. Still, patients with CNS involvement remain at high risk for early death, and prevention of late CNS relapses remains a priority. Future studies combining rational targeted agents with DA-EPOCH-R or -RR may further improve the cure rate.

Keywords
B-cell lymphoma, Burkitt lymphoma, non-Hodgkin lymphoma

## Introduction

Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin lymphoma (NHL) of mature B cells that accounts for 20% to 30% of pediatric lymphomas but only approximately 1% of adult NHL in the United States, for an estimated 1480 cases annually.[1] BL derives

its name from Denis P. Burkitt, an Irish surgeon who, while working in Uganda, reported unusual cases of children with rapidly growing tumors affecting the jaw and abdominal regions.[2,3] It is now recognized that BL can be subclassified into 3 clinicopathologic variants: endemic; sporadic; and arising in the setting of immunodeficiency, typically infection with HIV.[4,5] Each variant has distinct epidemiologic associations, clinical manifestations, and relationships to coinfections, but the general treatment approach is uniform.[6-8]

BL is characterized by a hallmark translocation that juxtaposes the *MYC* proto-oncogene to an immunoglobulin enhancer, resulting in the unregulated proliferation of tumor cells.[9] Hence, the clinical presentation of BL is often dramatic and associated with tumor cell doubling times of 24 to 48 hours.

BL is highly sensitive to chemotherapy and can be cured with highly intensive combination chemotherapy regimens that include agents that penetrate the central nervous system (CNS), along with intensive supportive care. The anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen) further improves survival when added to standard regimens for BL.[10] Most regimens, however, are adapted from protocols that were developed to treat children and young adults with acute lymphoblastic leukemia (ALL), and rely on maximal dose intensity. Patients older than 30 years and those with comorbid conditions, ongoing end-organ dysfunction, and/or HIV are at high risk for acute toxicities. Further, children and young adults must face the prospect of infertility, neurocognitive impairment, and a lifelong risk for treatment-related cancers.[11-13] This review focuses on the clinical management of adults with BL in resource-replete areas, and emphasizes critical supportive care measures necessary for cure.

## Clinical Variants of Burkitt Lymphoma

Of the 3 clinical variants, endemic BL is the most common worldwide, with an incidence in equatorial Africa of 3 to 6 children per 100,000. Endemic BL accounts for 30% to 50% of cases of childhood cancer in this region.[2,3] Endemic BL shows a 2:1 male predominance and a median age at presentation of 4 to 7 years.[14,15] The incidence is highest in areas with a high prevalence of *Plasmodium falciparum* malaria and early exposure to Epstein-Barr virus (EBV), such as equatorial Africa, Brazil, and Papua New Guinea. In fact, EBV derives its name from the virologists Michael A. Epstein and Yvonne Barr, who discovered the viral particles within the tissue of BL tumors in 1964.[16] Virtually all cases of endemic BL are positive for EBV, and high serologic titers of EBV are associated with an increased risk of BL.[16] Children with endemic BL present with rapidly growing masses in the jaw or periorbital region, and extranodal sites including the ileum, cecum, gonads, kidney, and breasts (Table 1).[15,17] Notably, the bone marrow is involved in fewer than 10% of cases at initial presentation (a lower rate than other clinical variants) but often is a complication of disease relapse.[15,18] CNS involvement is also uncommon at diagnosis, but it is important to recognize that it typically presents as leptomeningeal disease manifested by cranial nerve palsies, whereas parenchymal brain involvement is very rare.[15]

Sporadic BL refers to cases that occur in immunocompetent patients outside of endemic regions. Sporadic BL is found primarily in North America and Western Europe, and accounts for 30% to 50% of pediatric NHL but only 1% to 2% of adult lymphomas. Sporadic BL in adults displays a slight male predilection, and the median age of diagnosis is between 30 and 40 years. Bimodal peaks occur at 10 and 75 years of age.[19] In contrast to endemic BL, only 40% of cases of sporadic BL are positive for EBV.[15] The abdominal region is frequently involved, with the most common site of involvement being the ileocecal region (Table 1). Therefore, patients may present with acute symptoms of abdominal pain, nausea, and vomiting that mimic small bowel obstruction or acute appendicitis, prompting urgent surgical consultation.[20,21] It is critical for clinicians to recognize the possibility of BL in patients with rapidly dividing abdominal masses prior to surgical intervention because complete resection is unnecessary. Bone marrow involvement occurs more commonly in sporadic BL than in endemic BL, and some cases are categorized as leukemia with extensive involvement of blasts (>25%) in the marrow. CNS involvement is present at diagnosis in 10% to 20% of cases.[21]

Immunodeficiency-associated BL most commonly arises in patients infected with HIV, although cases can occur after solid organ or stem cell transplant.[22] This variant makes up approximately 20% of cases seen in the United States annually.[22] Notably, BL often arises in cases of well-controlled HIV, when the CD4 count remains above 200 cells/mm$^3$, and the incidence of BL in HIV has not significantly declined despite the widespread use of highly active antiretroviral therapy (HAART).[23,24] HIV-associated BL typically includes nodal involvement but has a high frequency of dissemination to extranodal sites at diagnosis, including the CNS (~20%-30%), bone marrow (~30%), breast, gonads, and adrenals.[18]

Despite epidemiologic and clinical differences between the subsets of BL, the diagnostic work-ups are similar. Treatment approaches are not modified by the presence of EBV. The main difference across variants involves supportive care; patients with endemic BL may not have access to comprehensive medical care, and

**Table 1.** Clinical and Pathologic Features Across Burkitt Lymphoma Variants

| | Endemic | Sporadic | HIV-Associated |
|---|---|---|---|
| Annual Incidence | 5-15/10[5] | 2-3/10[6] | Unclear |
| Epidemiology | Equatorial Africa, malaria-endemic areas | Worldwide | Worldwide |
| Age | Median age, 4-7 y | Median age, 30 y | Median age, 44 y |
| Sex | M > F | M > F | M=F |
| Commonest Site(s) | Jaw/orbit | Ileocecal region | Extranodal sites |
| Bone Marrow | <10% | ~30% | ~30% |
| CNS (Leptomeningeal) | <10% | 10%-20% | 20%-30% |
| EBV-Associated | 100% | ~40% | 25%-40% |
| c-MYC Translocation | ~80% t(8;14); ~15% t(2;8); ~5% t(8;22) | | |

CNS, central nervous system; EBV, Epstein-Barr virus; F, females; M, males; NHL, non-Hodgkin lymphoma; y, year(s).

patients with an underlying immunodeficiency require careful attention to the risk of opportunistic infections and immune recovery after treatment.

## Pathobiology of Burkitt Lymphoma

BL is diagnosed based on morphologic, immunophenotypic, and molecular features. Morphologically, BL tumors show complete effacement of the normal lymph node architecture, with monotonous-appearing B cells. These B cells are small to intermediate in size and have round, basophilic nuclei and coarse chromatin.[18] Tumor cells may have small vacuoles and frequent mitoses, with proliferation rate growth fractions approaching 100%.[18] The biopsy specimen may have a characteristic "starry sky" appearance produced by intermittent benign histiocytes that have ingested apoptotic debris.[18,25]

The cell of origin in BL is a mature B cell derived from a germinal center. Immunohistochemistry on biopsy specimens or flow cytometry from fine needle aspirations will identify the malignant cells as positive for CD20, CD10, BCL6, CD79a, and CD45.[25,26] BL is negative for terminal deoxynucleotidyl transferase (TdT) and CD5, and in most cases cells do not express BCL-2.[5,25] The presence of EBV can be determined with in situ hybridization, such as Epstein-Barr encoding region (EBER) in situ hybridization. EBV is found in all cases of endemic BL and in approximately 20% to 40% of cases of sporadic and immunodeficiency-associated BL.[17,18] The establishment of an association between endemic BL and EBV was the first example of a human tumor to be causally associated with a virus.[15] It is postulated that latent EBV proteins induce genomic instability, dysregulate telomeres, and provoke DNA damage in endemic BL.[18,27] The frequent coinfection with malaria is also hypothesized to play a role in pathogenesis. In vitro studies suggest that *Plasmodium falciparum* deregulates expression of activation-induced cytidine deaminase (AID), an enzyme that induces hypervariable region mutations and class switch recombination in activated B lymphocytes.[3] Further, the dysregulation of AID induces the *MYC* translocation in cells latently infected with EBV.

BL was also the first NHL in which a chromosomal translocation was identified as the source for pathogenesis.[15] *MYC* gene activation is the hallmark of BL and is present across all clinical variants. The *MYC* gene, located at chromosome 8q24, is activated through 1 of 3 translocations involving an enhancer from either the immunoglobulin (Ig) heavy or light chain locus.[9] *MYC* is translocated to the Ig heavy chain locus on chromosome 14 (t[8;14]) in 70% to 80% of patients, near the kappa light chain on chromosome 2 (t[2;8]) in 15% of cases, and on the lambda light chain gene at chromosome 22 (t[8;22]) in 5% of cases.[5,28] The functional consequence of translocation places the master transcription factor, MYC, under the deregulated control of an Ig enhancer, leading to constitutive activation of cellular growth and proliferation signals. Importantly, some cases with morphologic features that resemble BL harbor no detectable *MYC* translocation.[4] The most recent lymphoma World Health Organization (WHO) classification system recognizes a provisional entity known as Burkitt-like lymphoma, which has an 11q aberration that typically lacks *MYC* translocations.[4] It remains unclear whether morphologic BL without *MYC* translocations represents a unique entity, or whether *MYC* is altered by alternative mechanisms.[4,5]

*MYC* translocations are not sufficient for tumorigenesis, and additional genetic events are required.[29] RNA sequencing studies have shown that 70% of cases harbor mutations in *TCF3* or its negative regulator *ID3*.[30] The functional consequence of these somatic mutations

is activation of the prosurvival phosphoinositide 3-kinase (PI3K) pathway and induction of antigen-independent B-cell receptor signaling. An in vivo study by Sander and colleagues demonstrated that constitutive MYC expression and PI3K activity in germinal center B cells lead to tumors with remarkable BL resemblance and an aggressive nature.[31] Other mutations described in BL include *CCND3, TP53, RHOA, SMARCA4,* and *ARIDIA,* but these occur in fewer than 40% of cases.[30] Such highly recurrent mutations may represent cooperative pathways in BL pathogenesis and possible future therapeutic targets.[32]

## Diagnosis of Burkitt Lymphoma

In patients with rapidly enlarging masses, particularly those involving the ileocecal region, BL should be suspected. Given the importance of prompt initiation of therapy, expedited biopsy of the mass with adequate tissue sampling is imperative. Up to 10% of patients may develop spontaneous tumor lysis syndrome, and clinicians should assess for electrolyte disturbances and prevent renal impairment.[33] Owing to rapid cell proliferation and turnover, serum lactate dehydrogenase (LDH) levels are significantly elevated. A diagnostic lumbar puncture with cytology and flow cytometry should be done in all patients because 15% to 30% will have CNS involvement.[34] Bone marrow involvement is defined as more than 5% malignant cells in 1 or more aspirates or bone marrow biopsies, whereas the term "Burkitt leukemia" refers to cases that include more than 25% blasts in the peripheral blood or bone marrow.[18,35] All tumor and/or bone marrow specimens should be evaluated for the presence of a *MYC* rearrangement using an appropriate fluorescence in situ hybridization (FISH) probe or conventional karyotyping.[36]

BL shares many biologic features with ALL. Historically, BL with extensive bone marrow involvement (>25%) was classified as Burkitt-type L3 ALL per the French-American-British (FAB) classification of hematologic diseases. L3 is a distinct morphologic ALL entity with cytogenetic (*MYC* translocations) and immunophenotypic characteristics identical to BL.[21,37] The WHO currently considers lymphoma and the leukemic phases of BL to be a single biologic entity.[21]

A persistent diagnostic challenge remains in distinguishing BL from diffuse large B-cell lymphoma (DLBCL) and other high-grade B-cell lymphomas that may have *MYC* translocations. Other aggressive B-cell lymphomas may have similar morphologic features, with evidence of germinal center origin.[3] Further, *MYC* rearrangements are not specific for BL, and can be seen in approximately 10% of adults with newly diagnosed DLBCL and up to 50% of high-grade B-cell lymphomas.[5,26,32] Given these overlapping features, the 2016 revised WHO classification of lymphoid malignancies removed the term "Burkitt-like lymphoma" and now specifies BL as a distinct entity from "Burkitt-like lymphoma with 11q aberration," "High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement," and "High-grade B-cell lymphoma, not otherwise specified."[4]

Gene expression profiling (GEP) studies have successfully distinguished between BL and DLBCL as distinct entities within the aggressive B-cell lymphoma spectrum.[36] For example, Dave and colleagues demonstrated that BL was readily distinguished from DLBCL via GEP, with an accuracy of 98% to 100%, and elucidated prominent clusters of BL-specific coordinately expressed gene signatures.[26] BL tumors demonstrated less overall genomic complexity, higher expression of the gene signature associated with germinal center B cells, and lower expression of nuclear factor–kappa B target genes.[26] Because GEP is not routinely available at initial diagnosis, pathologic confirmation of BL by an experienced hematopathologist is imperative. Immediate classification of BL as a distinct entity from DLBCL is crucial because patients treated with less dose-intensive regimens demonstrate poor survival.[10,38]

## Special Scenarios: HIV Seropositivity and CNS Involvement

Historically, the presence of immunodeficiency has complicated the use of intensive chemotherapy and has been associated with poor prognosis.[39] Patients with HIV often can tolerate intensive chemotherapy, but are at high risk for opportunistic infections.[40] Hoffman and colleagues retrospectively compared the use of ALL-like regimens with conventional chemotherapy based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in HIV-BL, and found that less-intensive therapy resulted in fewer cures.[40] Significantly more patients in the intensive chemotherapy group achieved remission, with fewer relapses and a trend toward improved survival.[40] With recent improvements in HAART and supportive care, patients with HIV-BL should not be treated with less-intensive regimens.

CNS involvement is a strong predictor of poor survival across multiple studies and in all age groups.[17,18] CNS involvement occurs more frequently in BL than in other NHL subtypes and has myriad clinical presentations, including cranial nerve palsies, headaches, and vomiting.[41] In a 2007 retrospective analysis of 2381 children with NHL, CNS involvement was diagnosed in 8.8% of patients with BL vs only 2.6% of patients with DLBCL. CNS involvement was typically associated with advanced-

stage disease.[7] Across all patients, CNS involvement was a stronger predictor of treatment failure than elevated LDH or bone marrow involvement.[7]

## Therapeutic Approaches

BL is highly sensitive to chemotherapy, and should be treated with curative intent.[35,36,38,42-45] Cure of BL requires systemic chemotherapy in all scenarios, including rare situations of completely resected disease. It is clear that common regimens used for DLBCL, such as CHOP, are inadequate; fewer than 30% of patients are cured with this approach. In a retrospective analysis of 28 patients with molecularly verified BL, those treated with a high-intensity chemotherapy backbone experienced longer survival than those treated with a CHOP-like regimen (2-year overall survival [OS], 55% vs 20%).[26]

In resource-rich areas, BL is often treated with high-intensity, fractionated ALL-type chemotherapy regimens, which have demonstrated excellent outcomes in pediatric and adolescent populations, albeit with significant short- and long-term complications. For instance, serious acute toxicities of these regimens include a high rate of grade 3/4 mucositis (40%-70%), myelosuppression (80%-100%), serious infections (60%-80%), prolonged hospitalization, and toxic death rates of 5% to 8%.[46,47] Toxicities are even more pronounced in adult populations because underlying comorbidities contribute to poor outcomes. The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) cancer registry database of BL cases from 2002 to 2008 confirms that estimated survival declines after age 40 years.[22]

Originally developed at the NCI, the combination of cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M) plus ifosfamide, mesna, etoposide, and cytarabine (IVAC) was among the first BL-specific regimens, and was described by Magrath and colleagues in 1996.[35] Using multiple known active agents, the regimen alternates cycles of CODOX-M with those of IVAC plus intrathecal (IT) methotrexate and cytarabine. The study by Magrath evaluated this regimen in 41 patients with newly diagnosed BL and B-cell ALL.[35] Using a risk-stratified approach, low-risk patients received 3 cycles of CODOX-M, whereas high-risk patients received 4 cycles of alternating CODOX-M/IVAC.[35] In this trial, CODOX-M/IVAC demonstrated a 2-year event-free survival (EFS) rate of 92% in a mixed adult and pediatric population. The rates of serious complications were high, however, with prolonged neutropenia in 100%, septicemia in 22%, and neuropathy in 26%, and a treatment-related mortality rate of 5% (Table 2).[35] Two international, prospective, confirmatory trials evaluated CODOX-M/IVAC in older adults with newly diagnosed BL but ultimately were unable to reproduce similar results, principally owing to the toxicity of the regimen.[36,42] The 2-year EFS and OS rates were 65% (95% CI, 51%-77%) and 72% (95% CI, 59.4%-86.3%), respectively.[36,42] Further, reductions in methotrexate dosing did not translate to improved tolerability, given that high rates of neutropenic fever (80%) and mucositis (45%) were observed.

Other adaptations of pediatric BL regimens to adult populations have been limited by treatment-related toxicity. The French Société Française d'Oncologie Pédiatrique published the results of LMB-89, a multicenter, prospective therapeutic trial of 561 children with mature B-cell lymphoma and ALL.[43] At diagnosis, patients were stratified into 1 of 3 risk groups: group A (resected stage I and abdominal stage II, no IT therapy, 2 induction cycles planned), group B (neither group A nor C, 4 induction cycles planned), or group C (CNS involvement or >70% blasts in bone marrow, 8 induction cycles planned). Treatment intensity was increased through the use of induction cyclophosphamide, vincristine, prednisone, and doxorubicin (COPAD) and the addition of consolidation and maintenance cycles (varying doses of methotrexate, cytarabine, vincristine, prednisone, and etoposide). Treatment was escalated based on the initial risk group and preliminary response to prephase treatment with cyclophosphamide, vincristine, and prednisone (COP).[43] Five-year EFS rates were 98% (95% CI, 90%-100%) in risk category A, 92% (95% CI, 89%-95%) in risk category B, and 84% (95% CI, 77%-90%) in risk category C. Acute toxicities were significant (Table 2), however, with 85% of patients developing neutropenic fever and 54% developing grade 3 or higher mucositis.[43] When the same protocol used in LMB-89 was adapted to an adult population, the 2-year EFS was 65% and the treatment-related mortality rate was 4%.[38]

Other trials have used risk adaptation and high-intensity, brief-duration chemotherapeutic regimens to maximize efficacy, but these approaches do not adequately overcome the problem of tolerability in adult patients (Table 2). The Berlin-Frankfurt-Münster (BFM) cooperative group developed a risk-adapted approach to pediatric BL, with de-escalation of treatment based on response to initial therapy. In the NHL-BFM 90 trial, 413 patients with NHL or B-ALL were risk stratified based on resection status, LDH levels, and burden of extranodal disease.[44] The number of fractionated cycles and the intensity of CNS treatment were predicated on risk category (R1: completely resected; R2: extra-abdominal, LDH <500 U/L; R3: abdominal primary, LDH ≥500 U/L, or bone marrow/CNS/multifocal bone disease) and response to prephase treatment.[44] The 6-year EFS rates corresponded with risk group, at 100% for R1, 96% for R2, and 78% for R3.[44]

**Table 2**. Outcomes and Toxicities of Select Regimens

| Reference (y) | Regimen | N | Median Age, y (range) | EFS/PFS/ FFP | OS | TRM | Grade 3/4 Neutropenia (Febrile/ Septic) | Other Grade 3/4 Toxicities |
|---|---|---|---|---|---|---|---|---|
| Magrath (1996)[35] | CODOX-M/IVAC | 41 | BL: 12 (3-17) B-ALL: 25 (18-59) | EFS: 92% @ 2 y | NA | 5% | 97.7%-100% (22%) | Mucositis: 58%; neuropathy: 63% |
| Mead (2002)[42] | Risk-adapted CODOX-M/IVAC | 52 | 35 (15-60) | EFS: 64.6% @ 2 y | 73% @ 2 y | 7% | 100% | Mucositis: 53%; diarrhea: 8% |
| Mead (2008)[36] | DM-CODOX-M/ IVAC | 53 | 37 (17-76) | EFS: 55% @ 2 y | 67% @ 2 y | 8% | 99% (80%) | Mucositis: 45%; neuropathy: 8% |
| Patte (2001)[43] | LMB-89 | 561 | 8 (2-18) | EFS: 92% @ 5 y | 92% @ 5 y | 1% | 85% (25%) | Mucositis: 54%; 2° malignancies: 1.4% |
| Diviné (2005)[38] | Modified LMB-89 | 72 | 33 (18-76) | EFS: 65% @ 2 y | 70% @ 2 y | 4% | (40%) | Mucositis: 12%-14% |
| Reiter (1999)[44] | NHL-BFM 90 | 413 | 9 (1.2-17.9) | EFS: 89% @ 6 y | NA | 2% | (37%) | Mucositis: 48% |
| Thomas (1999)[45] | Hyper-CVAD | 26 | 58 (17-79) | NA | 49% @ 3 y | 19% | (86%) | Atrial arrhythmia: 7% |
| Thomas (2006)[64] | R-hyper-CVAD | 31 | 46 (17-77) | EFS: 80% @ 3 y | 89% @ 3 y | 0% | 100% (25%-45%) | NA |
| Ribrag (2016)[10] | LMB + rituximab | 257 | <40 (39%), 40-60 (38%), >60 (23%) | EFS: 75% @ 3 y | NA | NA | 15%-17% | Mucositis: 9% |
| Dunleavy (2013)[59] | DA-EPOCH-R | 19 | 25 (15-88) | FFP: 95% @ 7 y | 100% @ 7 y | 0% | 52% (22%) | Mucositis: 6%; neuropathy: 21% |
| Dunleavy (2013)[59] | SC-EPOCH-RR | 11 | 44 (24-60) | FFP: 100% @ 6 y | 90% @ 6 y | 0% | 31% (10%) | Mucositis: 9%; neuropathy: 9% |
| Roschewski (2017)[60] | DA-EPOCH-R | 113 | 49 (18-86) | PFS: 85.7% @ 3 y | NA | 3% | NA | NA |

2°, secondary; B-ALL, B-cell acute lymphocytic leukemia; BFM, Berlin-Frankfurt-Münster regimen; BL, Burkitt lymphoma; CODOX-M, cyclophosphamide, vincristine, doxorubicin, and methotrexate; DA, dose-adjusted; EFS, event-free survival; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin; FFP, freedom from progression of disease; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; IVAC, ifosfamide, mesna, etoposide, and cytarabine; LMB, modified lymphoma malign B protocol; NA, not applicable; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; R, rituximab; RR, double dose of rituximab; SC, short-course; TRM; treatment-related mortality rate; y, year(s).

Even with a risk adaptation and de-escalation approach, however, substantial acute toxicity was observed, with 11 treatment-related deaths (9 from septicemia/enterocolitis) and 2 reported secondary malignancies.[44] In the early 2000s, investigators at the MD Anderson Cancer Center evaluated hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (hyper-CVAD) in patients with Burkitt-type (L3) ALL.[45] The 3-year OS rate in this study was 49% for the entire population, but treatment-related complications of prolonged myelosuppression were frequent. A high percentage of patients experienced neutropenic fever (86%) despite the use of granulocyte colony–stimulating factor, and the induction death rate was 19%.[45] Although many ALL-like regimens can achieve cure, the acute toxicity profiles remain significant barriers to effective treatment.

Providers must be cognizant of the potential for long-term complications in patients treated with high-intensity BL regimens. The 2006 Childhood Cancer

Survivor Study was a retrospective cohort analysis that tracked the health status of more than 10,000 survivors of pediatric cancer, including those treated for NHL, along with their healthy siblings.[47] In this study, 44% of adult survivors reported having at least 1 domain of health status that was moderately or severely affected, including general heath, mental health, functional status, activity, cancer-related pain, and cancer-related fear or anxiety.[48] Multiple long-term studies of NHL survivors have reported increased risks of developing second cancers compared with healthy population controls.[49] Radiation treatment, types of antecedent chemotherapeutic agent, and age at diagnosis are all risk factors for development of secondary malignancies.[50,51] In a 2011 meta-analysis of 23 long-term NHL survivor studies, the relative risk was 1.88 for secondary malignant neoplasms overall and 1.32 for solid tumors.[51] Patients must be counseled on the risk for potential chemotherapy-induced infertility prior to initiation of therapy. Although childhood survivors of acute leukemia or NHL are at relatively low risk for infertility or delayed puberty, pretreatment counseling and fertility preservation are recommended.[52] In a small retrospective analysis of long-term gonadal toxicity after therapy for NHL, 1 of 10 women (10%) and 3 of 14 men (21%) showed signs of gonadal dysfunction following intensive combination chemotherapy.[53] In young adults, the use of therapeutic strategies that reduce short-term and long-term chemotherapy-induced toxicities should be balanced against aggressive treatments that aim to cure.[38]

## CNS-Directed Therapy

Active treatment of CNS disease and CNS prophylaxis are essential components of the management strategy for BL. Most BL regimens employ high-dose methotrexate and/or cytarabine because these agents cross the blood-brain barrier, and they often include IT therapy. Still, it is controversial as to the most effective method for treating active CNS disease and preventing CNS recurrences. Notably, CNS progression and late relapses in the CNS occur despite the use of CNS-directed therapy in the ALL-like regimens.

In the CALGB-9251 trial (Combination Chemotherapy in Treating Patients With Non-Hodgkin's Lymphoma or Acute Lymphocytic Leukemia), patients received a combination of high-dose methotrexate triple IT chemotherapy along with whole-brain irradiation for CNS prophylaxis, but this approach was associated with severe neurologic toxicity.[54] Based on these results, prophylactic whole-brain irradiation is no longer considered acceptable and remains controversial in the treatment of active CNS disease.[55]

## Rituximab Added to Chemotherapy Improves Survival

Rituximab is a monoclonal antibody targeting CD20 that has been shown to be safe and effective in multiple phase 2 studies in BL.[56-59] Recently, a randomized phase 3 study has confirmed that rituximab improves EFS by approximately 15% when added to chemotherapy regimens modeled from the LMB protocols in adults with BL.[10] In this study, 124 adult HIV-negative patients were risk-stratified prior to therapy as group B (no CNS or bone marrow involvement) or group C (CNS or bone marrow involvement; further stratified by age [<40 years, 40-60 years, and >60 years] with or without CNS involvement). Patients with limited disease (group A) were excluded.[10] All patients were first treated with a debulking prephase of cyclophosphamide at 300 mg/m² on day 1, vincristine at 1 mg/m² (maximum, 2 mg) on day 1, and prednisolone at 60 mg/m² on days 1 to 7 (COP) and then randomly assigned to receive 1 intravenous injection of rituximab on day 1 of induction therapy or be treated with chemotherapy without rituximab. Patients in group B who responded to the COP prephase received 2 cycles of fractionated cyclophosphamide, doxorubicin, high-dose methotrexate, prednisone, and vincristine (COPADM) as induction therapy, followed by 2 cycles of fractionated cytarabine, methotrexate, and methylprednisolone (CYM) as consolidation. Maintenance treatment consisted of 1 cycle of high-dose methotrexate. Patients in group C and those who did not respond to the debulking prephase of COP also received induction therapy and maintenance, but had intensified therapy with a higher dose of methotrexate, triple IT injections, and enforced consolidation with high-dose cytarabine and etoposide. The patients in group C with CNS involvement also received cranial irradiation at 18 Gy during maintenance. After a median follow-up of 38 months, patients who were treated with rituximab had a superior EFS (hazard ratio [HR], 0.59; 95% CI, 0.38-0.94; $P$=.025) and OS (HR, 0.51; 95% CI, 0.30-0.86; $P$=.012) compared with the no-rituximab group.[10] Toxicity profiles were similar across the 2 groups, showing similar rates of grade 3/4 infections and duration of grade 4 neutropenia for patients treated with rituximab as compared with controls in each risk category. This study firmly established rituximab added to chemotherapy as the standard of care in BL.

## Infusional Regimen: Dose-Adjusted EPOCH-R or -RR

In contrast to high-intensity, rapid cycling strategies in ALL-based regimens, the therapeutic principle behind the infusional regimen of dose-adjusted etoposide,

prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) is based on length of exposure time, not maximal dose concentration. In vivo studies have demonstrated that lower-intensity therapy with prolonged exposure time renders BL cells susceptible to genotoxic stress, and thus maximizes tumor cell kill.[59] In addition to improved tolerability, advantages to this regimen include outpatient administration and omission of high-dose systemic methotrexate and cytarabine, leading to lower rates of severe myelosuppression.

The investigators from the NCI published a single-institution study challenging the principle that highly intensive ALL-based therapy was required for cure in adult patients with BL.[59] This study included 19 patients with sporadic BL and 11 patients with HIV-associated BL. Patients with sporadic BL were treated with 6 to 8 cycles of DA-EPOCH-R, and patients with HIV-associated BL were given short courses of EPOCH plus a double dose of rituximab each cycle (EPOCH-RR) for 3 to 6 cycles. One compelling reason to abbreviate the duration of therapy in HIV was to enable HAART to be withheld during chemotherapy. All patients were screened for the presence of CNS disease prior to therapy with flow cytometry of the cerebrospinal fluid (CSF). Patients with active CNS disease received twice-weekly IT methotrexate until clearance, followed by 6 weekly doses of IT methotrexate, and then 6 monthly doses of IT methotrexate. Patients without active CNS disease received CNS prophylaxis with IT methotrexate twice weekly during cycles 3 to 6, for a total of 8 doses. No intravenous methotrexate was allowed on this study.

After a median of 86 months of follow-up, the rates of freedom from progression of disease (FFP) and OS within the sporadic BL group were 95% and 100%, respectively. Among the HIV-BL patients, who were treated with short-course (SC) EPOCH-RR, FFP was 100% and OS was 90%.[59] Febrile neutropenia was observed in 10% of the SC-EPOCH-RR patients and 22% of the standard EPOCH-R patients, but no treatment-related deaths occurred.[59] The findings of this study suggested that most adults with BL could be cured without the use of maximal dose-intense ALL-like regimens.

Roschewski and colleagues presented preliminary results from NCI 9177 (Multicenter Prospective Phase II Study of DA-EPOCH-R), a confirmatory multicenter study using risk-adapted DA-EPOCH-R or -RR in 113 adult patients with either sporadic or HIV-associated BL (Figure).[60] All participants were older than 18 years, and patients with active CNS disease were included. Patients with and without HIV were treated with the same risk-adapted strategy. Study participants were considered low risk at diagnosis if they had Ann Arbor stage I or II disease, a normal LDH level, an Eastern Cooperative Oncology Group performance status of 0 or 1, and no tumor mass of 7 cm or greater, whereas all other patients were considered high risk. Low-risk patients received 2 cycles of DA-EPOCH-RR (2 doses of rituximab on day 1 of 5 of each cycle) and underwent a positron emission tomography (PET) scan. If the PET scan after 2 cycles was negative, they received only 1 additional cycle of DA-EPOCH-RR. If the PET scan after 2 cycles was positive, they crossed over into the high-risk arm. Low-risk patients were treated without any CNS-directed prophylaxis.

High-risk patients were treated with 2 cycles of DA-EPOCH-R and then underwent a PET scan. Regardless of the PET scan result, these patients were treated with 4 additional cycles of DA-EPOCH-R. Similar to the single-center study, all patients were screened for the presence of CNS disease prior to therapy with flow cytometry of the CSF. Patients with active CNS disease received twice-weekly IT methotrexate until clearance, followed by 6 weekly doses of IT methotrexate, and then 6 monthly doses of IT methotrexate. Patients without active CNS disease received CNS prophylaxis with IT methotrexate twice weekly during cycles 3 to 6 for a total of 8 doses. No intravenous methotrexate was allowed in this study.

Initial results after a median follow-up of 35.7 months for the entire cohort of 113 patients revealed an EFS of 85.7% (95% CI, 77.3%-91.1%), and all patients with low-risk disease (n=14) were cured.[60] Notably, age did not affect the outcomes, given that patients between the ages of 18 to 39 years, 40 to 50 years, and 60 years or older showed no difference in EFS, with rates of 83.3% (95% CI, 68.1%-91.1%), 87.1% (95% CI, 71.6%-94.4%), and 87.4% (95% CI, 65.2%-95.8%), respectively. Similarly, patients with HIV had an EFS that was identical to that of patients with sporadic BL. Patients with bone marrow or CNS involvement had an EFS of only 62.8% (95% CI, 42.9%-77.4%). Upon close examination of these cases, patients with active CNS disease at diagnosis had a high risk for early toxic death during cycle 1, and none had progression in the CNS. Six of 10 patients with active CNS disease were successfully treated, and the other 4 patients all died within the first 3 cycles of therapy, mostly from multisystem organ failure caused by sepsis. It is unlikely that more intensive ALL-like regimens would have prevented these early toxic deaths, but patients with active CNS disease remain a group that have a poorer prognosis across all regimens for BL.

The preliminary results from this multicenter study have confirmed that DA-EPOCH-R cures most adults with BL, regardless of HIV status or age. If the final published results are similar, then this will likely be the new standard of care for most adult patients with BL given the

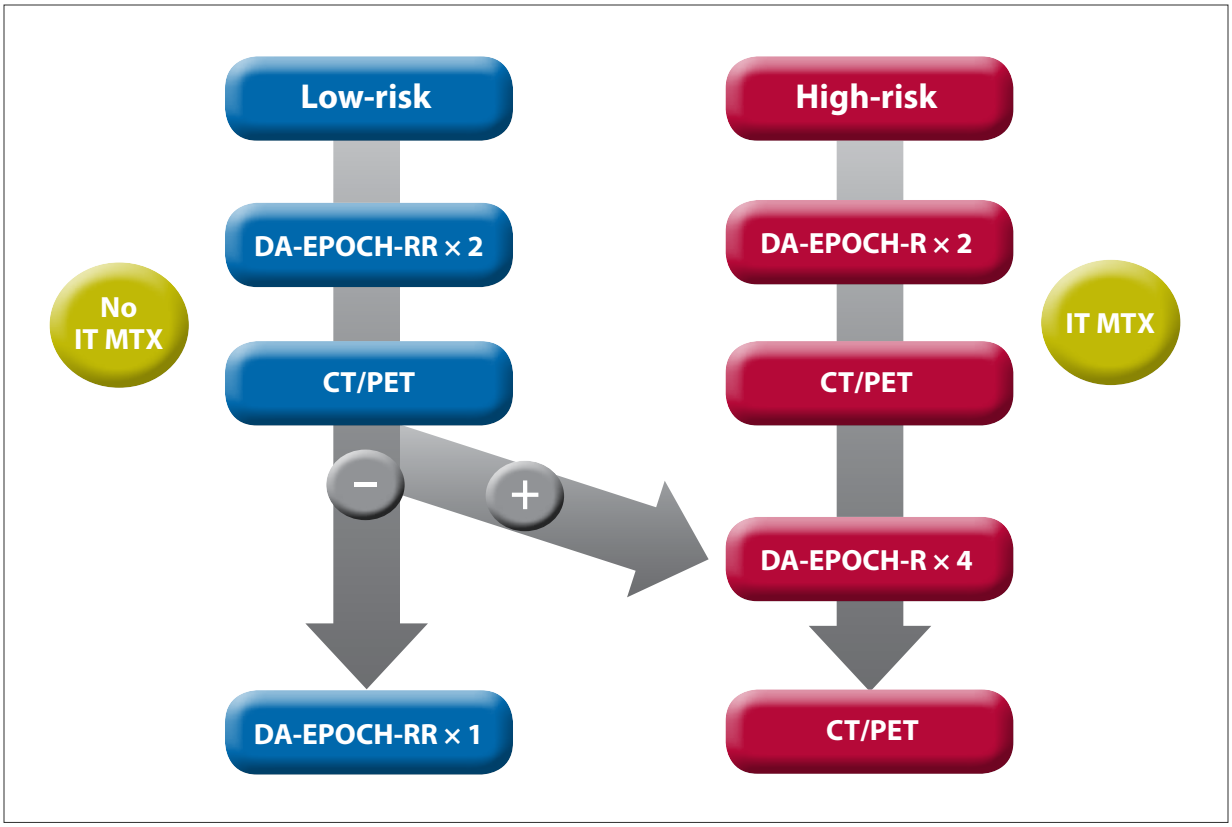


**Figure.** NCI 9177 treatment schema. Adult patients with Burkitt lymphoma were stratified into low-risk (Ann Arbor stage I or II disease, normal LDH, ECOG performance status of 0 or 1, and no tumor mass ≥7 cm) and high-risk (all other patients) categories. Low-risk patients received 2 cycles of DA-EPOCH-RR, then underwent a PET scan. If the PET scan was negative after 2 cycles, patients received only 1 additional cycle of DA-EPOCH-RR without CNS-directed prophylaxis. If the PET scan was positive, patients crossed over into the high-risk arm for 4 additional cycles of DA-EPOCH-R. High-risk patients were treated with 2 cycles of DA-EPOCH-R followed by interim PET scan. Irrespective of the PET scan result, high-risk patients were treated with 4 additional cycles of DA-EPOCH-R and CNS prophylaxis with intrathecal methotrexate.

Source: Roschewski M et al. ASH abstract 188. *Blood*. 2017;130(suppl 1).[60]

CT, computed tomography; DA-EPOCH-R, dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DA-EPOCH-RR, DA-EPOCH-R with a double dose of rituximab; IT, intrathecal; MTX, methotrexate; PET, positron emission tomography.

favorable toxicity profile and comparable results. Patients with low-risk disease can be cured without IT prophylaxis and only 3 cycles of therapy. An ongoing phase 3 study comparing R-CODOX-M/R-IVAC vs DA-EPOCH-R may further define the most effective regimen for adults with BL (EudraCT Number 2013-004394-27).

## Relapsed BL

Patients with BL who are not cured with frontline therapy have an extremely poor prognosis, and no clinical trials have established a standard approach to relapsed or refractory BL. In small retrospective analyses, patients with late relapse (>6 months from the time of first remission) had a median OS of 5 months, whereas patients with refractory disease or early relapse (<6 months) had a median OS of only 1.4 months ($P$<.001).[61] Salvage chemotherapy backbones have included hyper-CVAD; EPOCH; ifosfamide, carboplatin, and etoposide (ICE); methotrexate, vincristine, pegylated L-asparaginase, and dexamethasone (MOAD); and most recently, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, with varying degrees of success.[61,62] Although pediatric studies have demonstrated long-term survival of 30% to 35% with stem cell transplant (autologous and allogeneic) as consolidation following salvage therapy, limited data exist in the adults.[61] Clinical trial referral remains the preferred approach to relapsed or refractory BL.

## Supportive Care

Regardless of the treatment regimen, all patients with BL require advanced supportive care measures to decrease morbidity and limit treatment delays and dose reductions. Owing to rapid tumor cell proliferation, patients with BL may develop tumor lysis syndrome. Close monitoring of electrolytes, adequate hydration, and early institution of dialysis, if needed, should be instituted in all cases. Allopurinol should be initiated before chemotherapy, and the recombinant urate oxidase (rasburicase; Elitek, Sanofi-Aventis) can be used to prevent acute kidney injury if early evidence of laboratory tumor lysis syndrome is present. Prolonged myelosuppression is an expected risk of many of the ALL-like regimens. The use of granulocyte colony–stimulating factors can limit the duration of neutropenia, mitigate the incidence of neutropenic fever, and prevent treatment delays. In addition to prompt recognition and empiric treatment of suspected infections with appropriate antibacterial and antifungal agents, prophylactic antimicrobials may be considered.[63]

## Conclusion

BL is a highly aggressive B-cell lymphoma that can be cured with prompt diagnosis and timely administration of dose-intensive chemotherapy and supportive care. Owing to its dramatic presentation, clinicians must maintain a high index of suspicion and consider this a medical emergency. Delays in starting chemotherapy and arbitrary dose reductions may reduce the chance for cure. Even with prompt initiation of therapy, patients with BL are at risk for early complications, including early toxic death. Given the propensity of BL to spread to extranodal sites including the CNS, staging must include evaluation of the CSF, and most patients will require CNS-directed therapies.

Although dose intensity is critical for the cure of adults with BL, it appears equally possible to cure patients with regimens such as DA-EPOCH-R or -RR, which maintains high rates of cure with less toxicity than standard BL regimens that were developed in pediatric ALL. The improved toxicity profile of DA-EPOCH-R or -RR enables older patients to complete therapy and may spare younger patients the long-term risks associated with ALL regimens. Still, patients with CNS involvement at diagnosis remain at high risk for early death, and future trials should incorporate novel agents that penetrate the CNS to further improve the cure rate.

### *Disclosures*

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