How I Treat Burkitt lymphoma in adults

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Burkitt lymphoma (BL) is an aggressive B-cell non-Hodgkin lymphoma that is almost uniformly associated with translocations involving the gene for MYC on chromosome 8. The 3 subtypes of BL, endemic, sporadic, and immunodeficiency-associated, differ from epidemiologic and clinical perspectives but may be genetically similar. Prompt administration of multiagent immunochemotherapy regimens is associated with favorable outcomes for the majority of patients. Survival is inferior in older patients, likely reflecting increased therapy-related toxicity, possibly resulting in decreased treatment intensity. Central nervous system prophylaxis, tumor lysis prevention and treatment, and management of infectious complications from myelosuppressive regimens are critical. Prognosis of refractory or relapsed disease is poor and patients are best treated on clinical trials when available. (Blood. 2014;124(19):2913-2920)

Case

BG is a 40-year-old man with past medical history significant for type 2 diabetes, obesity, and hypertension who presented with hemoptysis. After receiving antibiotics for presumed sinusitis, he was started on prednisone with worsening bleeding. Subsequent laryngoscopic evaluation revealed a nasopharyngeal mass (4.8 x 2.2 cm on magnetic resonance imaging). On biopsy, the histologic appearance and immunophenotype (CD20 and CD10 positive, bcl-2 negative) were consistent with Burkitt lymphoma (BL). Fluorescence in situ hybridization confirmed t(8;14). Positron emission tomography (PET)/computed tomography (CT) revealed additional sites of disease in the liver and bone. Bone marrow biopsy showed 25% involvement. He had no fevers but complained of nondrenching sweats and 10-pound weight loss. Laboratory studies were notable for normal creatinine and complete blood count. Uric acid and lactate dehydrogenase (LDH) were elevated at 9.1 mg/dL and 538 U/L, respectively.

Introduction

BL is a highly aggressive B-cell non-Hodgkin lymphoma (NHL) with a doubling time of 25 hours. It is characterized by deregulation of the gene encoding MYC as a result of a chromosomal translocation most commonly involving the MYC gene locus on chromosome 8 and the immunoglobulin heavy chain (IgH) locus on chromosome 14 (t(8;14)). The first description of this disease was by Sir Albert Cook in 1887, although the disease was later described and defined by Dr Denis Burkitt in the 1950s.1,2 Today, we recognize 3 distinct subtypes of BL: endemic (African) BL, sporadic BL, and immunodeficiency-associated BL.

Epidemiology

Endemic BL is highly prevalent, with ~3 to 6 cases per 100 000 children per year in equatorial Africa.3 The incidence of endemic BL, which is uniformly Epstein-Barr virus (EBV) positive, has increased, coincident with an increase in HIV infection and malaria.4 Although Plasmodium falciparum is not felt to be oncogenic, the geographic colocalization of endemic BL and malaria has led to speculation that coinfection with P falciparum relates to the oncogenic potential of EBV.5 Although HIV infection is associated with an increased risk of immunodeficiency-associated BL, these lymphomas are often EBV negative. Sporadic BL is rare, accounting for 30% of pediatric lymphomas, and <1% of adult NHLs in the United States and Europe, or 2 to 3 cases per million persons per year.6,7 It is more common in younger individuals, with a peak incidence at 11 years of age in pediatric patients, and at 30 years of age in adults.8 Whites have a higher incidence of the disease, and men are more commonly affected at 3 to 4:1.6,9,10 These lymphomas are EBV-associated only 10% to 20% of the time.

Finally, immunodeficiency-associated BL is prevalent among patients with HIV infection, as opposed to patients with other causes of immunodeficiency. Because BL can develop regardless of a patient’s CD4 count, the incidence of immunodeficiency-associated BL has not declined in the era of antiretroviral therapy.11

Pathobiology

Genetics and pathogenesis

The discovery of the hallmark translocation t(8;14) in BL led to an appreciation of the role of MYC in human cancers.12-14 This translocation brings MYC under the control of IgH enhancer elements, resulting in its constitutive expression. BL typically has a simple karyotype.15 However, this translocation alone is not sufficient for malignant transformation and additional synergistic mutations are required.16-18 Many of these mutations, although common in BL, are uniformly absent in diffuse large B-cell lymphoma (DLBCL) and are therefore felt to be pathogenic. Thirty-eight percent of sporadic BL harbor mutations in the CCND3 gene encoding cyclin D3, which regulates the G1 to S transition during the cell cycle.19 Additional
common mutations include mutations that downregulate the activation of the proapoptotic protein, Bim\(^16\); inactivating mutations in TP53 (35%); deletions or inactivating mutations in CDK2NA, encoding p16 (17%)\(^{18}\), and mutations involving TCF-3 (E2A) and/or its negative regulator ID3\(^{16,18}\).

Gene expression profiling of BL reveals a pattern that is similar to normal germinal center centroblasts.\(^{15,20,21}\) Normally, centrocytes in the germinal center demonstrate a MYC gene expression pattern which is lost as centrocytes become centroblasts, perhaps due to repression by BCL6.\(^{22,23}\) The translocation involving MYC in BL results in the loss of upstream BCL6 binding sites and inappropriate MYC expression. MYC may augment the transcription of genes characteristic of the centroblast phenotype, and/or activate additional genes normally lacking in the centroblast. A majority of all BL harbor TCF-3 and/or ID3 mutations, and all BLs depend on TCF-3 for survival and proliferation, including cases in which these genes are not themselves mutated.\(^{17,18}\) The TCF-3 transcriptional program may endow the centrocyte-derived BL cell with a centroblast gene expression pattern.\(^{18}\) GEP in BL differs from DLBCL, with BL demonstrating higher expression of MYC target genes and a sub-group of germinal center B-cell genes, and decreased expression of major histocompatibility complex class I genes and NFκB target genes.\(^{15,20}\) Micro-RNA profiles from each of the BL subtypes are fairly homogenous and are distinct compared with DLBCL.\(^{24}\)

Although nearly all endemic BL, and a minority of sporadic BL, are EBV positive, the exact mechanism whereby EBV is pathogenic is not fully understood. EBV-encoded latency proteins expressed in EBV-transformed but nonmalignant lymphoblastoid cell lines modulate pathways such as phosphatidylinositol 3-kinase (PI3 kinase) and NFκB.\(^{25,26}\) However, BL primarily expresses the latent viral protein EBNA1, which is not clearly oncogenic in transgenic mouse models.\(^{27}\) One hypothesis is that cells expressing only EBNA1 are selected for because cells expressing other latent viral proteins are selected against by T cells that are specific for these other latent viral proteins, and that EBNA1-positive cells have been sufficiently transformed such that they are no longer dependent on these latent viral proteins for survival.\(^{28}\)

Pathology

Biopsies of BL demonstrate complete effacement of the normal tissue architecture by sheets of atypical lymphocytes which are medium-sized and highly monomorphic with round nuclei, multiple prominent nucleoli, and basophilic cytoplasm with prominent cytoplasmic lipid vacuoles. Interspersed among these atypical lymphocytes are benign histiocytes that are large and irregularly shaped and have ingested apoptotic tumor debris, which gives the classic “starry sky” appearance (Figure 1). The growth fraction, as measured by Ki-67, approaches 100%. In addition, BL cells are positive for IgM surface immunoglobulin (sIg) and surface light chains (κ > λ), CD19, CD20, CD22, CD79a, CD10, BCL6, HLA-DR, and CD43. They are negative for CD5, BCL-2, TdT, and CD23. BCL6 staining is independent of a translocation involving the BCL6 gene. EBV-associated BL will express CD21, the EBV/C3d receptor. MYC gene rearrangement is detected in up to 95% of BL with 80% of cases harboring a t(8;14) translocation. Fifteen percent and 5% of cases demonstrate translocations involving either the κ light chain gene on chromosome 2 (t(2;8)) or the λ light chain gene on chromosome 22 (t(8;22)), respectively.\(^{13,15,22}\) Twenty five percent of lymphomas that otherwise meet the morphologic, immunophenotypic, and genetic features of BL do not harbor a MYC gene rearrangement.\(^{30}\) The chromosomal breakpoints differ between endemic and sporadic BL, with the IgH joining region and the region just upstream of the MYC gene involved in endemic cases as opposed to the IgH switch region and intron 1 of the MYC gene in sporadic cases.\(^{31}\) Although EBV-negative BL exhibits low levels of somatic hypermutation and no signs of antigen selection, suggestive of an early centrocyte, EBV-positive BL has higher levels of somatic hypermutation and evidence of antigen selection so may arise from a B cell later in development.\(^{32}\)

The histopathology and immunohistochemical profile of BL is distinct from DLBCL and B-cell lymphoma unclassifiable with features intermediate between BL and DLBCL (B-cell lymphoma unclassifiable with features intermediate between BL and DLBCL [B-UNC/BL/DLBCL]) (Table 1). DLBCL is more heterogeneous with larger cells that resemble either centroblasts, or immunoblasts, which are larger cells with very prominent nucleoli and abundant cytoplasm, often with plasmacytoid features. Like BL, DLBCL expresses pan-B-cell markers including CD19, CD20, CD22, and CD79a. A majority express sIg, usually IgM, and BCL6.\(^{33}\) Unlike BL, these lymphomas can express BCL2, and rarely CD30 or CD5.\(^{34-36}\) CD10 expression and Ki67 staining are variable. B-UNC/BL/ DLBCL is characterized by intermediate/large cells with a high Ki67 index and are uniformly CD10\(^{+}\). They differ from BL in that the cells are more variable in size, are often BCL2\(^+\), and can be BCL6\(^+\) and have a lower Ki67 index (~90%). Both DLBCL and B-UNC/BL/ DLBCL can harbor translocations involving the MYC gene on chromosome 8, but whereas the partner gene is the IgH gene on chromosome 14 in 80% of BL cases, the partner is variable in these 2 entities. DLBCL and B-UNC/BL/DLBCL can be classified as “double hit” lymphomas, in 10% and 30% to 45% of cases, respectively, when they have coincident translocations involving the MYC gene and a second translocation, commonly involving the BCL2 gene, and these lymphomas are associated with a poor prognosis.\(^{37}\)

Clinical presentation and initial evaluation

Given the doubling time of this lymphoma, patients with BL typically present with rapidly enlarging masses and evidence of spontaneous tumor lysis and high serum LDH levels. Sporadic BL has a predilection for involving the abdomen and involves the bone marrow and central nervous system (CNS) in 30% and 15% of cases, respectively. Endemic BL classically presents with a jaw or facial bone tumor; it has a tendency to spread to extranodal sites but bone marrow involvement at presentation is uncommon. Immunodeficiency-associated BL principally involves lymph nodes, the bone marrow, and the CNS but may also present with peripheral blood involvement.\(^{30}\)

The initial evaluation of patients with BL determines the extent and prognosis of the disease. Pathologic diagnosis should be made by an experienced hematopathologist expert in lymphomas, given the overlap between this and other aggressive B-cell lymphomas (see Table 1). Laboratory evaluation includes a complete blood count and metabolic panel with liver function tests, as well as an LDH and uric acid. Testing for HIV and hepatitis B is indicated. Staging includes not only a CT scan of the chest, abdomen, and pelvis, but may also include a PET scan. A bone marrow biopsy is indicated, as is a staging lumbar puncture with cerebrospinal fluid analysis for cytology and flow cytometry, often with the administering of intrathecal (IT) therapy. The Murphy staging system, developed for the staging of childhood NHL, is predictive of outcomes; disease can also be classified as low or high risk based on the number of sites and bulk of disease, and LDH.\(^{38,39}\) Given the use of anthracyclines in treatment,
a pretreatment assessment of cardiac function is indicated. If there is evidence of spontaneous tumor lysis as evidenced by an elevated uric acid level, hyperphosphatemia, hyperkalemia, and an elevated LDH, patients should be started on allopurinol and IV hydration and rasburicase should be considered prior to beginning therapy.

In reported clinical trials, the prognosis for BL is generally favorable, with median survivals of 75% to 90% with modern chemoimmunotherapy regimens.40,41 An analysis of the Surveillance Epidemiology and End Results (SEER) database was less encouraging, however, with a 5-year overall survival (OS) of 56%, and better survival seen in younger patients with lower risk disease (87% and 71% for patients aged 0-19 years and for patients with low-risk disease, respectively).42,43 The impact of age on outcomes is likely multifactorial and reflects increased treatment toxicity or

Table 1. Histopathology, immunohistochemistry, and genetics of BL, DLBCL, and B-UNC/BL/DLBCL

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>DLBCL</th>
<th>B-UNC/BL/DLBCL</th>
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<tbody>
<tr>
<td><strong>Histopathology</strong></td>
<td>Medium-sized and highly monomorphic cells; multiple prominent nucleoli; basophilic cytoplasm; prominent cytoplasmic vacuoles. Interspersed benign histiocytes (classic “starry sky” appearance). Ki67 index &gt;95%.</td>
<td>Heterogeneous with larger cells; vesicular chromatin; multiple peripheral nucleoli; narrow rim of basophilic cytoplasm. Ki67 variable but usually &lt;90%.</td>
<td>Intermediate to large neoplastic cells but monomorphic.</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>CD19, CD20, CD22, CD79a, CD10, BCL6, HLA-DR, and CD43 positive. BCL-2, CD5, TdT, and CD23 negative.</td>
<td>CD19, CD20, CD22, and CD79a positive. BCL6 positive 60%-70% of time.</td>
<td>CD19, CD20, CD33, CD79a positive. BCL6 variable but often positive. Uniformly CD10 positive. Commonly BCL2 positive.</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>t(8;14) 80%; t(2;8) 15%; t(8;22) 5% No translocation involving BCL6 or BCL2.</td>
<td>No single cytogenetic change that is typical. “Double hit” cytogenetics with coincident translocations involving MYC and another locus, most often BCL2 30%-50%.</td>
<td>“Double hit” cytogenetics with coincident translocations involving MYC and another locus, most often BCL2 10%.</td>
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B-UNC/BL/DLBCL, B-cell lymphoma unclassifiable with features intermediate between BL and DLBCL.
were treated and the event-free survival (EFS) was 92% at 2 years. 40 Forty-one patients, including 20 adults, with a median age of 25 years, i received 2 cycles each of CODOX-M and IVAC. Toxicity was typ- with normal LDH received 3 cycles of CODOX-M. All other patients a single mass of disease recurrence. 40, 44 Patients with low-risk disease, de chemotherapy and severe myelosuppression was universal, and 20% of patients were unable to complete all therapy. In a subsequent study, investigators reduced the dose of methotrexate to 3 gm/m² for patients younger than 65 years of age and 1 gm/m² for patients older than 65 years of age and also reduced the dose of cytarabine in older patients to 1 gm/m². 46 Fifty-three patients with a median age of 37 years were treated. The 2-year progression free survival for all patients was 55% and was 85% and 49% for low- and high-risk patients, respectively. Similarly, the Cancer and Leukemia Group B (CALGB) developed a regimen consisting of a prephase of cyclophosphamide and prednisone, followed by 3 cycles each of ifosfamide, methotrexate, vincristine, cytarabine, etoposide, dexamethasone alternating with cyclophosphamide, methotrexate, vincristine, doxorubicin, dexamethasone. Initially, patients received 2400 Gy of cranial irradiation and 12 doses of IT chemotherapy. 47 Given severe neurologic toxicity, the study was amended and only patients with marrow involvement received radiotherapy (RT) and the number of IT doses decreased to 7. The 5-year OS in 92 patients was 52%. In a follow-up study, 105 patients were treated with the addition of rituximab in cycles 2 to 7. 48 The 2-year EFS and OS were 74% and 78%, respectively. Toxicity was significant with 7 therapy-related deaths.

Multiple groups in Europe have used ALL regimens in BL. The French LMB group treated 72 patients, median age 33 years, with L3

Table 2. Regimens and outcomes for the upfront therapy of BL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>N</th>
<th>Median age, y</th>
<th>Risk</th>
<th>TRM</th>
<th>EFS/PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>CODOX-M/IVAC</td>
<td>41 (20 adults)</td>
<td>25</td>
<td>High risk</td>
<td>0</td>
<td>2-y EFS</td>
<td>92%</td>
</tr>
<tr>
<td>45</td>
<td>CODOX-M/IVAC</td>
<td>52</td>
<td>35</td>
<td>High risk</td>
<td>5</td>
<td>2-y EFS</td>
<td>2-y OS</td>
</tr>
<tr>
<td>46</td>
<td>CODOX-M/IVAC</td>
<td>53</td>
<td>37</td>
<td>High risk</td>
<td>9</td>
<td>2-y PFS</td>
<td>2-y OS</td>
</tr>
<tr>
<td>47</td>
<td>CALGB regimen</td>
<td>Cohort 1</td>
<td>52</td>
<td>IPI ≥ 3</td>
<td>10</td>
<td>3-y EFS</td>
<td>3-y OS</td>
</tr>
<tr>
<td></td>
<td>CALGB regimen</td>
<td>Cohort 2</td>
<td>40</td>
<td>High LDH</td>
<td>7</td>
<td>2-y EFS</td>
<td>2-y OS</td>
</tr>
<tr>
<td>48</td>
<td>CALGB regimen</td>
<td>105</td>
<td>44</td>
<td>IPI ≥ 3</td>
<td>47%</td>
<td>74%</td>
<td>78%</td>
</tr>
<tr>
<td>49</td>
<td>HyperCVAD</td>
<td>26</td>
<td>58</td>
<td>High LDH</td>
<td>5</td>
<td>3-y CCR</td>
<td>3-y OS</td>
</tr>
<tr>
<td>51</td>
<td>SC-REPOCH-RR</td>
<td>11 (HIV+)</td>
<td>44</td>
<td>High LDH</td>
<td>0</td>
<td>EFS†</td>
<td>OS†</td>
</tr>
</tbody>
</table>

CALGB, Cancer and Leukemia Group B; CCR, continuous completer remission; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; DA-REPOCH, dose-adjusted rituximab, etoposide, vincristine, cyclophospha- mide, doxorubicin; EFS, event-free survival; IPI, International Prognostic Index; IVAC, ifosfamide, etoposide, cytarabine; LDH, lactate dehydrogenase; LMB, lymphoma malign B; OS, overall survival; PFS, progression-free survival; SC-REPOCH-RR, short-course REPOCH with a double dose of rituximab; TRM, treatment-related mortality.

*Median follow-up 86 mo.
†Median follow-up 73 mo.
ALL and BL with a risk-adapted regimen. Patients with resected stage I or stage II abdominal disease (8%) were treated with 3 cycles of vincristine, cyclophosphamide, and doxorubicin. Patients with high-risk disease (22%) defined as marrow and/or CNS disease received 8 courses of therapy including a prephase and high-dose methotrexate, cytarabine, and etoposide with IT methotrexate. All other patients (70%) received 5 cycles of therapy similar to the high-risk patients. The 2-year EFS and OS were 65% and 70%, respectively.

In a regimen designed to preserve efficacy while reducing toxicity, Dunleavy and colleagues studied the infusional regimen, dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, adriamycin) plus rituximab (DA-REPOCH). CNS prophylaxis consists of 8 doses of IT methotrexate with additional doses for patients with leptomeningeal involvement. HIV-positive patients received 1 cycle beyond complete remission (3-6 cycles) and were not dose adjusted. All other patients received 2 cycles past complete remission (6-8 cycles). Thirty patients were treated, including 11 with HIV. With a median follow-up of >6 years, the DA-REPOCH patients achieved a freedom from progression of 95% and OS of 100%. The failure-free survival and OS in the SC-EPOCH-RR (short-course REPOCH with a double dose of rituximab) patients were 100% and 90%, respectively. Febrile neutropenia rates were low and no treatment related deaths occurred. Although the results of the DA-REPOCH regimen are excellent, the patients treated in the study were quite favorable. The median age of the HIV-negative patients was 25 years. Overall, 53% of patients had an elevated LDH at baseline, including only 37% of the HIV-negative patients, and only 1 patient had CNS disease. A confirmatory multi-institutional study is currently ongoing. In addition, the European HOVON group is conducting a randomized study of DA-REPOCH vs CODOX-M/IVAC.

### Role of rituximab

The impact of rituximab has not been as well studied in BL compared with many other B-cell NHLs. Preliminary results of a large randomized study in 257 adults comparing the LMB regimen with and without rituximab demonstrated significant improvement in 3-year EFS and OS in the rituximab containing arms at 76% vs 64% and 82% vs 71%, respectively. Toxicity was comparable in both groups. In comparing the 2 HyperCVAD trials, the outcome in the rituximab-containing study was clearly superior. Both a lower median age and improvements in supportive care over time, however, may also have contributed to the better outcome in the R-HyperCVAD study. In addition, Barnes et al also compared outcomes in 80 patients treated with CODOX-M/IVAC with or without rituximab and found a trend toward improved survival with PFS and OS of 74% vs 61% and 77% vs 66%, respectively.

### Stem cell transplantation

Several studies have evaluated the role of autologous transplantation for patients in first remission. Forty-three patients with BL were treated with various relatively less-intensive induction regimens, 27 of whom underwent transplant with the majority of remaining patients having chemorefractory disease. The 3-year EFS and OS were 42% and 45%, respectively. These results highlight the importance of the rapid institution of aggressive, multiagent chemotherapy. The HOVON group evaluated brief initial high-dose chemotherapy consisting of 2 cycles of cyclophosphamide, doxorubicin, etoposide, mitoxantrone, and prednisone followed by autologous stem cell transplantation using carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning. The 5-year EFS and OS for 27 patients was 73% and 81%, respectively.

A retrospective analysis of 117 patients with BL who underwent autologous stem cell transplant between 1984 and 1994 in first remission revealed an OS of 53% at 3 years. Disease status at transplant was predictive of outcome with 3-year OS of 72% for those in first complete remission, 37% for patients with chemotherapy-sensitive, and only 7% for those with chemotherapy-resistant disease. For patients who underwent upfront autologous stem cell transplant, the PFS appears to be comparable to aggressive chemotherapy alone.

### Relapsed or refractory disease

 Patients with BL who fail initial chemotherapy typically experience progressive disease during or soon after the completion of upfront treatment. Unfortunately, few studies have evaluated salvage regimens in this setting, and the majority of patients have already received the most active agents in this disease. As above, patients with chemotherapy-sensitive disease may achieve long-term remissions, but the outcome of patients with chemotherapy-resistant disease is dismal.

### HIV-positive BL

Several recent studies suggest that patients with HIV-related BL experience similar outcomes compared with HIV-negative patients when treated with the same intensive chemotherapy regimens. In the majority of studies, with the exception of REPOCH, patients receive concurrent highly active antiretrovirals. One hundred eighteen patients (80 HIV-negative and 38 HIV-positive) were treated with intensive chemotherapy plus rituximab. Patients with bulky stage I-II disease received 4 cycles of treatment and all others received 6 cycles, and dose reductions were applied to patients >55 years of age. The 4-year disease free survival and OS were not significantly different in HIV-positive compared with HIV-negative patients at 77% and 63% vs 80% and 78%.

### Recommendation

In patients younger than 60 years of age, including those with well-controlled HIV, and those up to 70 years of age with good baseline functional status, previously normal marrow reserve and immune status without significant underlying cardiac or renal dysfunction, we favor the modified-Magrath regimen. Patients with extensive disease and elevated LDH receive 2 cycles each of R-CODOX-M and R-IVAC (Table 3). For patients with low-risk disease, defined as a single site of disease <10 cm with a normal LDH, we administer 3 cycles of R-CODOX-M. Although the regimen is associated with significant toxicity, the inclusion of high-dose methotrexate and cytarabine provides excellent therapy and prophylaxis against disease involving the CNS. One minor alteration in the regimen, suggested by the AIDS Malignancy Consortium, is to administer high-dose...
methotrexate on day 15 after giving peg-filgrastim on day 3. By doing so, methotrexate is not administered during the nadir from CODOX when patients are susceptible to the development of febrile neutropenia. R-IVAC is administered following count recovery and clearance of methotrexate, typically on day 22. Approximately 21 days following the initiation of R-IVAC, the absolute neutrophil count and platelets have reached 1500 and 100,000, respectively, and patients start cycle 2 of R-CODOX-M. The first dose of rituximab should be delayed until at least day 3 in patients with elevated LDH to minimize the risk of tumor lysis and infusional reactions. Growth factors and blood product support are necessary to maintain dose intensity, which is critical for this highly aggressive disease.

Patients must receive tumor lysis prophylaxis with aggressive hydration and allopurinol. Patients with LDH >2 times the upper limit of normal, renal dysfunction who cannot tolerate brisk intravenous fluids, or patients who develop evidence of active tumor lysis should receive rasburicase. Intensive supportive care is critical with careful monitoring of cytopenias and nearly all patients will require blood product support. Febrile neutropenia is a frequent complication, particularly after R-IVAC, and patients must be counseled to seek immediate medical attention with fevers and antibiotic prophylaxis, particularly directed against gram-negative bacteria, should be considered.

For patients with preexisting organ dysfunction, or significant comorbidities and patients older than 60 years of age with low-risk disease, defined as low volume disease with a normal LDH, we prefer DA-REPOCH. In patients who are not candidates for more aggressive approaches and who have leptomeningeal disease or are at high risk for CNS recurrence with circulating disease, we consider incorporating high-dose systemic methotrexate, as we have seen patients with CNS recurrence with IT therapy only. The optimal timing, however, has not been well studied and the intercalation of methotrexate between cycles of REPOCH may impact the ability to appropriately dose escalate, and/or lead to delays in initiating the subsequent cycle. One option is to administer IT therapy during REPOCH and then administer systemic methotrexate upon the completion of cycle 6.

On occasion, a patient with BL will present with hyperbilirubinemia as a result of hepatic infiltration by disease and cannot receive doxorubicin or vincristine, given both drugs are metabolized by the liver. In this situation, we use the CALGB prephase of cyclophosphamide (200 mg/m² × 5 days) with 100 mg/m² of prednisone for 7 days. At the completion of the cycle, the bilirubin has typically normalized and we then initiate CODOX-M/IVAC. We also use the prephase in patients with very high white counts due to circulating disease and extensive marrow infiltration by lymphoma to prevent severe tumor lysis. With the availability of rasburicase, the incidence of tumor lysis syndrome has decreased. During cycle 1, we withhold rituximab until at least day 3, but often until cycle 2, as patients with significant disease burden are likely to experience severe infusion-related events.

For relapsed or refractory disease in patients who have not received prior cytarabine, regimens such as dexamethasone, cytarabine, cisplatin or etoposide, methylprednisolone, cytarabine, cisplatin may be considered. Gemcitabine-based regimens, such as gemcitabine, dexamethasone, and cisplatin, are an option for patients who have received cytarabine. Unfortunately, the vast majority of patients will not respond to additional chemotherapy. Responders should undergo stem cell transplantation, but the outcome for patients with active disease at the time of transplant is dismal. We encourage patients to consider well-designed clinical trials, though given the rapid progression of disease in BL, many will not be eligible. The bromo and extra terminal (BET) bromodomain inhibitors which target MYC are currently in clinical trials and may eventually improve outcomes in newly diagnosed and relapsed patients.

**Case**

B.G. was treated with CODOX. Rituximab was attempted on day 3 but was complicated by a grade 3 infusion reaction. His symptoms rapidly resolved and his LDH normalized by day 16 when he received methotrexate and vincristine with rituximab. He went on to complete the full course of 2 cycles each of R-CODOX-M/IVAC. His course was complicated by febrile neutropenia and pancytopenia after both cycles of R-IVAC, as well as reversible acute kidney injury, likely secondary to antibiotics. He achieved a complete remission.

**Conclusion**

BL is a highly aggressive disease, driven by the overexpression of MYC, with a favorable outcome when treated with intensive multiagent chemotherapy and rituximab. Therapy is toxic and results in significant myelosuppression and potentially life-threatening complications. Current studies are under way to compare less-intensive therapy to more traditional approaches. Novel therapies targeting MYC and other contributing pathways, including inhibitors of BET
bromodomain and PI3 kinase hold the promise of further improving outcomes in BL.

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