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 three subtypes of BL, endemic, sporadic, and immunodeficiency-associated, differ from epidemiologic and clinical perspectives but may be genetically similar. Prompt administration of multi-agent 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.

Case
BG is a 40 year old male 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 MRI). On biopsy, the histologic appearance and immunophenotype (CD20 and CD10 positive, bcl-2 negative), were consistent with Burkitt lymphoma. FISH confirmed t(8;14). PET/CT revealed additional sites of disease in the liver and bone. Bone marrow biopsy showed 25% involvement. He had no fevers but complained of non-drenching sweats and ten pound weight loss. Laboratory studies were notable for normal creatinine and CBC. Uric acid and LDH were elevated at 9.1 mg/dL and 538 U/L respectively.

Introduction
Burkitt Lymphoma (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 three distinct subtypes of BL: endemic (African) BL, sporadic BL, and immunodeficiency-associated BL.

Epidemiology
Endemic BL is highly prevalent, with approximately 3-6 cases/100,000 children/year in equatorial Africa.5 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 While 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 While 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 2-3 cases per million persons/year.6,7 It is more common in younger individuals, with a peak incidence at age 11 in pediatric patients, and at age 30 in adults.8 Caucasians have a higher incidence of the disease, and men are more commonly affected at 3-4:1.6,9,10 These lymphomas are EBV-associated only 10-20% of the time.
Finally, immunodeficiency-associated BL is prevalent amongst 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, while common in BL, are uniformly absent in diffuse large B cell lymphoma (DLBCL) and are therefore felt to be pathogenic. 38% of sporadic BL harbor mutations in the CCND3 gene encoding cyclin D3, which regulates the G1 to S transition during the cell cycle.18 Additional common mutations include mutations that downregulate the activation of the proapoptotic protein, Bim;19 inactivating mutations in TP53 (35%); deletions or inactivating mutations in CDKN2A, encoding p16 (17%);18 and mutations involving TCF-3 (E2A) and/or its negative regulator ID3.16-18 Gene expression profiling (GEP) 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 subgroup of germinal center B cell genes, and decreased expression of major histocompatibility-complex (MHC) class I genes and NFκB target genes.15,20 Micro RNA (miRNA) profiles from each of the BL subtypes are fairly homogenous and are distinct compared to 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 non-malignant lymphoblastoid cells lines modulate pathways such as 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 (kappa > lambda), 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. 15% and 5% of cases demonstrate translocations involving either the kappa light chain gene on chromosome 2 (t(2;8)) or the lambda light chain gene on chromosome 22 (t(8;22)) respectively. 13,15,29 5% 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 While 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-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 two entities. DLBCL and B-UNC/BL/DLBCL can be classified as “double hit” lymphomas, in 10% and 30-45% 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 lactate dehydrogenase (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 a computed tomography (CT) scan of the chest, abdomen and pelvis, but may also include a positron emission tomography (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 intravenous (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 75-90% 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 decreased treatment intensity in older individuals, as well as the potential misclassification of disease in this population.

Initial Therapy
The optimal initial therapy of BL has not been clearly defined given the paucity of randomized studies in this uncommon disease. Multiple intensive regimens demonstrate excellent activity in BL and are comprised of doxorubicin, alkylators, vincristine, and etoposide combined with therapy directed at the eradication and/or prevention of CNS disease (Table 2).

In the late 1980’s Magrath and colleagues developed CODOX-M/IVAC (cyclosphosphamide, doxorubicin, vincristine, methotrexate, ifosfamide, cytarabine and etoposide) given that more than half of children and adults treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with methotrexate experienced disease recurrence.40,44 Patients with low risk disease, defined as a single mass of <10cm or completely resected abdominal disease with normal LDH received 3 cycles of CODOX-M. All other patients received 2 cycles each of CODOX-M and IVAC. Toxicity was typified by severe myelosuppression and infections, including sepsis. 41 patients, including 20 adults, with a median age of 25, were treated and the event free survival (EFS) was 92% at 2 years.40
Subsequent studies of CODOX-M/IVAC in adult patients with BL demonstrate good activity of the combination, though the outcome of adult patients is inferior compared to that of children and young adults. The inclusion of patients with atypical BL almost certainly contributes to the lower OS, as evidence suggests that a portion of these patients may have double hit lymphomas. In 52 adult patients with BL, median age 35, treated with CODOX-M/IVAC, the 2 year OS in low and high-risk patients, as defined by the original Magrath study, was 82% and 70% respectively. As expected, 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 < 65 and 1 gm/m² for patients > 65 and also reduced the dose of cytarabine in older patients to 1 gm/m². 53 patients with a median age of 37 were treated. The 2 year progression free survival (PFS) 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 cGY of cranial irradiation and 12 doses of IT chemotherapy. 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 2-7. The 2 year EFS and OS were 74% and 78% respectively. Toxicity was significant with seven therapy-related deaths.

The group at MD Anderson developed HyperCVAD to treat acute lymphoblastic leukemia (ALL) and BL. Patients receive 4 cycles each of hyperfractionated cyclophosphamide with doxorubicin, vincristine and dexamethasone alternating with 4 cycles of metotrexate and high dose cytarabine. In their initial study of 26 adults, five patients died during induction. The 3 EFS was 49% and was 77% and 17% for patients under and over age 60 respectively. In a subsequent prospective study of 31 patients treated with rituximab plus HyperCVAD, the 3 year OS was significantly improved at 89%. 73% of patients completed all therapy and severe myelosuppression was universal.

Multiple groups in Europe have employed ALL regimens in BL. The French LMB group treated 72 patients, median age 33, with L3 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 etopoide 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, adraimycin) 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 one cycle beyond complete remission (3-6 cycles) and were not dose adjusted. All other patients received 2 cycles past complete remission (6-8 cycles). 30 patients were treated, including 11 with HIV. With a median follow-up of more than 6 years, the DA-REPOCH patients achieved a freedom from progression of 95% and OS of 100%. The failure free survival (FFS) and OS in the SC-EPOCH-RR patients were 100% and 90% respectively. Febrile neutropenia rates were low and no treatment related deaths occurred. Although the results of DA-REPOCH regimen are excellent, the patients treated in the study were quite favorable. The median age of the HIV-negative patients was 25. 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 versus CODOX-M/IVAC.

**Role of rituximab**

The impact of rituximab has not been as well studied in BL compared to 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 two 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 towards 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. 43 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, multi-agent chemotherapy. The HOVON group evaluated brief initial high dose chemotherapy consisting of 2 cycles of cyclophosphamide, doxorubicin, etoposide, mitoxantrone, and prednisone followed by ASCT 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 Burkitt lymphoma 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.56

HIV-Positive BL
Several recent studies suggest that patients with HIV related BL experience similar outcomes compared to 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 anti-retrovirals.57118 patients (80 HIV negative and 38 HIV positive) were treated with intensive chemotherapy plus rituximab.58 Patients with non-bulky stage I-II disease received 4 cycles of treatment and all others received 6 cycles, and dose reductions were applied to patients >55. The 4 year disease free survival (DFS) and OS were not significantly different in HIV-positive compared with HIV-negative patients at 77% and 63% versus 80% and 78%.

Recommendation
In patients <60, including those with well controlled HIV, and those up to age 70 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.59 Patients with extensive disease and elevated LDH receive 2 cycles each of R-CODOX-M and R-IVAC (Figure 2). For patients with low risk disease, defined as a single site of disease less than 10cm 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 pegfilgrastim on day 3.60 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 1,500 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 rasbusicase. 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 pre-existing organ dysfunction, or significant co-morbidities and patients >60 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 have leptomeningeal disease or 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 employ the CALGB prephase of cyclophosphamide (200mg/m2 x 5 days) with 100mg/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 TLS 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 DHAP or ESHAP may be considered. Gemcitabine based regimens, such as gemcitabine, dexamethaone 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 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:
Burkitt lymphoma is a highly aggressive disease, driven by the overexpression of MYC, with a favorable outcome when treated with intensive multi-agent chemotherapy and rituximab. Therapy is toxic and results in significant myelosuppression and potentially life-threatening complications. Current studies are underway to compare less intensive therapy to more traditional approaches. Novel therapies targeting MYC and other contributing pathways,
including inhibitors of BET bromodomain and PI3kinase hold the promise of further improving outcomes in BL.

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Table 1. Histopathology, immunohistochemistry, and genetics of Burkitt Lymphoma (BL), diffuse large B cell lymphoma (DLBCL), and B cell lymphoma unclassifiable with features intermediate between BL and DLBCL (B-UNC/BL/DLBCL)

<table>
<thead>
<tr>
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<th>BL</th>
<th>DLBCL</th>
<th>B-UNC/BL/DLBCL</th>
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<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 Ki67 intermediate between BL and DLBCL but high (~90%)</td>
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<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. BCL2, CD10, CD5, CD30 and CD5 variable.</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%</td>
<td>No single cytogenetic change that is typical &quot;Double hit&quot; cytogenetics with coincident translocations involving MYC and another locus, most often BCL2 10%</td>
<td>&quot;Double hit&quot; cytogenetics with coincident translocations involving MYC and another locus, most often BCL2 30-50%</td>
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Table 2. Regimens and outcomes for the upfront therapy of Burkitt Lymphoma

<table>
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<tr>
<th>Reference</th>
<th>Regimen</th>
<th>N</th>
<th>Median Age</th>
<th>Risk</th>
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<th>EFS/PFS</th>
<th>OS</th>
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<tr>
<td>Magrath 1996</td>
<td>CODOX-M/IVAC</td>
<td>41</td>
<td>25</td>
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<td>2 yr EFS 92%</td>
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<td></td>
<td>20 adults</td>
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<td></td>
<td>2 yr PFS 65%</td>
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<td>52</td>
<td>35</td>
<td>high risk</td>
<td>5</td>
<td>2 yr EFS 77%</td>
<td>2 yr OS 73%</td>
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<tr>
<td>Mead 2008</td>
<td>CODOX-M/IVAC</td>
<td>53</td>
<td>37</td>
<td>high risk</td>
<td>9</td>
<td>2 yr PFS 79%</td>
<td>2 yr OS 67%</td>
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<td>Rizzieri 2004</td>
<td>CALGB regimen</td>
<td>52</td>
<td>44</td>
<td>IPI ≥ 3</td>
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<td>3 yr EFS 79%</td>
<td>3 yr OS 54%</td>
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<td></td>
<td>Cohort 1</td>
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<td>2 yr PFS 45%</td>
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<td>Cohort 2</td>
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<td></td>
<td>2 yr OS 50%</td>
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<tr>
<td>Rizzieri 2014</td>
<td>CALGB regimen</td>
<td>105</td>
<td>44</td>
<td>IPI ≥ 3</td>
<td>7</td>
<td>3 yr EFS 74%</td>
<td>2 yr OS 78%</td>
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<td>(IPI &gt; 3)</td>
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<td>Thomas 1999</td>
<td>HyperCVAD</td>
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<td>high LDH</td>
<td>5</td>
<td>3 yr CCR 61%</td>
<td>3 yr OS 49%</td>
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<tr>
<td></td>
<td>(IPI &gt; 3)</td>
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<td>Thomas 2006</td>
<td>R-HyperCVAD</td>
<td>31</td>
<td>46</td>
<td>high LDH</td>
<td>1</td>
<td>3 yr EFS 80%</td>
<td>3 yr OS 89%</td>
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<tr>
<td>Divine 2005</td>
<td>LMB regimen</td>
<td>72</td>
<td>33</td>
<td>high LDH</td>
<td>0</td>
<td>2 yr EFS 65%</td>
<td>2 yr OS 70%</td>
</tr>
<tr>
<td></td>
<td>(IPI &gt; 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunleavy 2013</td>
<td>DA-REPOCH</td>
<td>19</td>
<td>25</td>
<td>High LDH</td>
<td>0</td>
<td>EFS*** 95%</td>
<td>OS*** 100%</td>
</tr>
<tr>
<td></td>
<td>(HIV-)</td>
<td></td>
<td></td>
<td>37%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dunleavy 2013</td>
<td>SC-REPOCH-RR</td>
<td>11</td>
<td>44</td>
<td>High LDH</td>
<td>0</td>
<td>EFS*** 90%</td>
<td>OS*** 100%</td>
</tr>
<tr>
<td></td>
<td>(HIV+)</td>
<td></td>
<td></td>
<td>82%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*EFS – event free survival; PFS – progression free survival; OS – overall survival; CODOX-M/IVAC – cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine; CALGB – Cancer and Leukemia Group B; DA-REPOCH – dose adjusted rituximab, etoposide, vincristine, cyclophosphamide, doxorubicin; SC-REPOCH-RR – short course REPOCH with a double dose rituximab

** Median follow-up 86 months

***Median follow-up 73 months
References


60. *A Modified Dose Intensive R- CODOX-M/IVAC For HIV-Associated Burkitt and Atypical Burkitt Lymphoma(BL) Demonstrates High Cure Rates and Low Toxicity: Prospective Multicenter Phase II Trial Of The AIDS Malignancy Consortium (AMC 048).* Vol 1222013.

Figure 1. Histopathology of Burkitt Lymphoma (courtesy of Dr. Scott Rodig, Harvard Medical School, Brigham and Women's Hospital Department of Pathology). Low (A) and high (B) power field hematoxylin and eosin stain; CD20 (C), CD10 (D), MYC (E) and Ki67 (F) immunostains.
**Figure 2.** Modified Magrath regimen of R-CODOX/R-IVAC (R – rituximab; C-cyclophosphamide; O – vincristine; DOX – doxorubicin; I – ifosfamide; V – etoposide; AC – cytarabine)

### R-CODOX

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m²</td>
<td>D1*</td>
</tr>
<tr>
<td>Cyclophosphamide 800 mg/m²</td>
<td>D1, D2</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/m²</td>
<td>D1</td>
</tr>
<tr>
<td>Vincristine 1.4 mg/m² (cap 2 mg)</td>
<td>D1, 15</td>
</tr>
<tr>
<td>Peg-filgrastim 6 mg</td>
<td>D3</td>
</tr>
<tr>
<td>Methotrexate 3000 mg/m²</td>
<td>D15**</td>
</tr>
<tr>
<td>IT methotrexate/cytarabine</td>
<td>D1</td>
</tr>
<tr>
<td>IT cytarabine 50 mg</td>
<td>D3</td>
</tr>
</tbody>
</table>

### R-IVAC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m²</td>
<td>D1</td>
</tr>
<tr>
<td>Ifosfamide 1500 mg/m² (with MESNA)</td>
<td>D1-D5</td>
</tr>
<tr>
<td>Etoposide 60 mg/m²</td>
<td>D1-D5</td>
</tr>
<tr>
<td>Cytarabine 2000 mg/m² q 12 hours</td>
<td>D1-D2</td>
</tr>
<tr>
<td>IT methotrexate</td>
<td>D5</td>
</tr>
<tr>
<td>Peg-filgrastim</td>
<td>D6</td>
</tr>
</tbody>
</table>

*During cycle 1, rituximab should be administered no earlier than day 3

** methotrexate is administered as a bolus over 2 to 4 hours once urine pH > 7. Leucovorin 200 mg/m² IV given once 24 hours later and then 15 mg/m² q 6 hours until level is less than 0.1. IVF with 3 amps of sodium bicarbonate should be administered until methotrexate has cleared.
How I treat Burkitt lymphoma in adults

Caron Jacobson and Ann LaCasce