Adult Burkitt’s Leukemia and Lymphoma

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Abstract

The World Health Organization Classification of Lymphoid Neoplasms identifies Burkitt’s lymphoma/leukemia as a highly aggressive mature B-cell neoplasm consisting of endemic, sporadic, and immunodeficiency-associated variants. These subtypes share many morphologic and immunophenotypic features, but differences exist in their clinical and geographic presentations. All of these subtypes possess chromosomal rearrangements of the \(c\)-\textit{myc} oncogene, the genetic hallmark of Burkitt’s lymphoma that contributes to lymphomagenesis through alterations in cell cycle regulation, cellular differentiation, apoptosis, cellular adhesion, and metabolism. Brief duration, high intensity chemotherapy regimens containing aggressive central nervous system prophylaxis have had remarkable success in the treatment of this disease, with complete remission rates of 75-90% and overall survivals reaching 50-70% in adults. Although Burkitt’s lymphoma cells are extremely chemosensitive, biologically targeted therapies should be developed as current treatment options are suboptimal for patients with poor prognostic features or in the setting of relapsed disease.
First described by Dennis Burkitt in 1958, Burkitt’s lymphoma (BL) is a highly-aggressive non-Hodgkin’s lymphoma (NHL) often presenting in extranodal sites or as an acute leukemia. Originally thought to represent two different lymphoproliferative disorders, BL was historically classified as a small non-cleaved cell lymphoma in patients with a solid tumor or nodal mass, and as L3 acute lymphoblastic leukemia (FAB L3 ALL) in patients with > 25% bone marrow involvement. However, on the basis of shared molecular and genetic features, the recently adopted World Health Organization (WHO) Classification of Lymphoid Diseases recognizes the lymphoma and leukemic phases of BL as a single entity; a mature B-cell neoplasm, subtype Burkitt’s lymphoma/Burkitt cell leukemia. The hallmark of this disease is the over-expression of c-Myc, most commonly resulting from t(8;14), although variant translocations have been described.

Clinical presentation of BL

Three different clinical variants of BL have been described: endemic, sporadic, and immunodeficiency BL. While there is considerable overlap, unique clinical and genetic features have been described among these variants. The endemic form is most commonly observed in equatorial Africa, in children ages 4-7, with frequent involvement of the jaw and kidneys, although ileal, cecal, ovarian, and breast involvement have also been reported. The particularly high incidence of BL in equatorial Africa (50-fold higher than in the United States) and the geographic distribution of this tumor, corresponding to the distribution of endemic malaria, have led to its designation as endemic BL. In contrast, in other geographic areas, the majority of patients present with abdominal tumors with no specific geographic/climatic distribution. This clinical variant, designated sporadic BL, accounts for 1-2% of all adult lymphomas in Western Europe and the United States. The immunodeficiency subtype is frequently observed in the setting of human immunodeficiency virus (HIV) infection, and unlike other HIV-related lymphomas, is frequently noted in patients with CD4 counts exceeding 200 cells/µL. Adult patients with sporadic or immunodeficiency-associated BL typically present with extranodal disease, with the abdomen being the most frequent site of involvement. Symptoms can include abdominal pain, nausea, vomiting, bowel obstruction, gastrointestinal bleeding, or syndromes mimicking acute appendicitis or intussusception. Intra-abdominal presentations usually affect the bowel or intra-abdominal lymph nodes, although kidney, pancreas, liver, spleen, breast, or ovarian involvement can occur. At diagnosis,
patients usually have bulky disease and elevated lactate dehydrogenase and uric acid levels. Bone marrow and CNS involvement is reported in 30-38% and 13-17% of adults, respectively.\textsuperscript{9-11}

Due to the frequency of extra-nodal disease, several different staging systems have been used for BL. Adult trials frequently reference the Ann Arbor system, although some authors find this system inadequate due to its inability to fully describe the extent of extra-nodal involvement. Therefore, some trials, report stage according to the St. Jude or Murphy staging schema (Table 1). It is important to note that this staging system recognizes Burkitt’s leukemia as a separate entity, unlike the current WHO classification.\textsuperscript{5} Also, this staging system was developed when surgery was often used for both diagnostic and therapeutic purposes, with the goal of surgery often being complete resection of intra-abdominal disease. Current therapy of BL does not routinely incorporate de-bulking surgery due to the existence of highly effective chemotherapy and an increased rate of local complications and toxic death with early surgery.\textsuperscript{12}

\textit{Morphology and immunophenotype of BL}

In addition to the different clinical variants of BL, two morphologic variants have been identified: classic BL and atypical or Burkitt’s-like lymphoma (BLL).\textsuperscript{5,13} Medium-sized cells with abundant, basophilic cytoplasm, often containing lipid vacuoles; round nuclei with clumped chromatin and multiple nucleoli; and a diffuse, monotonous pattern of infiltration are characteristic of classic BL.\textsuperscript{7,13} A “starry sky” appearance has been described in this type of NHL due to its abundant proliferative rate, frequent apoptoses, and numerous macrophages containing ingested apoptotic tumor cells (Figures 1A and 1B). The Burkitt-like variant, a provisional entity in the REAL classification\textsuperscript{19} and a subcategory of BL in the WHO classification,\textsuperscript{5} has greater pleomorphism in nuclear size and shape, with fewer nucleoli than classic BL. In many cases, BLL has features intermediate between diffuse large B-cell lymphoma (DLBCL) and BL, making pathologic diagnosis difficult. In fact, the degree of consensus among pathologists making the diagnosis of BLL was only 53% using the REAL classification.\textsuperscript{14} This lack of reproducibility may be related to the histologic, clinical, and genetic heterogeneity of BLL, with a variety of reviews reporting differing characteristics of BLL, including translocation of t(14:18), lack of \textit{c-myc} rearrangements, and more frequent nodal presentations.\textsuperscript{15,16} Currently, the WHO Classification of
Lymphoid Diseases requires that BLL demonstrates a high growth fraction, with Ki-67 staining exceeding 99%, with cytogenetic evidence of a c-myc rearrangement, when cytogenetic analysis is available.5

BL cells express surface IgM, Bcl-6, CD19, CD20, CD22, CD10, and CD79a, and are negative for CD5, CD23, and TdT (Figures 1-2). In contrast, precursor B-cell ALL is usually TdT positive and does not express surface immunoglobulin. The expression of Bcl-6 and CD10 suggest a germinal center origin for BL. Sequence analysis of the Ig variable heavy chain and light chain genes in BL confirms that the endemic, sporadic, and immunodeficiency-associated variants of BL have all arisen from a germinal center B-cell, with evidence of somatic hypermutation.17-20

Genetic features of BL

Eighty percent of BL cases harbor t(8;14), resulting in the juxtaposition of the c-myc gene on chromosome 8 with IgH enhancer elements on chromosome 14 (Figure 3) which drive c-Myc mRNA and protein production.21 In the remaining 20% of BL cases, translocations occurring between chromosomes 2 and 8, t(2;8)(p12;q24), or chromosomes 8 and 22, t(8;22)(q24;q11), place the c-myc gene adjacent to either κ or λ light chain loci and enhancer elements (Figure 3), respectively.21-23 As heavy chain and light chain loci are specifically active in mature B-cells, it is not difficult to understand how c-myc transcription is favored in BL harboring t(8;14), t(2;8), or t(8;22).

Different breakpoints have been identified on chromosomes 8 and 14 depending on the clinical variant of BL (Figure 3, reviewed in Hecht et al.21 and Boxer et al.24). Although not a strict association, in endemic BL, the breakpoint on chromosome 8 generally occurs >100 kb upstream from the first coding region of the c-myc gene, with chromosome 14 breakpoints in the joining segments of the IgH gene. This t(8;14) translocation in endemic BL places the c-myc promoter in exon 1 under the control of the IgH Eµ enhancer element.21,22,25,26 In contrast, in sporadic and HIV-associated BL, the breakpoints occur between exons 1 and 2 of the c-myc gene and within the Sµ switch region of the IgH gene.21,22,25-27 In sporadic BL, the Eµ IgH enhancer is eliminated during the translocation, indicating that other IgH elements such as the Eα enhancer may be responsible for driving c-myc transcription.21,28
**Pathogenesis of BL**

C-Myc, a helix-loop-helix leucine zipper transcription (bHLH-LZIP) factor, influences the transcription of a variety of proteins involved in cell cycle regulation, apoptosis, cell growth, cell adhesion, and differentiation (Figure 4, reviewed in Hecht et al., 21 San-Beato et al., 29 and Dang et al. 30), making it difficult to attribute any single alteration to lymphomagenesis. Oligonucleotide array analysis has identified 27 genes that are consistently induced with c-Myc over-expression, including *cyclin D2*, genes for the nucleolar proteins nucleolin and fibrillarin, the apoptosis gene *TRAP1* (a tumor necrosis factor receptor), the major histocompatibility gene *HLA-DRB1*, and the mitochondrial chaperone heat shock 60-kD protein 1 (*HSPD1*). 31 In addition, 9 genes including genes for the cyclin dependent kinase inhibitor p21 CIP1, fibronectin, collagen, and platelet-derived growth factor receptor alpha (PDGFRα) are consistently repressed with c-Myc over-expression. 31 Other targets of c-Myc identified in knockout or over-expression cellular or animal models include cyclin D1, cyclin dependent kinase 2 (CDK2), cyclin dependent kinase 4 (CDK4), p27, lactate dehydrogenase A (LDH A), p19ARF, p53, Bax, Fas, and Fas ligand. 24,32-34

In addition to the *c-myc* translocations found in virtually all variants of BL, a number of other mutations affecting *c-myc* or other genes may be responsible for the evolution and progression of BL. Deletion or mutation or several negative regulatory elements within the *c-myc* gene may further enhance protein expression. 35-37 C-Myc over-expression may also be related mutations in the threonine 58 residue of c-Myc. 38-42 With this mutation, proteasome-mediated degradation of c-Myc is substantially impaired, allowing further accumulation of this oncoprotein. 38,39 Mutations in p53, 43-45 methylation of death associated protein kinase (DAP-kinase), 46 and EBV-induced FLICE inhibitory protein (FLIP) expression 47 may all contribute to impaired apoptosis in BL. Likewise, changes in other cellular proteins, i.e. down-regulation of p16INK4a or p15INK4b via gene hypermethylation, 48 may promote cell cycle progression, providing additional hits to the cell cycle regulatory machinery in BL.

**Treatment of BL**
Historically, treatment of BL mimicked the high intensity, prolonged regimens used for the treatment of ALL with induction, consolidation, and maintenance phases. Such therapy is generally ineffective for most patients with BL and results in low frequency of cure. The high growth fraction of BL (doubling time of approximately 25 hours) favors re-entry of remaining viable malignant cells into the cell cycle and rapid growth between chemotherapy cycles with subsequent development of resistance. Short duration, intensive regimens that minimize treatment delays and maintain serum drug concentrations over at least 48-72 hours have the greatest efficacy in BL.

Short-duration combination chemotherapy, first used in children with BL, consisting of intensive therapy with several known active agents in BL, including cyclophosphamide, vincristine, methotrexate, doxorubicin, and cytarabine, has improved upon the outcomes observed with ALL-like regimens, with 2-year disease-free survivals (DFS) reaching 75-89% in pediatric patients with advanced stage BL. Several therapeutic strategies including fractionated cyclophosphamide, alternation of non-cross-resistant cytotoxic agents between treatment cycles, a shortened duration of therapy, minimal treatment delays, and aggressive CNS prophylaxis may be responsible for this success. With frequent involvement of the CNS and the bone marrow, adults were once thought to have a less favorable outcome than pediatric patients with BL; however, several recent studies suggest that treatment with intensive chemotherapy and adequate CNS prophylaxis can be curative even in the setting of advanced stage disease or immunodeficiency. With high intensity, brief duration regimens, 65-100% of adults achieve a complete response (CR), with 47-86% of patients maintaining these remissions at least one year following therapy (Table 2). Several pediatric regimens, modified for use in adults, have been quite successful in the treatment of adult BL including the French LMB 81, 84, 86, and 89 regimens, the German Berlin-Frankfurt-Munster (BFM) protocols, and CODOX-M/IVAC. Additional protocols including the Stanford regimen, Hyper-CVAD, and Cancer and Leukemia Group B (CALGB) 9251, 56,58,62,63 have been evaluated primarily in adults, but incorporate many of the chemotherapeutic principles found to be effective in the treatment of pediatric BL. Comparison of these treatment regimens is difficult in adult BL due to: 1.) differences in patient populations among the trials, particularly in regards to patient age and stage, 2.) differences in pathology (Burkitt’s leukemia or BLL is excluded in some trials), and
3.) differences in staging, with several trials employing the St. Jude system, while others use the Ann Arbor system.

Some of the earliest reports of successful treatment regimens for adult BL include the Vanderbilt and Stanford regimens. After noting poor outcomes with conventional intermediate grade lymphoma regimens like BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine and prednisone) and COMP (cyclophosphamide, vincristine, methotrexate, and prednisone), McMaster et al. treated 20 patients with two intensive inpatient induction courses. With this regimen containing high dose cyclophosphamide, methotrexate (200 mg/m²), bleomycin, vincristine, and doxorubicin, CRs were achieved in 85% of patients, and 5-year DFS reached 60%. The Stanford group achieved similar results with a regimen containing high-dose cyclophosphamide (1500 mg/m²) and mid-cycle high dose methotrexate (3000 mg/m²) administered over 6-9 cycles (Figure 5). With this regimen, 2-year overall survival (OS) reached 66.8%; however, the best responses were noted in patients with limited stage disease (a single extra-abdominal tumor site or a completely resected intra-abdominal disease), where 2-year OS was 100%, compared to 53.8% in the advanced setting.

In 1995 and 1996, two reports were published documenting the success of adapting the pediatric French LMB and the German BFM regimens to the treatment of adult BL. In a retrospective review of 65 adults treated according to the pediatric LMB 81, 84, 86, and 89 regimens, 58 (89%) patients achieved a CR with a 3-year OS of 74%, despite the fact that the majority of patients had advanced stage disease or evidence of leukemic involvement. Seven of 12 patients who presented with CNS involvement remained disease-free up to 56 months after therapy. These LMB protocols (Figure 5) consist of an initial cytoreductive phase using cyclophosphamide and prednisone to rapidly diminish the tumor burden and minimize the risk of tumor lysis, followed by two induction cycles, 1-2 consolidation cycles, and 1-4 maintenance cycles. A prospective study of the LMB protocol in adults confirmed the retrospective findings, with a CR rate of 83% and a 2-year OS of 66%.
Based on their success in pediatric BL with the BFM protocols, the German Multicenter Study Group for the treatment of adult ALL (GMALL) developed two protocols, B-NHL 83 and B-NHL 86, for the treatment of adult Burkitt’s leukemia. Similar to the LMB trials, these studies also included a cytoreductive phase to minimize the risk of tumor lysis. Following this pre-phase, 6 cycles of alternating chemotherapy regimens were given, with fractionated cyclophosphamide, methotrexate, and low dose cytarabine in each of these alternating cycles. The B-NHL 86 regimen (Figure 5) escalated the dose of methotrexate to 1500 mg/m² and added ifosfamide to the B-NHL 83 regimen. Results were comparable to those noted in the French LMB trials, with 4-8 year OS reaching 49%-51%.

Magrath et al pioneered the use of the CODOX-M/IVAC regimen in children and adults with BL. This regimen incorporates 3 cycles of CODOX-M for patients with low-risk disease (a single extranodal site or completely resected intra-abdominal disease and a normal LDH) and 4 cycles of alternating CODOX-M/IVAC for patients with high risk disease (Figure 5). CODOX-M/IVAC combines fractionated cyclophosphamide with higher doses of methotrexate (6720 mg/m²) and cytarabine (2000 mg/m²) than administered in the LMB and B-NHL trials, with the exception of LMB 86 where patients received up to 8000 mg/m² of methotrexate. In the initial publication, two-year event free survival (EFS) was 85% in children and 100% in adults, with all 20 adult patients achieving a CR. In an updated report, CRs were noted in 24/26 adult patients treated, with 22 patients alive and disease-free, at a median follow-up of 47 months (range 12-91 months). While the results of this study seem remarkable, it is important to recognize that this study involved a relatively young adult patient population, with a median age of 25, although 70% of patients had advanced stage disease by both the St. Jude and the Ann Arbor staging systems. A trial using this regimen in Europe reported 2-year EFS and OS of 64.6% and 72.8%, respectively, in 52 patients with a median age of 35. In 14 patients with a median age of 47, the Magrath regimen produced responses in 86% of patients, with 72% alive and disease free after 21 months of follow-up. In this older group, myelosuppression was universal, and treatment-related deaths were reported in 5 patients.

Two other regimens have been examined exclusively in adults, namely Hyper-CVAD and a CALGB regimen, CALGB 9251. With the Hyper-CVAD regimen (Figure 5), a modified Murphy-regimen used to treat adult
Burkitt’s leukemia at M.D. Anderson, 81% of patients achieved a CR, and the 3-year OS was 49%. Notably, this study contained a much older population of patients (median age of 58) than reported in other trials and patients 60 or older had an inferior outcome (3-year OS of 17% v. 77%). The CALGB regimen contains a cytoreductive phase, followed by 3 cycles each of 2 different regimens administered every 3 weeks (Figure 5). In 54 evaluable patients, CRs were noted in 80%, with 4-year DFS of 50%. However, severe neurologic toxicity (transverse myelitis, peripheral neuropathy, aphasia, cortical blindness, and dementia) was observed in 10 of 74 patients enrolled on this trial, attributed to the combination of high dose methotrexate (1500 mg/m²), triple intrathecal chemotherapy, and whole brain irradiation (24 Gy) used for CNS prophylaxis. The cranial radiation was subsequently eliminated for patients without bone marrow involvement at presentation and the rate of neurologic events decreased. In the CALGB study, only 32% of patients over 50 were able to complete 6-7 cycles of treatment, compared to 79% of younger patients. Mortality (21% v. 9%), disease progression (32% v. 3%), and toxicity (16% v. 9%) were noted to be higher in those patients over 50. The higher rate of relapse in elderly patients with BL implies that these poor outcomes may not simply be related to treatment related toxicity. Thomas et al. noted an increased incidence of complex cytogenetic abnormalities in older patients, including \textit{bcl-2} gene rearrangements, which may contribute to a more aggressive phenotype.

As demonstrated by the trials previously discussed and as is summarized in Table 3, several issues remain unresolved in the treatment of adult BL; in particular, the optimal dose and fractionation schedule of cyclophosphamide, the optimal dosage of methotrexate and cytarabine, and the necessity of ifosfamide. Murphy et al. piloted the use of fractionated cyclophosphamide (six doses of 300 mg/m² every 12 hours) in pediatric patients with BL, postulating that a fractionated schedule would ensure exposure of every dividing tumor cell to the active alkylating metabolites of cyclophosphamide. The optimal fractionation schedule remains unclear, with administration of cyclophosphamide varying from every 12 hours to every 24 hours. In addition, it is also unclear if the fractionation or simply the dose intensity is important in BL. For example, the Stanford regimen incorporates a single dose of high dose cyclophosphamide. Nevertheless, several recent studies have incorporated fractionated cyclophosphamide into adult BL regimens on the basis of the efficacy described in the pediatric literature with the Murphy, German BFM, and the French LMB regimens. The appropriate dosage of methotrexate and cytarabine also remains unsettled. While the
majority of trials incorporate high dose methotrexate and cytarabine to improve CNS prophylaxis, the benefit is unclear and escalated doses increase toxicity, particularly in older patients. Treatment with up to 8000 mg/m$^2$ of methotrexate and 3000 mg/m$^2$ of cytarabine have been reported; however, lower doses (1000-3000 mg/m$^2$ of methotrexate and 100-150 mg/m$^2$ of cytarabine) may be equally efficacious. Last, it is unclear if ifosfamide provides any benefit in addition to the cyclophosphamide routinely incorporated into initial therapy, with two recent trials failing to demonstrate any improvement in EFS or OS with the addition of ifosfamide to the therapy of advanced-stage pediatric patients with BL.

Several investigators have incorporated upfront autologous stem cell transplantation into their treatment regimens for BL. To date none of these studies appear to improve upon the results observed with brief duration, intensive chemotherapy alone for BL. Three-year OS rates of 60-72% have been reported following autologous stem cell transplantation in first CR, similar to that attained with chemotherapy alone. Treatment-related mortality may exceed that of chemotherapy alone in those patients receiving up-front transplants, as demonstrated by data from the French LMB trials where 54% (7/13) of patients who underwent transplantation in first CR (6 allogeneic and 7 autologous) survived, compared to 89% (40/45 patients) of patients receiving chemotherapy only. Therefore, on the basis of these small studies, there is no role for transplantation in first CR in BL.

Central Nervous System Prophylaxis in BL

As CNS involvement is common in BL, CNS prophylaxis is required for the treatment of all adults with BL. Most BL regimens take a combination approach to CNS prophylaxis, relying on the efficacy of high dose methotrexate, high dose cytarabine, and intrathecal chemotherapy in the prevention of CNS relapse. Some earlier studies have incorporated whole brain and occasionally spinal radiation into the prophylaxis regimen (Table 3); however, there is no data to support that these modalities improve outcomes over combination therapy with intravenous and intrathecal chemotherapy alone. In addition, as demonstrated by the CALGB trial, the risk of long-term, severe neurotoxicity is higher with the addition of radiation to intrathecal chemotherapy and high dose methotrexate. Therefore, currently there is no role for prophylactic cranial or
spinal irradiation in the treatment of BL when CNS prophylaxis is provided by intrathecal chemotherapy coupled with high dose systemic methotrexate and/or cytarabine.

**Treatment of limited stage BL**

Several studies have noted very favorable results in early stage (Ann Arbor stages I-III or St. Jude stages I-II) BL, with CR rates of 100% and 2 to 5-year freedom from progression (FFP) rates of 95-100%, compared to CR rates of 57% and 2 to 5-year FFP rates of 29-60% in the advanced setting. On the basis of these very encouraging results, 3 cycles of CODOX-M or the Stanford protocol may be suitable for those patients who present with limited disease. With the Magrath regimen, low-risk patients received 3-cycles of CODOX-M without alternating IVAC, while in the Stanford series, patients with limited stage disease received 6 cycles of therapy rather than 9. Two-year EFS of 83-100% have been observed with these regimens in low-risk patients. Therefore, very brief duration regimens may be feasible in early stage BL.

**Therapy-related toxicity in BL**

In most trials, the most commonly encountered toxicities have consisted of myelosuppression and infections. With the Vanderbilt and Stanford regimens, leukopenia was reported in 100% and 23.4% of cycles, respectively, with 3 treatment-related deaths due to either tumor lysis syndrome or sepsis. With the LMB, B-NHL 83 and 86, CODOX-M/IVAC, and Hyper-CVAD regimens, neutrophil counts below 500 cells/µL were reported in 81-100% of cycles, platelet transfusions were required in 35-71%, and severe infections reported in 19-55% of patients. Mucositis, cerebellar toxicity, and thrombocytopenia-related hemorrhage have also been reported. In order minimize some of these toxicities, many regimens incorporate fungal, bacterial, and viral prophylaxis, and administer colony-stimulating factors, although the value of these agents is unknown. All patients treated with Hyper-CVAD received granulocyte colony-stimulating factor (GCSF) at a dose of 10 µg/kg starting 24 hours after chemotherapy. With GCSF, the average time to neutrophil recovery was 17 days, and was similar in both the < 60 and the ≥ 60 age groups. With the Magrath regimen, low risk and high risk patients were randomized to receive granulocyte-macrophage colony stimulating factor (GM-CSF). There was no difference in the control and GM-CSF arms with respect to incidence of documented infection, duration of neutropenia, and incidence of fever of unknown origin; however, GM-CSF treated patients did experience
delayed platelet recovery. In regards to prophylactic antibiotics, anti-fungals, and anti-virals, limited data is available addressing their use in this setting, with such treatment incorporated into the Hyper-CVAD regimen, but not reported as part of the CODOX-M/IVAC, B-NHL, LMB, or CALGB regimens. It is the authors’ approach to administer GCSF in adult patients with BL and to apply aggressive prophylactic measures similar to that recommended for the management of acute leukemia.

Prognostic features, salvage therapy, and stem cell transplantation (SCT) in BL

While debate is ongoing over the most relevant prognostic factors in BL, several studies have identified advanced age, advanced stage, poor performance status, CNS or bone marrow involvement, anemia, the presence of circulating blasts, and an elevated LDH as indicative of a poor outcome in adult BL. Not all series report bone marrow or CNS involvement as poor prognostic features, suggesting that the incorporation of fractionated cyclophosphamide, high dose methotrexate, cytarabine, or intensive intrathecal chemotherapy into the current treatment regimens may improve outcomes in this historically poor performing group. The validity of these prognostic factors remains questionable; however, as many of these factors were identified in single institution phase II studies with selected patient populations.

The majority of patients attain CR within 4-6 weeks of initiating therapy for BL. With the Hyper-CVAD regimen, the median time to CR was 22 days and 70% of patients achieved a CR within the first four weeks of therapy. For those patients who relapse, this generally occurs within the first year, although relapses have been reported 17-55 months after the completion of therapy. Failure to achieve a CR is a particularly poor prognostic sign. All patients who achieve a PR have been found to relapse and die of progressive disease without additional therapy. Therefore, patients should be followed very closely for a response, with disease assessed after 6-8 weeks of therapy, and alternative therapy rapidly initiated for those patients failing to achieve a CR. Patients with bulky abdominal masses who fail to have complete radiographic resolution of this mass may require repeat biopsy or imaging with PET or gallium scan to ascertain CR.

For those patients with a PR or relapsed disease, the optimal salvage strategy is unknown. Combination chemotherapy with non-cross-reactive agents including cytarabine, ifosfamide, or cisplatin can be provided,
particularly if these agents were not used front-line. However, even with non-cross-resistant chemotherapy, few to no BL patients respond at the time of relapse. Autologous or allogeneic stem cell transplant may represent an alternative strategy in the salvage setting; however, published series addressing high dose therapy in BL are confounded by both selection bias and absence of detailed pathologic review. In a retrospective review from the European Group for Blood and Marrow Transplantation (EBMT), 10 adult patients with BL or BLL in first partial remission, 15 patients in second or greater remission, and 14 patients with primary refractory disease received an autologous stem transplant. Three-year OS was 37% for patients with chemosensitive relapse and 7% for patients with chemo-refractory disease. In adult patients treated according to the LMB protocols, 3 patients who received an autologous transplant for refractory disease died. In this same trial, 1 of 2 patients treated with an allogeneic transplant and one patient treated with an autologous transplant at the time of second CR were alive 24 and 59 months following the transplant. Even less data is available regarding the efficacy of related or unrelated allogeneic transplantation in patients with BL. From 1982-1998, 71 patients (ages 4 - 48) with BL were reported to have received allogeneic transplant (63 matched related, 3 matched unrelated, and 4 unmatched related) at the time of either 1st CR or relapse. Seventy-three percent of patients had chemosensitive disease, while 20% were reported to have chemo-resistant disease. As has been seen with autologous transplant, disease status at transplantation (1st CR and chemosensitivity) have a significant effect on OS. Interestingly the presence of acute graft-versus-host disease had no impact on survival. In matched patients treated with an autologous transplant, the relapse rate was equivalent between the allogeneic and autologous arms and OS was superior in the autologous arm. This data calls into question the existence of a graft-versus-lymphoma effect in BL. In conclusion, with few effective salvage strategies for BL and limited data regarding the role of stem cell transplantation at the time of relapse, the authors recommend that patients with BL participate in a clinical trial at the time of relapse, with consideration given to a stem transplantation in those patients who demonstrate chemosensitivity.

*Treatment of immunodeficiency associated BL*

HIV positive patients have been included in several of the previously described chemotherapy trials in BL. Twelve of 13 HIV-positive patients receiving Hyper-CVAD (9 of whom received therapy in conjunction with...
with highly active antiretroviral therapy – HAART) achieved a CR, with 8 patients remaining in CR a median of 31 months after diagnosis. The median survival was 12 months, and this correlated with the addition of HAART to the treatment regimen. All 4 patients not receiving HAART in conjunction with chemotherapy died. All 13 patients receiving Hyper-CVAD required multiple red cell and platelet transfusions, and 21% required dose modifications due to prolonged myelosuppression. Thirty-five percent of cycles were complicated by fever or infections, including fungal pneumonia, CMV retinitis, and *Xanthomonas maltophilia* sepsis. Therefore, HIV positive patients with BL can be successfully treated with intensive chemotherapy, but close observation with transfusion support and antibiotic therapy is necessary. The addition of HAART to these regimens may improve outcomes and minimize the risk of opportunistic infections, but further evaluation is needed.

*New modalities for the treatment of BL*

Despite the improvement in CR, DFS, and OS rates with intensive chemotherapy in BL, novel treatment regimens are needed, particularly for patients with poor prognostic features at diagnosis, patients who fail to attain a CR, and patients who relapse. With the frequent expression of CD20 in BL, the monoclonal anti-CD20 antibody rituximab may improve outcomes in BL in both the front-line and relapsed settings. Rituximab has recently been incorporated into the Hyper-CVAD regimen (R-Hyper-CVAD), with dosing on days 1 and 11 of cycles 1 and 3 and on days 1 and 8 of cycles 2 and 4. To date, 20 patients (80% with Ann Arbor stage III-IV disease) have received R-Hyper-CVAD, with CRs reaching 89%, and a 1-year DFS of 86%. The CALGB has also incorporated rituximab into its latest BL regimen (CALGB 10002), with rituximab administration occurring during each cycle except the cytoreductive phase. This study is currently accruing patients and is expected to take 3 years to complete. Other monoclonal antibodies directed at other common B-cell antigens, namely CD22 and HLA-DR may also have a future role in the treatment of BL.

Other novel therapies that may have potential benefit, but have not yet been evaluated in BL include DNA methyltransferase inhibitors, histone deacetylase inhibitors, antisense oligonucleotides targeting c-Myc, proteasome inhibitors, cyclin dependent kinase inhibitors, selective serotonin re-uptake inhibitors (SSRIs), and blockade of EBV-related viral proteins. Hypermethylation of DAP-kinase, p16INK4a, and p15INK4B, and
the interaction of the Myc/Max heterodimers with a histone acetyltransferase in BL suggests that epigenetic modifications are important in BL and could be therapeutically targeted by DNA methytransferase inhibitors (i.e. decitabine or 5-azacytidine) or histone deacetylase inhibitors (i.e. depsipeptide, MS-275, or suberoylanilide hydroxamic acid). Pilot studies with antisense oligonucleotides directed at several different sites of human c-Myc mRNA have been reported to decrease proliferation of HL-60 and Raji cells in vitro. In a murine model of BL, treatment with a DNA phosphorothioate oligonucleotide complementary to c-myc codons 1-5 or 384-388 delayed tumor onset by 3-6 days and decreased total tumor mass by 40%-65%, compared to controls. Proteasome inhibition may also effectively induce apoptosis in BL cell lines, despite previously demonstrated defects in proteasome-mediated degradation of c-Myc in BL. In severe combined immunodeficiency mice bearing BL tumors, treatment with a proteasome inhibitor (Z-LLF-CHO) led to tumor regression. Serafeim et al, have recently published intriguing in vitro data suggesting that SSRIs (fluoxetine, paroxetine, and citalopram) rapidly trigger apoptosis of BL cells, with little effect on normal germinal center B-cells. The mechanism of SSRI-mediated apoptosis remains unclear; however, preliminary studies suggest that this may occur independently of blockade of the serotonin transporter. Finally, although EBV-related viral proteins are detected in only about 20-50% of sporadic and immunodeficiency-associated BL, inhibition of viral proteins (EBNA-1 and EBNA-2, in particular) can inhibit cell growth and lead to apoptosis of EBV-immortalized cells, in vitro. Hopefully, in the future, many of these therapeutic strategies targeting known molecular and genetic abnormalities of BL will prove to be effective for adult patients with relapsed or refractory BL.

In conclusion, a remarkable shift in the therapeutic paradigm of BL has occurred. Once thought to be incurable in adults due to its high proliferative rates, BL has proven to be quite chemosensitive even in patients with CNS or bone marrow involvement at presentation. Important strides continue to be made within the field of BL with the incorporation of several active agents from fractionated cyclophosphamide to high dose methotrexate into a variety of promising treatment regimens. While the optimal therapeutic strategy for BL is unknown, continued progress in the development of targeted therapies will potentially improve outcomes in this disease.
References:

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Figure 1A. Typical morphology of bone marrow with involvement by BL. Characteristic immunophenotype illustrated by immunohistochemistry: CD20+, CD10+, Ki67+ (100%), TdT- and CD34 -. Classical translocation involving c-myc and immunoglobulin heavy chain genes is illustrated by FISH analysis with probes for 14q32 (IgH): green, 8q24 (MYC): red, and chromosome 8 centromere probe: aqua. Fusion product t(8;14)(q24;q32) in yellow (indicated by arrows).
Figure 1B. Typical morphology of lymph node with involvement by BL. Characteristic immunophenotype illustrated by immunohistochemistry: CD20+, CD10+, Ki67+ (100%), TdT- and CD34 -. Classical translocation involving c-myc and immunoglobulin heavy chain genes is illustrated by FISH analysis with probes for 14q32 (IgH): green, 8q24 (MYC): red, and chromosome 8 centromere probe: aqua. Fusion product t(8;14)(q24;q32) in yellow (indicated by arrows).
Figure 2. **Typical morphology of Burkitt’s leukemia.** Characteristic immunophenotype is illustrated by flow cytometric analysis: CD10+, CD19+, CD20+ (bright), surface immunoglobulin light chain lambda restricted (bright) and CD5-.
Figure 3: Positions of c-myc, IgH, Igκ, or Igλ breakpoints in t(8;14), t(2;8), or t(8;22) Burkitt’s lymphoma. The breakpoints for t(8;14) in endemic BL (eBL), sporadic BL (sBL), and immunodeficiency BL (HIV BL) are depicted. Juxtaposition of the Eµ enhancer on the IgH gene of chromosome 14, Eι and E3’ enhancers in the κ locus of chromosome 2, and HuEλ enhancer in the λ locus of chromosome 22 with the c-myc gene on chromosome 8 drive c-Myc over-expression in BL with t(8;14), t(2;8), and t(8;22), respectively.
Figure 4: Direct and indirect consequences of c-Myc over-expression in Burkitt’s lymphoma (reviewed in 21,24).

**c-MYC**

**CELL CYCLE PROGRESSION:**
- Increases Cyclin D1
- Increases Cyclin D2
- Activates CDK4
- Activates CDK2
- Decreases P21\(^{CIP1}\)
- Decreases P27

**APOTOPSIS:**
- Induces p19\(^{ARF}\)
- Increases p53
- Activates FAS/FASL
- Upregulates Bax

**CELLULAR GROWTH AND DIFFERENTIATION:**
- Suppresses gas1
- Suppresses gadd45

**CELLULAR ADHESION:**
- Decreased LFA-1
- Downregulates collagen production
- Decreases fibronectin

**CELLULAR METABOLISM:**
- Stimulates LDHa production
- Increases glucose transporter 1 (GLUT1)
- Activates phosphofructokinase
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A single tumor (extranodal) or a single anatomic area (nodal) with the exclusion of the mediastinum or abdomen.</td>
</tr>
<tr>
<td>II</td>
<td>A single extranodal tumor with regional node involvement. Two single extranodal tumors on the same side of the diaphragm with or without regional node involvement. Primary gastrointestinal tumor with or without involvement of associated mesenteric nodes only. Two or more nodal areas on the same side of the diaphragm.</td>
</tr>
<tr>
<td>IIR</td>
<td>Completely resected intra-abdominal disease.</td>
</tr>
<tr>
<td>III</td>
<td>Two single extranodal tumors on opposite sides of the diaphragm. All primary intrathoracic tumors (mediastinal, pleural, thymic). All paraspinal or epidural tumors, regardless of other tumor sites. All extensive primary intra-abdominal disease. Two or more nodal areas on opposite sides of the diaphragm.</td>
</tr>
<tr>
<td>IIIA</td>
<td>Localized, but non-resectable intra-abdominal disease.</td>
</tr>
<tr>
<td>IIIB</td>
<td>Widespread multiorgan abdominal disease.</td>
</tr>
<tr>
<td>IV</td>
<td>Any of the above with initial CNS and/or bone marrow involvement (&lt;25% involvement, &gt; 25% is defined as L3 ALL).</td>
</tr>
</tbody>
</table>
Table 2. Results of Treatment of Adult BL

<table>
<thead>
<tr>
<th>Reference</th>
<th>Protocol</th>
<th>Number of Patients Treated</th>
<th>Median Age (Range)</th>
<th>CR</th>
<th>DFS</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein et al 56</td>
<td>Stanford</td>
<td>18</td>
<td>25 (15-75)</td>
<td>78%</td>
<td>71.3% at 1 year*</td>
<td>N/A</td>
<td>66.8% at 2 years</td>
</tr>
<tr>
<td>Lopez et al 71</td>
<td>MD Anderson 81-01 and 84-30</td>
<td>44</td>
<td>32 (17-72)</td>
<td>80%</td>
<td>60% at 5 years*</td>
<td>N/A</td>
<td>52% at 5 years</td>
</tr>
<tr>
<td>McMaster et al 19</td>
<td>Vanderbilt</td>
<td>20</td>
<td>44.5 (21-69)</td>
<td>85%</td>
<td>60% at 5 years</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Longo et al 68</td>
<td>ProMACE-MOPP</td>
<td>17</td>
<td>36 (19-90)</td>
<td>64.7%</td>
<td>61% at 15 years</td>
<td>100%</td>
<td>35% at 15 years</td>
</tr>
<tr>
<td></td>
<td>ProMACE-Cytobom</td>
<td>8</td>
<td></td>
<td></td>
<td>86% at 15 years</td>
<td>N/A</td>
<td>88% at 15 years</td>
</tr>
<tr>
<td>Divine et al 73</td>
<td>ACVBP</td>
<td>52</td>
<td>34</td>
<td>85%</td>
<td>N/A</td>
<td>47% at 5 years</td>
<td>53% at 5 years</td>
</tr>
<tr>
<td>Soussain et al 53</td>
<td>LMB 81, 84, 86, and 89</td>
<td>65</td>
<td>26 (17-65)</td>
<td>89%</td>
<td>N/A</td>
<td>71% at 3 years</td>
<td>74% at 3 years</td>
</tr>
<tr>
<td>Divine et al 11,59</td>
<td>LMB 81, 84, 86, and 89</td>
<td>51</td>
<td>33</td>
<td>83%</td>
<td>N/A</td>
<td>61% at 2 years</td>
<td>66% at 2 years</td>
</tr>
<tr>
<td>Hoelzer et al 55</td>
<td>BNHL83</td>
<td>24</td>
<td>33 (15-38)</td>
<td>63%</td>
<td>50% at 8 years</td>
<td>74%</td>
<td>49% at 8 years</td>
</tr>
<tr>
<td></td>
<td>BNHL86</td>
<td>35</td>
<td>36 (18-65)</td>
<td>74%</td>
<td>71% at 4 years</td>
<td>N/A</td>
<td>51% at 4 years</td>
</tr>
<tr>
<td>Todeschini et al 60</td>
<td>Modified POG 8617</td>
<td>8</td>
<td>35 (19-64)</td>
<td>100%</td>
<td>N/A</td>
<td>75% at 28 months</td>
<td>N/A</td>
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<tr>
<td>Magrath et al 64</td>
<td>CODOX-M/IVAC</td>
<td>26</td>
<td>25 (18-59)</td>
<td>92.3%</td>
<td>N/A</td>
<td>84% at 1 year</td>
<td>N/A</td>
</tr>
<tr>
<td>LaCasce et al 61</td>
<td>CODOX-M/IVAC</td>
<td>14</td>
<td>47</td>
<td>86%</td>
<td>72% at 21 months</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mead et al 9</td>
<td>CODOX-M/IVAC</td>
<td>52</td>
<td>35 (15-60)</td>
<td>75%</td>
<td>N/A</td>
<td>64.6% at 2 years</td>
<td>72.8% at 2 years</td>
</tr>
<tr>
<td>Thomas et al 56</td>
<td>Hyper-CVAD</td>
<td>26</td>
<td>58 (17-79)</td>
<td>81%</td>
<td>61% at 3 years*</td>
<td>N/A</td>
<td>49% at 3 years</td>
</tr>
<tr>
<td>Cabanillas et al 62</td>
<td>R-Hyper-CVAD</td>
<td>20</td>
<td>52 (27-77)</td>
<td>89%</td>
<td>N/A</td>
<td>86% at 1 year</td>
<td>N/A</td>
</tr>
<tr>
<td>Lee et al 65</td>
<td>CALGB 9251</td>
<td>54</td>
<td>44 (18-71)</td>
<td>80%</td>
<td>50% at 4 years</td>
<td>N/A</td>
<td>52% at 4 years</td>
</tr>
</tbody>
</table>

* In the Stanford 56, Vanderbilt 10 and MD Anderson 56 studies, these values represent 1-year relapse-free survival, 5-year freedom from progression, and 3-year continuous CR rate, respectively. DFS and EFS are not reported in these series.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Protocol Description</th>
<th>Duration</th>
<th>Cyclophosphamide**</th>
<th>Methotrexate**</th>
<th>Cytarabine**</th>
<th>Ifosfamide**</th>
<th>IT Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein et al</td>
<td>Stanford</td>
<td>6 - 9 cycles</td>
<td>1200 mg/m²</td>
<td>3000 mg/m²</td>
<td>None</td>
<td>None</td>
<td>IT MTX</td>
</tr>
<tr>
<td>Lopez et al</td>
<td>MD Anderson 81-01 and 84-30</td>
<td>15 cycles</td>
<td>1000 mg/m² x 1 dose</td>
<td>1000 mg/m²</td>
<td>20 mg/m² x 8 hrs x 15 doses</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>McMaster et al</td>
<td>Vanderbilt</td>
<td>2 cycles</td>
<td>1500 mg/m² x 2 doses</td>
<td>200 mg/m²</td>
<td>None</td>
<td>None</td>
<td>Given at investigator’s discretion</td>
</tr>
<tr>
<td>Longo et al</td>
<td>ProMACE-MOPP</td>
<td>6 - 9 cycles</td>
<td>9 cycles</td>
<td>500-650 mg/m² x 1-2 doses</td>
<td>1200 mg/m² x 1 dose</td>
<td>3000 mg/m²</td>
<td>Cytoreduction: None</td>
</tr>
<tr>
<td>Divine et al</td>
<td>ACVBP</td>
<td>8 cycles</td>
<td>1200 mg/m²</td>
<td>None</td>
<td>3000 mg/m² as maintenance for patients with a CR only</td>
<td>For patients in CR only</td>
<td>IT MTX and HC</td>
</tr>
<tr>
<td>Divine et al</td>
<td>LMB 81, 84, 86, and 89</td>
<td>4 - 7 months</td>
<td>Cytoreduction: 300 mg/m² x 1 dose</td>
<td>Induction: 500-1000 mg/m² x 3 doses</td>
<td>Consolidation: None</td>
<td>None</td>
<td>For patients in CR only</td>
</tr>
<tr>
<td>Hoelzer et al</td>
<td>B-NHL 83</td>
<td>6 cycles</td>
<td>Cytoreduction: 200 mg/m² x 5 doses</td>
<td>Treatment: 200 mg/m² x 5 doses</td>
<td>Cytoreduction: 300 mg/m²</td>
<td>None</td>
<td>CNS XRT if BM positive</td>
</tr>
<tr>
<td>Magrath et al</td>
<td>CODOX-M/IvAC</td>
<td>Low risk - 3 cycles</td>
<td>CODOX-M</td>
<td>800 mg/m² x 1 dose &amp; 200 mg/m² x 4 doses</td>
<td>6720 mg/m²</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>Hyper-CVAD</td>
<td>8 cycles</td>
<td>300 mg/m² x 12 hrs x 6 doses for 4 cycles</td>
<td>1000 mg/m² for 4 cycles</td>
<td>3000 mg/m² x 2 doses for 4 cycles</td>
<td>None</td>
<td>IT MTX and ARA-C</td>
</tr>
<tr>
<td>Lee et al</td>
<td>CALGB 9251</td>
<td>6 cycles</td>
<td>Cytoreduction: 200 mg/m² x 5 doses</td>
<td>Treatment: 200 mg/m² x 5 doses</td>
<td>1500 mg/m²</td>
<td>None</td>
<td>IT MTX, ARA-C, HC, and CNS XRT</td>
</tr>
</tbody>
</table>

*Please note that the reported regimens also contain several chemotherapeutic agents including doxorubicin, vincristine, dexamethasone or prednisone, etc. not reported in this table.

** All chemotherapy doses are total doses per cycle unless otherwise noted.

**Figure 5.** Common chemotherapy regimens used in the treatment of BL.

- **Cyclophosphamide**: 1200 mg/m² day 1
- **Doxorubicin**: 40 mg/m² day 1
- **Vincristine**: 1.4 mg/m² (maximum 2 mg) day 1
- **Prednisone**: 40 mg/m² days 1-5
- **Methotrexate**: 3000 mg/m² (with leucovorin rescue) day 10
- **IT Methotrexate**: 12 mg days 1 & 10

**STANFORD REGIMEN**
Cytoreductive phase (COP)
Cyclophosphamide 300 mg/m² day 1
Vincristine 2 mg day 1
Prednisone 60 mg/m²/day, days 1-7
IT Methotrexate and Hydrocortisone day 1

Induction (COPADM1)
Cyclophosphamide 500 mg/m²/day, days 2-4
Doxorubicin 60 mg/m² day 2
Vincristine 2 mg day 1
Methotrexate 3000 – 8000 mg/m² over 3 hrs day 1 (with leucovorin)
Prednisone 60 mg/m²/day, days 1-7
IT Methotrexate and Hydrocortisone days 2 & 8

Induction (COPADM2)
Cyclophosphamide 1000 mg/m²/day, days 2-4
Doxorubicin 60 mg/m² day 2
Vincristine 2 mg days 1 & 6
Methotrexate 3000 – 8000 mg/m² over 3 hrs day 1 (with leucovorin)
Prednisone 60 mg/m²/day, days 1-7
IT Methotrexate and Hydrocortisone days 2 & 8

Consolidation x 2
Etoposide 200 mg/m² (LMB 86 only)
Methotrexate 3000 mg/m² over 3 hrs day 1 (with leucovorin)
Cytarabine 100 mg/m²/day days 1-5 (LMB 84) or 3000 mg/m²/day
days 2-5 (LMB 86)
IT Methotrexate and Hydrocortisone day 2, IT Cytarabine and
Hydrocortisone day 7

Maintenance (1-4 cycles)
Cyclophosphamide 500 mg/m²/day, days 1-2
Doxorubicin 60 mg/m² day 2
Vincristine 2 mg day 1
Methotrexate 3000 mg/m² over 3 hrs day 1 (with leucovorin)
Prednisone 60 mg/m²/day, days 1-5
IT Methotrexate and Hydrocortisone day 2

LMB 84, 86, and 89
**Prephase**
Cyclophosphamide 200 mg/m²/day, days 1-5
Prednisone 60 mg/m²/day, days 1-5

**Cycle A**
Ifosfamide 800 mg/m²/day, days 1-5
VM26 100 mg/m²/day, days 4 & 5
Vincristine 2 mg day 1
Cytarabine 150 mg/m² q12 hrs x 4 doses, days 4 & 5
Methotrexate 1500mg/m² over 24 hours day 1 (with leucovorin)
Dexamethasone 10 mg/m²/day, days 1-5
IT Methotrexate 15 mg, IT Cytarabine 40 mg, IT Dexamethasone 4 mg, days 1 & 5

**Cycle B**
Cyclophosphamide 200 mg/m²/day, days 1-5
Doxorubicin 25 mg/m²/day, days 4 & 5
Vincristine 2 mg IV day 1
Methotrexate 1500 mg/m² over 24 hours day 1 (with leucovorin)
Dexamethasone 10 mg/m²/day, days 1-5
IT Methotrexate 15 mg, IT Cytarabine 40 mg, IT Dexamethasone 4 mg, day 1

**BNHL-86:** Prephase, followed by alternating A/B cycles for 6 cycles
Cyclophosphamide 800 mg/m² day 1 & 200 mg/m²/day, days 2-5
Doxorubicin 40 mg/m²/day, day 1
Vincristine 1.5 mg/m²/day, days 1 & 8 (no cap)
Methotrexate 1200 mg/m² over 1 h and then 240 mg/m²/hr for 23 hr (with leucovorin) day 10
IT Cytarabine 70 mg days 1 & 3, IT Methotrexate 12 mg day 15

**CODOX-M**

Ifosfamide 1500 mg/m²/day days 1-5 (with mesna)
Etoposide 60 mg/m²/day, days 1-5
Cytarabine 2000 mg/m² every 12 hours for 4 doses, days 1 & 2
IT Methotrexate 12 mg day 5

**IVAC**

*CODOX-M/IVAC: Alternate CODOX-M/IVAC cycles for 4 cycles*
**Cycle 1**
Cyclophosphamide 300 mg/m² q12 hours x 6 doses, days 1-3 (with mesna)
Doxorubicin 50 mg/m² day 4
Vincristine 2 mg/day, days 4 & 11
Dexamethasone 40 mg/day, days 1-4 & 11-14
IT Methotrexate 12 mg day 2 and IT Cytarabine 100 mg day 7

**Cycle 2**
Methotrexate 1000 mg/m² day 1 (with leucovorin rescue)
Cytarabine 3000 mg/m² q12 hours x 4 doses, days 2 & 3
IT Methotrexate 12 mg day 2 and IT Cytarabine 100 mg day 7

**Hyper-CVAD:** Alternate cycles 1 & 2 for 8 cycles
**Prephase**
Cyclophosphamide 200 mg/m²/day, days 1-5
Prednisone 60 mg/m²/day, days 1-5

**Cycles 2, 4, and 6**
Ifosfamide 800 mg/m²/day, days 1-5
Mesna 200 mg/m²/day, at 0, 4, & 8 hours after ifosfamide, days 1-5
Vincristine 2 mg day 1
Etoposide 80 mg/m²/days, days 4 & 5
Cytarabine 150 mg/m²/day continuous infusion, days 4 & 5
Methotrexate 150 mg/m² over 30 min, then 1.35 g/m² over 23.5 hrs, day 1 (with leucovorin rescue)
Dexamethasone 10 mg/m²/day, days 1-5
IT Methotrexate 15 mg, IT Cytarabine 40 mg, IT Hydrocortisone 50 mg, days 1 & 5

**Cycles 3, 5, and 7**
Cyclophosphamide 200 mg/m²/day, days 1-5
Doxorubicin 25 mg/m²/day, days 4 & 5
Vincristine 2 mg IV day 1
Methotrexate 150 mg/m² over 30 min, then 1.35 g/m² over 23.5 hrs, day 1 (with leucovorin rescue)
Dexamethasone 10 mg/m²/day, days 1-5
IT Methotrexate 15 mg, IT Cytarabine 40 mg, IT Hydrocortisone 50 mg, days 1 & 5 *
* Cranial irradiation 24 Gy in 12 fractions after cycle 3

**CALGB 9251:** Prephase, followed by alternating cycles 2-7
Adult Burkitt's Leukemia and Lymphoma

Kristie A Blum, Gerard Lozanski and John C Byrd

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