

Burkitt's Lymphoma

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Updates:

- ❖ Gene expression profiling of Burkitt's Lymphoma (BL)
- ❖ Checking hepatitis B and C serology
- ❖ Hydration and allopurinol
- ❖ Making c-Myc rearrangement assessment mandatory
- ❖ Reference to Dana Farber modification of adult Magrath regimen
- ❖ Recommendations regarding Rituximab addition
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Introduction

Burkitt's lymphoma is a highly aggressive lymphoma often presenting at extranodal sites or as an acute leukemia. It is synonymous with L3 B ALL in the FAB, small non-cleaved cell, Burkitt's type in the working formulation (WF). Historically, the prognosis in adults was poor despite early CR rates, however, recently more dose-intense regimens with CNS prophylaxis similar to pediatric regimens have demonstrated that cure may be achieved in a substantial number of cases [1-4]. There are limited sized series dedicated to this histologic subtype alone.

There are three clinical variants of BL with slightly different clinical presentations, morphologies or biologies. In all three clinical variants, patients are at risk for central nervous system involvement, EBV is found in a variable proportion of cases and the translocation involving Myc is a constant genetic feature.

1. **Endemic BL:** occurs in equatorial Africa and is the most common malignancy of childhood with a peak incidence at 4-7 years. EBV detectable in virtually 100%.
2. **Sporadic BL:** seen throughout the world mainly in young adults with an incidence of 1-2% of all lymphomas occurring at a median age of 30. M: F is 2:1. EBV detectable in < 30%.
3. **Immunodeficiency associated BL:** seen primarily in HIV occurring often as the initial manifestation of AIDS. EBV is identified in 25-40% of the cases. With HAART, the incidence has decreased. May also be seen in other immunodeficiency states e.g. post organ transplant.

Diagnosis

The diagnosis is made morphologically by adequate biopsy specimen, immunohistochemistry, flow cytometry and genetics.

Burkitt's lymphomas are monomorphic, medium sized cells with round nuclei, multiple nucleoli and abundant basophilic cytoplasm. This tumor has an extremely high rate of proliferation and spontaneous cell death. A starry sky pattern is usually seen, imparted by macrophages ingesting the apoptotic tumor cells. The immunophenotype is SigM+, B-cell associated antigens+ (CD19, CD20, CD22, CD79a), CD10+, BCL6 +, and CD23-). BL cells are negative for CD5, CD23, Bcl-2 and TdT. Virtually all express Ki-67, giving this tumor a growth fraction of 100%.

A defining feature of Burkitt's lymphoma is the presence of a translocation between c-Myc and the IgH gene (found in 80% of cases (t(8;14)) or between c-Myc and the gene for either kappa or lambda light chain (IgL) in the remaining 20% (t;2;8) or t (8;22) respectively. Other specific lymphoma associated translocations such as IgH/bcl-2 and translocation involving bcl-6 are absent.



The male to female ratio is 2-3:1. In non-endemic cases, the majority of the cases present in the abdomen, most often involving the distant ileum, cecum or mesentery; ovaries, kidneys or breasts may be involved. Rare cases present as acute leukemia with L3-ALL. Clinically, over 50% present with bulky or advanced stage disease [2, 5]. Bone marrow and central nervous system (CNS) involvement is reported in 30-38% and 13-17% of adults respectively [6, 7].

In the WHO classification, BL has two morphologic variants [8].

The two variants are:

1. **BL with plasmacytoid differentiation:** seen more commonly in children or immunodeficiency states.
2. **Atypical Burkitt/Burkitt-like:** composed of medium-sized Burkitt cells with greater pleomorphism in nuclear size and shape intermediate between typical large cell lymphoma (DLBCL) and classical BL. Diagnosis requires a growth fraction of nearly 100% and is reserved for cases with proven or strong presumptive evidence of Myc translocation. These are sometimes difficult to distinguish between high-grade DLBCL.

Distinguishing DLBCL or high grade NOS from BL or BLL

5-15% of DLBCL may also have Myc rearrangements although they tend to be more likely variant translocations and neoplastic cells tend to have more complex karyotypic abnormalities [9]. In one recent study [10], phenotypic and genotypic differences were detected between BLL and DLBCL archival pathology samples. Compared with DLBCL, BLL had a higher proliferative rate (mean Ki-67 88% vs. 53%), greater expression of CD10 (88% vs. 53%) and p53 expression (54% vs. 16%) and lower expression of Bcl-2 (15 vs. 53%). BLL cases had a consistent absence of one or more cell adhesion molecules (92% vs. 27%), low tumour infiltrating T-lymphocyte numbers and absence of CD44 homing receptor (92% vs. 14%). The t(8;14) translocation was found in 80% of BLL cases, but no patients with BLL had the t(14;18) translocation. Median survival for BLL was 1.2 years and 2.5 years for DLBCL. Although 5-year survivals were similar, 1-year survival in BLL was 50% compared with 85% in DLBCL. Double-hit lymphomas with both c-Myc and bcl-2 translocations lead to lymphomas with very poor prognosis[11].

Molecular diagnosis may also help distinguish BL from DLBCL. In a recent project of the lymphoma/leukemia molecular profiling project, gene expression classifiers readily distinguished BL from DLBCL by the high expression of c-Myc target genes, the expression of a subgroup of germinal-center B-cell genes, the low level of expression of MHC complex class I genes and nuclear factor-kB target genes. In this study, 7% of 232 patients with DLBCL expressed c-Myc translocation by FISH; 1/9 high-grade DLBCL cases were molecularly classified as BL and 8/26 (31%) of cases morphologically labeled as DLBCL or high-grade lymphoma NOS had molecular signatures of BL. Patients treated with CHOP had inferior clinical outcomes to those treated with more intensive chemotherapy regimens, highlighting the importance of better classification of BL by techniques other than morphology, immunophenotype and cytogenetics [12].

Detection of c-Myc translocations by FISH or PCR is mandatory. In the absence of this information, BLL cases with high mitotic indices (Ki67 staining exceeding 99%), strong CD10 expression and absent CD44 expression should be treated as BL. All patients should have CSF sampling for differential, flow cytometry and molecular testing at baseline. All other cases of BLL should receive CHOP-Rituxan.



Baseline Investigations

The nature of initial staging investigations depends on the treatment intent. Patients who are planned for intensive treatment should have the following investigations:

- ❖ CBC, differential
- ❖ Blood film
- ❖ Serum electrolytes and creatinine
- ❖ Liver function tests
- ❖ Serum LDH, uric acid
- ❖ Chest x-ray
- ❖ CT chest, abdomen, pelvis
- ❖ Bone marrow biopsy
- ❖ HIV blood test
- ❖ Hepatitis B and C serology
- ❖ LP for cell count and differential and flow cytometry and/or molecular clonality testing if applicable

Pathologists to request that c-Myc and BCL-2 be investigated by PCR or FISH for the commonly seen translocations.

Because of the rapid doubling time of this lymphoma, patients should be admitted for staging with aim to start therapy within 48 hours of diagnosis. Patients should be hydrated and placed on allopurinol for tumor lysis prophylaxis.

Cardiac Assessment

Patients planned for anthracycline-based chemotherapy should undergo 2D-echocardiogram or MUGA scan should be performed if they have a history of:

- ❖ Age > 65
- ❖ Hypertension
- ❖ Congestive heart failure
- ❖ Peripheral vascular disease
- ❖ Cerebrovascular disease
- ❖ Angina
- ❖ Cardiac arrhythmia
- ❖ Myocardial infarction

Anthracyclines should be **used with caution** in patients with an EF < 45%, recent MI (< 3 months) or severe arrhythmia.

Staging & Prognosis

Staging was historically performed according to the scheme proposed by St. Jude or Murphy and modified by Magrath. Staging is related to tumour burden and identifies patients with limited stage disease and patients with extensive intra-abdominal or intrathoracic tumour. Approximately 30% of patients present with limited-stage disease and 70% with advanced stage disease. The bone marrow is positive in 30-38% and the CNS is involved in 13-17% of adults [13].



Staging System for Burkitt's Lymphoma [8]

| Stage | Definition |
|-------------|---|
| Stage I | A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen. |
| Stage II | A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. |
| | Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. Primary gastrointestinal tract tumour, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only. |
| Stage II R | Completely resected abdominal disease. |
| Stage III | Two single tumours (extranodal) on opposite sites of the diaphragm. Two or more nodal areas above and below the diaphragm. |
| | All primary intrathoracic tumours (mediastinal, pleural, thymic). All paraspinal or epidural tumours, regardless of other tumour site(s). All extensive primary intraabdominal disease. |
| | Stage III A |
| Stage III B | Widespread multiorgan abdominal disease. |
| Stage IV | Any of the above with initial CNS and/or bone marrow involvement (< 25%) |

Today, it is acceptable to use the Ann Arbor staging system. **Adverse prognostic factors** include [4, 14-16]:

- ❖ Advanced stage: stage IV or intra-abdominal and extra-abdominal tumor
- ❖ LDH > 500
- ❖ Bulky mass > 10 cm
- ❖ Bone marrow or CNS involvement at presentation
- ❖ Age > 40
- ❖ Poor performance status
- ❖ Circulating blasts

At the MDACC, [14], The FFS and OS at 5 years were superior for patients with limited stage disease (Ann Arbor) and age < 40.

| | FFS | OS |
|------------|-----|-----|
| Stage I-II | 91% | 78% |
| Stage IV | 25% | 25% |
| Age <40 | 70% | 60% |
| Age >40 | 40% | 37% |

The IPI has been validated as a prognostic tool in patients without CNS or BM involvement [17].



Management

Systemic Chemotherapy is the Treatment of Choice in BL

Short-duration, intensive regimens that minimize treatment delays and maintain serum drug concentrations for at least 48 to 72 hours and CNS prophylaxis have the greatest efficacy in BL and surpass the prolonged ALL regimens. There are no randomized clinical trials in adult BL to guide therapy and the management of SNCL NHL is restricted to single centre phase II prospective or retrospective case series [7, 14-26] of limited size.

The French LMB 81, 84, 86 and 89 regimens, the German-Berlin-Frankfurt-Munster (BFM) protocols, CODOX-M-IVAC, HyperCVAD and CALGB 9251 are the most frequently cited regimens in the literature. Comparison between these treatment regimens is difficult in adult BL because of differences in patient populations (age, stage, HIV+) [15], staging classifications (St. Jude vs AA) and pathology (BL or BLL or both). Depending on the regimen and case series, 65-100% of adults achieve a CR and 47-86% maintain these remissions for > 1 year [13]. What unify these studies are the improved results achieved by the principles of CNS prophylaxis, dose escalation and fractionation of conventional chemotherapy agents, and the use of multi-agent alternating chemotherapy in a fashion to decrease drug resistance.

Maintenance chemotherapy has failed to avert relapse and is not indicated. Most patients destined to relapse do so within the first year of diagnosis, therefore it is unnecessary to prolong therapy for 1 year or longer.

Results of treatment of adult BL [13]

| Reference | Protocol | No. of Patients treated | Median age, y (range) | CR, % | DFS, % | EFS, % | OS, % |
|----------------------|--------------------|-------------------------|-----------------------|-------|-------------|-------------|-------------|
| Divine, et al. [27] | LMB 81, 84, 86, 89 | 72 | 33 | 83 | N/A | 65 at 2 y | 70 at 2 y |
| Adde, et al. [28] | CODOX-M/IVAC | 26 | 25 (18-59) | 92.3 | N/A | 84 at 1 y | N/A |
| LaCasce, et al. [29] | CODOX-M/IVAC | 14 | 47 | 86 | 72 at 21 mo | N/A | N/A |
| Mead, et al. [6] | CODOX-M/IVAC | 52 | 35 (15-60) | 75 | N/A | 64.6 at 2 y | 72.8 at 2 y |
| Thomas, et al. [30] | Hyper-CVAD | 26 | 58 (17-79) | 81 | 61 at 3 y | N/A | 49 at 3 y |
| Thomas, et al. [31] | R-Hyper-CVAD | 31 | 46 (27-77) | 86 | 88 at 3 y | 80 | 89 |
| Lee, et al. [32] | CALGB 9251 | 54 | 44 (18-71) | 80 | 50 at 4 y | N/A | 52 at 4 y |

One highly efficacious regimen was pioneered at the NCI by Magrath, et al. [24, 33]. It stratified patients according to low-risk and high-risk subgroups and treated them differently. The protocol consists of two alternating regimens: A. CODOX-M and B. IVAC (**see Appendix B**) [21]. Low-risk (LR) patients were defined as a single extra-abdominal mass or completely resected abdominal disease and a serum LDH < 350 (within the institution normal range) and received 3 cycles of protocol A (CODOX-M). All other patients were high-risk (HR) and received 4 alternating cycles of A, B, A, B. Patients with CNS disease at presentation received additional IT therapy during the first two cycles.

In a recent report [28] 66 patients with BL, BLL and DLBCL were treated with the Magrath protocol. Of the 26 adults included in this trial, 13 had BL and 7 had BLL. Sixty-one out of sixty-six patients achieved a complete response to therapy. The EFS was 85% at one year and beyond with a median follow-up of 48 months. The major toxicities were hematologic with grade IV neutropenia and thrombocytopenia commonly seen, stomatitis, severe neuropathy and infection. Toxic death rate was 5%.

Magrath Regimen in the Adult Population with Burkitt's Lymphoma

The United Kingdom Lymphoma Group (UKLG) LY06 [6] applied a modified-Magrath protocol to a primarily adult BL patient population with a median age of 35 yrs (83% > age 21). The study was multi-centre (39 centers) and excluded BLL (unlike Magrath study). Day 15 vincristine in CODOX-M was omitted in order to decrease neuropathy rates and vincristine was capped. IPI-based criteria were used to divide patients into prognostic groups. The patients with **all of the following features were regarded as low risk (LR): 1. Normal LDH 2. WHO performance status 0-1 and 3. No tumour mass ≥ 10 cm. All remaining patients were considered high risk (HR). Results:** 52 patients were evaluable with confirmed central



pathological review (12 LR and 40 HR). 41/52 completed protocol treatment with a 2-yr EFS of 64.6% (95% CI 50 to 79%) and 2-yr overall survival (OS) of 73% (95% CI 59 to 86%). For **LR**, 2 yr. EFS and OS were 83% and 81.5 %, and for **HR**, 2 year EFS and OS were 60% and 70% respectively (**see graphs on page 8-9**). The relapse rates for patients achieving CR were low (0% LR and 12.5% HR). Treatment related toxicity was severe. 21% of patients were unable to complete therapy and 43% of high-risk patients received full-dose therapy with 3 treatment related deaths. Poor **prognostic markers** included increased **age, IPI > 1 and BM involvement**. Similarly, a **Dana Farber** study of 14 adults with median age of 47 years treated with a different modified Magrath regimen (modified schedule of fractionated cyclophosphamide, capped vincristine, reduced dose HDMTX and escalated doxorubicin) demonstrated a 86% CR rate, 2 year EFS and OS of 64% and 71% for all patients respectively (100% for LR and 60% for HR). There were no therapy related deaths and all patients completed therapy [29]. This study reinforces the excellent clinical results achieved with the modified Magrath regimen in an older more homogeneous population and supports its continued use.

Hyper-CVAD [34] is another promising abbreviated chemotherapy protocol that has been applied as front-line therapy in adult patients with B-cell ALL. It is a modified regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with HDMTX and HDARAC-Ara-C for a total of 8 cycles and a total duration of 6 months. CNS prophylaxis consists of alternated IT MTX and ARA-C on days 2 and 11 of each course.

Recent results at the MD Anderson in a prospective non-randomized trial of 26 adult patients with Burkitt's Type ALL (L3) have found the CR rate to be 81%, the treatment related mortality to be 19% and the 3-year survival rate to be 49% (+/- 15%). The 3-year continuous CR rate was 61%. Regression analysis identified older age, anemia and the presence of peripheral blasts as independent factors associated with shorter survival. The 3-yr survival in patients < 60 was 77% (n=14) compared with 17% for patients older than age 60 (n=12). Patients could be stratified according to the presence and number of prognostic features into 3-year survival rates: 89%, 47% and 0% for 0-1, 2, or 3 adverse features [30]. Use of this protocol in 204 patients with all types of adult ALL (B and T) at the MD Anderson found the projected 5 yr survival rate to be 40% and EFS rate to be 38%, with 2 years of maintenance chemotherapy offered to all non-mature B-cell ALL [35, 36].

Another abbreviated regimen in adults is CALGB 9251 with CR 80% and 4 yr DFS 50% [32]. Both studies reported inferior DFS and increased toxicity/mortality in patients aged > 50-60. Though this protocol shows promise (**see table on page 5**), there is insufficient evidence at this point to justify its use as upfront therapy for Burkitt's lymphoma/leukemia, given the excellent results obtained with the Magrath regimen.

Odette Cancer Centre Policy

- ❖ The recommended first-line regimen for BL and atypical Burkitt/Burkitt-like lymphoma at the Odette Cancer Centre will be the modified UK Magrath regimen [6]. For patients greater than 60, it is reasonable to cap the MTX dose at 3 grams/m²

Management of Low-Risk or Localized Stage Disease

Low risk presentations of SNCL are rare (18-25%) and associated with favorable results (CR rates of 100% and 2-5 FFP rates of 95-100%).

At our center, they must meet all of these criteria:

1. Normal LDH
2. WHO performance status 0-1
3. No tumour mass ≥ 10 cm.

All patients should be fully staged including bone marrow biopsy and LP. Patients with Low risk disease should receive 3 cycles of modified CODOX-M of the Magrath protocol (**see Appendix B**).



Management of High-Risk Disease

All other patients should receive 4 alternating cycles (A, B, A, B) of the modified Magrath regimen with modification of vincristine dose not to exceed 2 mg (**see Appendix B**). Patients should be re-staged after 2 cycles to assess remission status. Patients with **CNS involvement at presentation** should receive intensified treatment with IT cytarabine and methotrexate as described in **Appendix B**. Patients with parenchymal disease may be considered for cranial irradiation.

Management of HIV + Associated Small Non-Cleaved NHL

BL constitutes approximately 30-40% of all HIV associated NHL, is frequently the AIDS- defining illness and is often associated with a relatively well preserved CD4 count. BL in HIV is EBV associated in 40%. Since the introduction of HAART in 1995/6, the incidence of NHL overall has decreased sixfold, and the survival for DLBCL has improved significantly [37]. The addition or maintenance of HAART while on chemotherapy has been demonstrated to result in increased CD4 counts and decreased viral load [38] and is currently recommended. In a recent Spanish retrospective survey of AIDS-related HAART-era NHL (n=210) inclusive of BL and BLL (n=40), CR was associated exclusively with tumor related-factors with inferior CR results seen with BL. IPI, CR and histologic subtype predicted for OS [39]. CHOP or CHOP-like chemotherapy in the era of HAART is insufficient treatment for the management of HIV associated BL [37]. In one small series at the MD Anderson, 12/44 patients with BL had HIV and were treated with protocols of moderate intensity and multi-drug combinations [15]. They had an 83% CR rate and an 83% five-year freedom from tumor mortality (FTM). OS at five years was 36% with most deaths from opportunistic infections (PCP, CMV, TB and KS). Burkitt-specific therapy was recently attempted in a small series (n=14) of AIDS related cases using CODOX-M/IVAC regimen at MSKK; a 63% CR rate and 60% 2 year EFS were seen with similar rates of myelosuppression and infectious complications as HIV negative patients [40]. Finally, the Germans showed that short intensive polychemotherapy (adapted from GMALL) is feasible and effective in AIDS-associated BL or BLL and superior to conventional CHOP-like chemotherapy [41].

Negative prognostic factors related to survival of patients with AIDS-related lymphoma: BM or kidney involvement, a history of prior opportunistic infections or Kaposi's sarcoma, or a CD4 count < 200/mm³ [42].

Odette Cancer Centre Policy

- ❖ HIV positive patients without Kaposi's sarcoma and a CD4 count > 200 on HAART should be treated according to protocol with adequate PCP and CMV prophylaxis. Patients with a CD4 count of < 200 who have never received HAART may also be considered for full dose modified Magrath regimen with the initiation of HAART treatment simultaneously. Patients with more advanced HIV should be offered palliative reduced dose CHOP chemotherapy with IT chemotherapy as CNS prophylaxis. HIV patients may require more aggressive transfusion and GCSF/ESA support.

Role of surgery: Surgical de-bulking is no longer recommended unless surgery for other reasons at presentation is necessary (e.g. perforation, intussusception, bleeding, etc.).

Role of Radiotherapy: Radiotherapy is not indicated, as the sole method of treatment in Burkitt's lymphoma and its role as an adjuvant is uncertain. There is no role for prophylactic cranial or spinal irradiation in the treatment of BL for CNS prophylaxis if IT and HD systemic chemotherapy (HDMTX, cytarabine) is administered.

Concomitant therapy, Dose Modification and Growth Factor Support: Patients are at increased risk of tumour lysis syndrome and should be started on allopurinol (if not contraindicated) and aggressive hydration prior to commencing chemotherapy. Given the > 40% rates of grade 4 neutropenia anticipated in most chemotherapy regimens for SNCL, and given the curative intent of administration, all patients would receive G-CSF at 5 µg/kg SQ daily to commence day 13 of CODOX-M and day 7 of IVAC. It should be continued until ANC > 1.0.



Rituximab in BL

The role of rituximab in combination with chemotherapy for BL is currently unknown. Case reports of its efficacy as monotherapy or in combination with low dose chemotherapy for relapsed or refractory disease are promising [43, 44,]. 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 2 and 8 of cycles 2 and 4. A total of 8 alternating courses were given (31, 45). To date, 31 patients with BL (17) or B-ALL (14) at the MD Anderson have received R-Hyper-CVAD according to this schedule with a CR rate of 86% and 3 yr DFS and OS of 88% and 89% respectively. These results were significantly superior to historical cohort of 48 patients who received Hyper-CVAD alone (3 year DFS and OS 53% and 60%) without an increase in myelosuppression or infectious toxicity [31]. The CALGB has also incorporated rituximab in its latest BL regimen (CALGB 10002) with rituximab administration occurring during each cycle except the cytoreductive phase. This planned study of 100 patients is still accruing. There are reports of its successes in use at relapse in pediatric B-ALL/BL [46]. It is reasonable to explore privately funded rituximab (375 mg/m² day 1 of each cycle of chemotherapy) despite lack of CCO reimbursement.

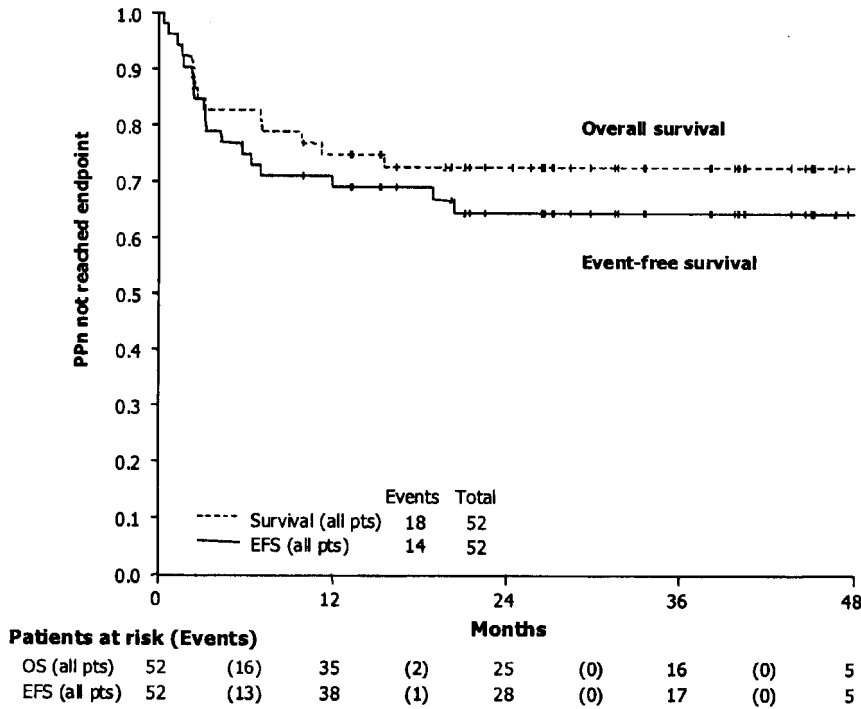
Management of Relapse or Partial Responders

All patients who achieve a PR have been found to relapse and die of progressive disease without additional therapy. When relapse occurs, it usually occurs within 1 year of diagnosis so those who survive 2 years without recurrence can be considered cured. Historically, the prognosis associated with relapse or incomplete response in BL was poor. With the advent of more aggressive salvage chemotherapy regimens, results have improved somewhat but are still disappointing. Nevertheless, most centres would treat such patient as extremely high-risk and it is recommended that eligible patients be referred for consolidative high-dose therapy followed by hematopoietic stem cell transplant depending on the timing of relapse, a reasonable choice for salvage chemotherapy could involve the MDACC Hyper-CVAD +/- R [30] or a regimen with non-cross-resistant chemotherapy agents such as ESHAP +/- R.

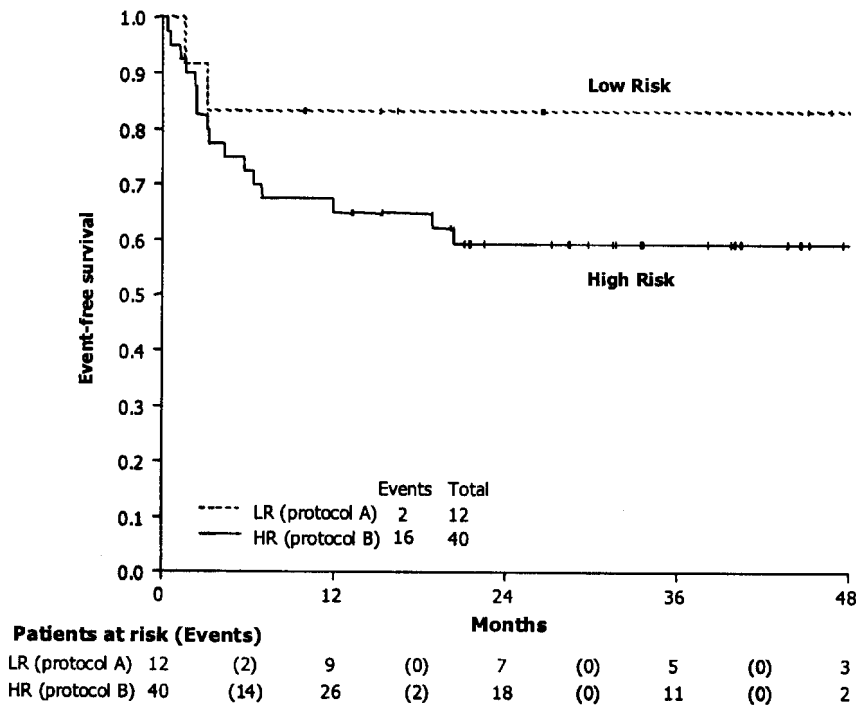
Given excellent results expected with current aggressive multi-agent conventional chemotherapy, there is insufficient evidence to support the routine consolidation of BL patients in CR1 with high dose chemotherapy/transplant. It should be considered in chemosensitive first relapse.



United Kingdom Lymphoma Group LY06 Study of Modified Magrath in 52 Adults



Overall and event-free survival for all patients (pts; n = 52) [6]



Event-free survival for all patients (n = 52) [6]

Mead, G.M., et al., *An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study*. Ann Oncol, 2002. 13(8): p. 1264-74. Copyright 2002 Oxford University Press. All rights reserved, used with permission.



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