Approach to the Diagnosis and Treatment of Adult Burkitt's Lymphoma

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ASSOCIATED CONTENT

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Abstract

Burkitt's lymphoma is a rarely encountered, aggressive B-cell lymphoma that is highly curable in children and young adults. In middle-aged and older adults, however, administering curative therapy may be challenging because standard Burkitt's lymphoma platforms are associated with high treatment-related toxicity in these age groups. Because of its high curability, the testing of alternative, less toxic approaches in Burkitt's lymphoma has been challenging. Although the critical role of *MYC* in Burkitt's lymphoma has been well described, recent biologic insights have identified several new mutations that cooperate with *MYC* in driving lymphomagenesis, paving the way for novel drug testing in this disease. Recently, intermediate-intensity approaches have been tested in Burkitt's lymphoma. Early multicenter results demonstrate good tolerability while maintaining high cure rates in all patient and age groups.

INTRODUCTION

Burkitt's lymphoma was originally described more than 50 years ago in Ugandan children with unusual jaw tumors in association with other specific anatomic sites.[1] This endemic variant occurs in specific geographic areas and typically affects boys between the ages of 4 and 7 years (Table 1). Sporadic Burkitt's lymphoma, in contrast, affects children and young adults in all regions of the world, and immunodeficiency-associated Burkitt's lymphoma is associated with HIV infection. Recently, with genomic technology advances, several novel mutations that cooperate with *MYC* and have key roles in Burkitt's lymphoma pathogenesis have been identified in all Burkitt's lymphoma subtypes. Although traditional treatment platforms for this disease are highly toxic, less toxic strategies that maintain the high cure rates of intensive standard treatments have recently been developed. Currently, the optimal treatment of adults with Burkitt's lymphoma is controversial.

PATHOLOGY AND BIOLOGY

Burkitt's lymphoma has a proliferation rate approaching 100%, and this accounts for its classic starry-sky appearance under the microscope (resulting from apoptotic tumor cells ingested by macrophages). Tumor cells are typically intermediate in size and nonpleomorphic with basophilic cytoplasm containing small vacuoles and round nuclei. The nuclear chromatin is granular with small nucleoli and frequent mitoses. Burkitt's lymphoma is of germinal center B-cell origin with tumor cells expressing CD10, BCL6, CD20, CD79a, and CD45; Epstein-Barr virus expression is detected in approximately 25% to 40% of sporadic and HIV-associated cases. The *MYC* translocation that is pathognomonic of the disease is typically at 8q24

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Table 1. Comparison of Endemic, Sporadic, and HIV-Associated Burkitt's Lymphoma

Variable	Endemic	Sporadic	HIV Associated
Epidemiology	Equatorial Africa and Papua, New Guinea. Regions of South America.	Worldwide	Worldwide
Incidence	Five to 10 cases per 100,000 people	Two to three cases per 1 million people	Six per 1,000 AIDS cases
Age and sex	Peak incidence: 4-7 years. Male/female ratio of 2:1.	Median age: 30 years. Male/female ratio of 2-3:1.	Median age: 44 years. Associated with CD4 counts $> 100/mm^3$.
Epstein-Barr virus positivity	100%	25% to 40%	25% to 40%
Genomics	*MYC* mutation, 100%; *ID3* and/or *TCF3* mutations, 40%; *CCND* mutations, 1.8%.	*MYC* mutation, 100%; *ID3* and/or *TCF3* mutations, 70%; *CCND* mutations, 38%.	*MYC* mutation, 100%; *ID3* and/or *TCF3* mutations, 67%; *CCND* mutations, 67%.
Clinical presentation	Jaw and facial bones in approximately 50% of cases. Also involves mesentery and gonads. Increased risk of CNS dissemination.	Ileocecal region is most common area of involvement. Other extranodal sites include bone marrow, ovaries, kidneys, and breasts. Increased risk of CNS dissemination.	Nodal presentation most common, with occasional bone marrow. Increased risk of CNS dissemination.

and causes deregulation of the *MYC* gene.[2,3] The translocation partner for *MYC* is usually the immunoglobulin heavy-chain locus on chromosome 14; otherwise, there is involvement of κ and λ light-chain loci on chromosomes 2 and 22.

RNA sequencing studies recently identified novel mutations that cooperate with *MYC* in sporadic Burkitt's lymphoma.[4-7] Approximately 70% of cases have mutations in *TCF3* or its negative regulator *ID3*, which encodes a protein that blocks *TCF3* activity. In addition, approximately one-third of sporadic cases have a mutation in *CCND3*, which encodes cyclin D3. Burkitt's lymphoma is of germinal center B-cell origin with a signature that has high expression of c-*MYC* target and germinal center–associated B-cell genes.[8,9] Differentiating Burkitt's lymphoma from diffuse large B-cell lymphoma (DLBCL) at initial diagnosis may be sometimes challenging and is important clinically because treatment of the two entities is typically distinct. Early gene expression profiling studies demonstrated that a subset of Burkitt's lymphoma cases diagnosed as DLBCL by histologic criteria actually fall into the Burkitt's lymphoma category by gene expression profiling.

CLINICAL PRESENTATION AND WORK-UP

The clinical presentation of Burkitt's lymphoma varies according to the epidemiologic variant and additional factors. In the United States, sporadic and immunodeficiency-associated Burkitt's lymphoma are the subtypes that are encountered and, in both of these, the ileocecal area is the most common site of disease involvement. CNS involvement (which is typically leptomeningeal rather than parenchymal) may occur at presentation, particularly when there is advanced-stage disease. Because of the high proliferation rate of the tumor, in cases where there is bulky disease, there is a high risk of tumor lysis syndrome developing after the institution of therapy (and, in some cases, even before any treatment is started [ie, auto tumor lysis]). Tumor lysis syndrome prophylaxis should therefore be considered and instituted as appropriate. In making the diagnosis of Burkitt's lymphoma, the distinction from other (non-Burkitt's lymphoma) cases of aggressive B-cell lymphomas that also harbor a *MYC* translocation is important and can sometimes be challenging. In addition to routine laboratory and imaging studies, a bone marrow aspirate and biopsy should be performed at diagnosis and CSF analysis should be done for tumor cells by cytology and flow cytometry. The Ann Arbor classification is widely used for staging. Unlike the case with DLBCL, in Burkitt's lymphoma there is no validated prognostic score, but population-based studies have identified prognostic factors such as age, black race, advanced stage, performance stage, and elevated lactate dehydrogenase (LDH) level.[10-13] Many studies have identified a low-risk category of Burkitt's lymphoma characterized by normal LDH level, Eastern Cooperative Oncology Group performance status 0 or 1, and Ann Arbor stage I or II plus no mass greater than 7 or 10 cm.[14,15]

APPROACH TO TREATMENT

HIV-Negative Adults With Burkitt's Lymphoma

Early strategies for the treatment of adults with Burkitt's lymphoma were modeled on dose-intensive approaches that had high efficacy in childhood acute lymphoblastic leukemia. For the most part, these types of treatments remain the standard. Although these are tolerated relatively well by children and young adults, toxicity is a huge challenge in treating adults, particularly older and immunosuppressed people.[16] This toxicity challenge led to the testing of risk-adaptive therapy where people with low-risk disease receive less intensive/shorter-duration therapy. This has been somewhat helpful in the treatment of adult Burkitt's lymphoma. However, it should be noted that, by the various definitions used, only a small proportion of newly diagnosed Burkitt's lymphoma cases have low-risk disease.[15] The risks of developing tumor lysis syndrome and CNS spread of disease are also important considerations at initial diagnosis. To reduce tumor lysis syndrome, many regimens use a prephase, where relatively low doses of chemotherapy drugs (typically cyclophosphamide) and prednisone are administered. High-dose intravenous methotrexate and cytarabine (as well as intrathecal administration of these agents), both of which have CNS penetration, are frequently administered in an attempt to reduce CNS spread of disease. Some have questioned the need for intrathecal therapy in low-risk disease. One study demonstrated a high cure rate and a low rate of CNS relapse without the use of intrathecal therapy in low-risk Burkitt's lymphoma.[17]

Compared with DLBCL, Burkitt's lymphoma is rare in adults. There is a paucity of clinical trials to inform decisions on optimal therapy, particularly in middle-aged and older adults for whom toxicity poses a significant challenge to successful outcomes.[18] Many of the standard approaches that are used in adults today were initially developed in children (Table 2).[15,18,19-28] For example, an early risk-adapted strategy in children (LMB89) was developed on the basis of tumor burden and early response to chemotherapy.[19] Three risk groups (A, B, and C) were defined, with group A receiving induction only; group B receiving prephase, induction, consolidation, and limited maintenance; and group C receiving extended maintenance and cranial irradiation in cases with involvement of the CNS. In groups B and C, autologous stem-cell transplantation was performed if a complete remission was not achieved. Overall, this strategy was successful, with 5-year event-free survival (EFS) and overall survival (OS) rates of 92% that led to its testing in adults with minor modifications: In 72 patients with a median age of 33 years, EFS and OS rates at 2 years were 65% and 70%, respectively.[20] The Berlin-Frankfurt-Munster group developed approaches that reduced the number of cycles on the basis of risk stratification; in 266 pediatric patients with Burkitt's lymphoma, the overall EFS rate was 89% at 6 years.[21] CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate [CODOX-M]/ifosfamide, cytarabine, and etoposide [IVAC]; Magrath regimen), which is commonly used today, was developed at the National Cancer Institute.[22] In initial studies, patients were risk-stratified according to clinical characteristics. Low risk constituted the group with a tumor mass less than 10 cm or completely resected abdominal disease and a normal LDH level. All other patients were designated high risk. Low-risk patients received three cycles of CODOX-M and high-risk patients received four cycles of alternating CODOX-M with IVAC. With this approach, in 41 patients including 20 adults (median age, 25 years), the EFS rate was 92% at 2 years. Other groups confirmed the efficacy of this regimen, although with lower survival rates. Mead et al[15] studied this approach in 52 adult patients and showed an overall EFS rate of 65% at 2 years (83% and 59% for the low- and high-risk arms, respectively). A modified Magrath regimen has been tested in older adults and was found to be effective and well tolerated. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD) is another effective strategy in Burkitt's lymphoma.[23,24] For standard treatment of adults with Burkitt's lymphoma, most have favored the Magrath or modified Magrath regimens (depending on risk group) with the addition of rituximab. The benefit of administering rituximab in front-line Burkitt's lymphoma therapy has been demonstrated in both adults and children, and it is standard treatment in both groups. A study using a lymphome malin B (LMB) chemotherapy backbone randomly assigned 260 adult patients to receive rituximab or no rituximab.[25] With a median follow-up of 38 months, 3-year EFS was superior in the arm that received rituximab (75% *v* 62%). Recently, an international Children's Intergroup performed a phase III study adding rituximab to the LMB96 chemotherapy backbone in children with Burkitt's lymphoma and DLBCL. The study planned to accrue 600 patients. However, an interim analysis of 310 patients demonstrated a survival advantage (1-year EFS rate of 94% *v* 81%) in the rituximab group, leading to cessation of the randomization.[29] Another recent large prospective multicenter trial looked at the feasability of short-intensive chemotherapy combined with rituximab in

Table 2. Selected Regimens for High-Risk Burkitt's Lymphoma

Regimen	No. of Patients	Histology	Median Age, Years (range)	Stage (%)	EFS
LMB 89[19]	561	Burkitt's/B-ALL	8 (0.17-18)	III-IV (79)	92% at 5 years
Modified LMB[20]	72	Burkitt's/B-ALL	33 (18-76)	III-IV (67)	65% at 2 years
BFM 90[21]	413	Burkitt's/B-ALL	9 (1.2-17.9)	III-IV (60)	89% at 6 years
CODOX-M/IVAC[22]	21 children	Burkitt's	12 (3-17)	III-IV (78)	85% (children) and 100% (adults) at 2 years
	20 adult	B-ALL	25 (18-59)		
CODOX-M/IVAC[15]	52	Burkitt's	35 (15-60)	III-IV (61)	65% at 2 years
Hyper-CVAD[23]	26	Burkitt's/B-ALL	58 (17-79)	NA	61% at 3 years for DFS
R-Hyper-CVAD[24]	31	Burkitt's/B-ALL	46 (17-77)	NA	80% at 3 years
GMALL-B-ALL/NHL 2002[28]	363	Burkitt's/B-ALL	42 (16-85)	III-IV (71)	PFS 75% at 5 years
DA-EPOCH-R[26]	19	Burkitt's	25 (15-88)	III-IV (58)	FFP 95% at 7 years
SC-EPOCH-RR[26]	11	Burkitt's HIV positive	44 (24-60)	III-IV (82)	FFP 100% at 6 years
LMB +/− R[25]	260	Burkitt's	NA	III-IV (62)	EFS 75% *v* 62% (+R/-R) at 3 years
AMC 048[27]	34	Burkitt's HIV positive	42 (19-55)	III-IV (74)	PFS 69% at 1 year
Modified R-CODOX-M/IVAC					
Modified R-CODOX-M/IVAC[15]	128	Burkitt's HIV negative	47 (IQR, 31-59)	III-IV (62)	EFS 75% at 3 years
RA-DA-EPOCH-R[18]	113	Burkitt's HIV negative and HIV positive	49 (18-86)	III-IV (64)	PFS 86% at 3 years

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; CODOX-M, cyclophosphamide, doxorubicin, vincristine, methotrexate; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DFS, disease-free survival; EFS, event-free survival; FFP, freedom from progression; GMALL-B-ALL/NHL, German Multi-Center Group for Adult ALL–B-cell Acute Lymphoblastic Leukemia/Non-Hodgkin Lymphoma; IVAC, ifosfamide, cytarabine, and etoposide; LMB, lymphome malin B; NA, not available; PFS, progression-free survival; R, rituximab; RA-DA-EPOCH-R, risk-adapted DA-EPOCH-R; R-CODOX-M/IVAC, rituximab, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and high-dose cytarabine; R-Hyper-CVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; SC-EPOCH-RR, short-course etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab, rituximab.

363 patients and reported a progression-free survival (PFS) and OS at 5 years of 71% and 80%, respectively, and much better outcomes in younger patients.[28] Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) is an intermediate-intensity strategy, which was tested in Burkitt's lymphoma because of its high efficacy in DLBCL and its hypothetical ability to overcome high tumor proliferation.[26,29] An early small, single-center study testing the strategy in 30 patients with sporadic[18] and immunodeficiency-associated[11] Burkitt's lymphoma demonstrated a freedom from progression rate greater than 90%, with low toxicity and low rates of tumor lysis syndrome. Recently, multicenter results of this approach were reported (completed accrual), where low-risk patients (all with stage I or II disease, normal LDH levels, Eastern Cooperative Oncology Group performance status of 0 to 1, and mass < 7 cm) received three cycles of therapy and high-risk patients (all others) received six cycles of therapy (Fig 1). In 113 accrued patients, PFS rates were 100% and greater than 80% in low- and high-risk groups, respectively, at more than 2 years follow up.[18] Older age or HIV status had no significant impact on outcome, and overall toxicity was low. The group with CNS involvement at diagnosis fared poorly compared with those who were CNS negative. However, it is not clear how much overlap there was with other

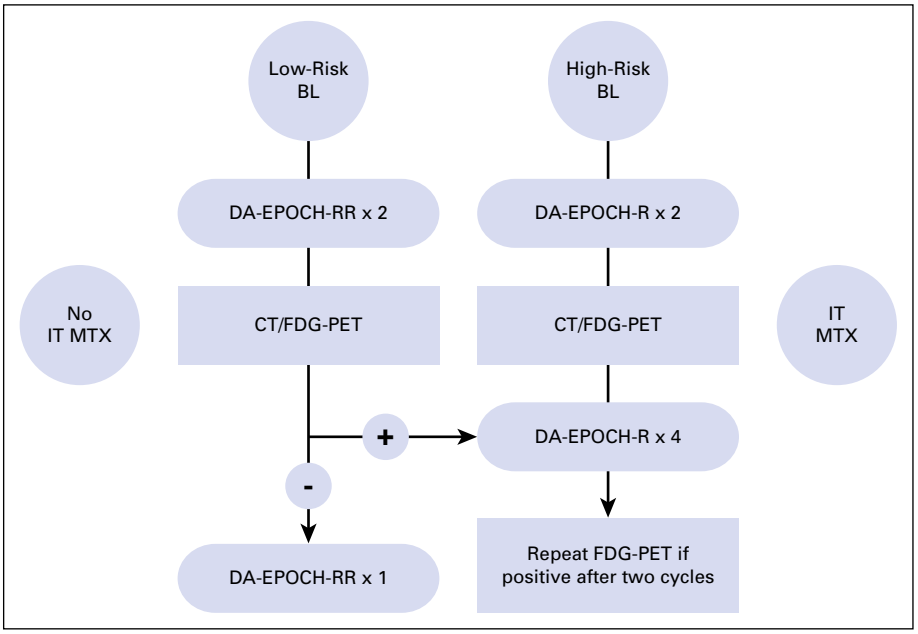

Fig 1. Risk-adapted DA-EPOCH-R in low-risk and high-risk Burkitt's lymphoma. BL, Burkitt's lymphoma; CT, computed tomography; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; DA-EPOCH-RR, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab, rituximab; FDG, fluorodeoxyglucose; IT, intrathecal; MTX, methotrexate; PET, positron emission tomography.

high-risk characteristics, and an analysis is ongoing to further investigate this. To compare this approach with standard therapy, a randomized trial comparing DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) with R-CODOX-M/R-IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, ifosfamide, etoposide, and high-dose cytarabine) is currently recruiting patients in several European countries.

HIV-Positive Adults With Burkitt's Lymphoma

Burkitt's lymphoma constitutes up to 20% of HIV-associated lymphomas and is usually seen with higher median CD4 counts than many other lymphoma types. Recent studies report excellent outcomes for this population that are equivalent to those in the HIV-negative setting.[26,27,30] As is the case with middle-aged/older adults, standard full-dose Burkitt's lymphoma regimens are usually considered too toxic for this population; hence, less toxic modifications of standard approaches have been investigated. A recent AIDS Malignancy Consortium study evaluated modified CODOX-M/IVAC-rituximab in 21 patients; the 1-year PFS rate in this group was 69%.[27] DA-EPOCH-R is well tolerated in this group with excellent clinical outcomes and, in a recently presented multicenter study, there were no differences in survival between HIV-negative and HIV-positive counterparts.[18]

Approach to Relapsed/Refractory Burkitt's Lymphoma

Treatment of Burkitt's lymphoma in the relapsed or refractory setting is typically associated with poor outcomes, and few patients survive.[31] One retrospective review reported an OS rate of 37% at 3 years for patients with a chemosensitive relapse but only 7% for those with chemoresistant disease following autologous stem-cell transplantation.[32] In an American Society for Blood and Marrow Transplantation report of data in 241 patients with Burkitt's lymphoma, among patients with relapsed disease in second or later complete remission, the 5-year OS rate was 44% following autologous stem-cell transplantation and 27% following allogeneic stem-cell transplantation. In patients with refractory disease, survival rates were significantly lower.[33]

RECOMMENDATIONS AND FUTURE DIRECTIONS

Although pediatric patients and young adults with Burkitt's lymphoma have excellent outcomes with traditional Burkitt's

lymphoma therapeutic regimens, high treatment-related toxicity (even with risk-adaptation approaches using less intensive modifications for low-risk disease) curtails the routine use of standard approaches such as CODOX-M/IVAC in adults, particularly in older age groups. Intermediate-intensity approaches such as DA-EPOCH-R are promising, with high cure rates and relatively low toxicity in all age groups in a multicenter setting. At this point, intermediate-intensity approaches are reasonable to consider as optimal therapy in adults with the disease. Although low-risk patients have excellent outcomes with abbreviated therapy and no CNS-directed therapy, the outcome is inferior for patients with CNS involvement. It is not clear if coexisting clinical characteristics contribute to this; however, this may be a group that should be approached differently. It is an exciting time in Burkitt's lymphoma biology as key molecular aberrations other than MYC continue to be elucidated and present interesting targets for drug development. New genomic findings (eg, *TCF3*, *ID3*, and *CCND3*) suggest potential activity of novel agents such as PI3 kinase inhibitors, inhibitors of *CDK6*, as well as inhibitors of *MYC*. Ultimately, as novel agents are incorporated into upfront Burkitt's lymphoma therapeutic regimens, they offer the possibility of curative strategies with less reliance on highly toxic agents. Anti-CD19 CAR-T cell therapy is interesting in Burkitt's lymphoma considering its biologic similarity to acute lymphoblastic leukemia; as such, anti-CD19 CAR-T cell therapy should be considered for testing in relapsed/refractory Burkitt's lymphoma.[34] JOP

Author's Disclosures of Potential Conflicts of Interest

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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