

Treatment Advances for Burkitt Lymphoma

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ABSTRACT

Burkitt Lymphoma (BL) is an uncommon but highly aggressive B-cell Non-Hodgkin Lymphoma (NHL). It is a subtype of mature B-cell lymphoma and can be treated successfully within a short period via high-intensity chemotherapeutic regimens. Diagnosis and initial work-up must be completed rapidly to begin treatment due to high proliferation. BL is associated with the Epstein-Barr Virus (EBV) and with a chromosomal translocation that activates the c-MYC gene. However, by implementing chemotherapy regimens, complete remission and overall survival for young patients with BL remains high. In contrast, in elderly patients and those with relapsed/refractory disease, the prognosis remains a medical challenge.

Rituximab, the chimeric monoclonal antibody against CD20, has improved the clinical management of B-cell malignancies. Because BL expresses a CD20 positive marker in their cell surfaces, rituximab has been shown to improve patient survival rate. However, because resistance can still occur, further treatment and evaluation is required, including inhibition of the MYC proto-oncogene through the use of bromodomain inhibitors. In this review, we highlight the treatment advances and progress in BL.

Keywords: Burkitt lymphoma; MYC; Epstein-Barr virus; Rituximab

INTRODUCTION

Burkitt Lymphoma (BL) is a highly aggressive but potentially curable type of B-cell Non-Hodgkin Lymphoma (NHL) with a cellular doubling time of 24-48 hours. Derived from B-cell germinal centers [1], BL was first described as a distinct clinical entity in 1958. It was one of the first human tumors found to have a relationship with a viral infection (EBV). BL is also associated with a chromosomal translocation that activates the MYC proto-oncogene and is the first lymphoma reported to be associated with Human Immunodeficiency Virus (HIV) infection [2]. BL is one of the most common pediatric malignancies in sub-Saharan African countries, with an incidence rate as high as 4.7 cases per year for males and 3.0 cases per year for females (per 100, 000 children under 15 years of age) [3]. Three subtypes of BL are recognized: Endemic, Sporadic, and Immunodeficiency-associated.

Endemic (African) BL, which mainly occurs in equatorial Africa (it also occurs in Papua Guinea), is the most common subtype in childhood and boys are more likely to be affected than girls (approximate ratio of 2:1). Endemic BL accounts for nearly 30%-50% of all childhood cases [4,5], and infection by EBV is found

in nearly 100% of all patients with endemic BL [6]. Moreover, although *Plasmodium falciparum* is not an agent of the MYC proto-oncogene, its possible oncogenic development of BL has been demonstrated through the shared geographic distribution of BL and malaria [7].

Sporadic BL is primarily observed in young adults, with an incidence of 1%-2% of all lymphomas occurring at a median age of 30 (M:F is 3:1 or 4:1), although in pediatrics, it represents 40% of all lymphomas. Moreover, EBV is detectable in <30% of sporadic BL [8-10] and the disease is more common in Caucasians than Africans or Asian-Americans. It may also be common in some areas of Central America (Guatemala) [11].

Immunodeficiency-associated BL, the third subtype, is seen primarily in HIV patients, often occurring as the initial clinical manifestation of AIDS. Indeed, an EBV infection is detected in approximately 40% of cases. Interestingly, immunodeficiency-associated BL is unlike other HIV-associated B-cell lymphomas because it typically occurs in patients with CD4 counts greater than 200 cells per μ L. As a result of antiretroviral therapy, the incidence has decreased, but it may also be seen in other immunodeficiency

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states (e.g. post organ transplant). These patients typically present with BL 4-5 years after organ transplantation [11,12]. This review discusses the treatment of advanced BL. In recent decades, researchers have discovered different combination chemotherapy regimens and combined them with rituximab as a new form of BL treatment. However, resistance can occur in some cases. We believe that this is the most up-to-date study to discuss the treatment of BL.

METHODS

A literature search of treatment advances for Burkitt lymphoma was performed for English-language review articles, using the electronic database of Pubmed. The following search terms were input: (Burkitt lymphoma) or (Burkitt's lymphoma) and (treatment) in (Title/Abstract). The first author and corresponding author investigated all relevant studies for quality and publication date. Importantly, a list of references was added manually.

Epstein-Barr virus and Burkitt lymphoma

Epstein-Barr Virus (EBV) is a ubiquitous virus that belongs to the β herpes virus subfamily, which is well-known for comprising tumor viruses that express viral cancer genes and immortalize infected-lymphocytes. Of these, EBV is the most common persistent viral infection in humans, with approximately 95% of the world's population exposed. Initial infection with EBV is often asymptomatic, but it can manifest as infectious mononucleosis [13]. In past decades, EBV was detected in cultured cells derived from a patient with BL [14]. However, EBV is not completely critical in the development of BL, which can develop in its absence. Nevertheless, the etiological role of virus infection is supported by the finding that, in EBV-positive cases, every tumor cell harbors monoclonal EBV genomes. More research is required regarding the precise details of BL pathogenesis, specifically in terms of the nature of the B-cell initially infected with EBV, whether EBV infection precedes or follows the c-MYC translocation, and which viral genes are involved at different stages of the tumor transformation process [15,16].

Clinical presentation and evaluation of BL

Because BL is highly aggressive, patients usually present with enlarged masses and signs of tumor lysis syndrome, with significantly elevated serum LDH and Ki-67 staining up to 95%. Bone marrow and Central Nervous System (CNS) involvement can be found in 15%-30% of all cases. Sporadic BL patients generally present with abdominal involvement, while endemic BL patients present with intra-oral masses, such as of the jaw or maxilla. Immunodeficiency-associated BL is primarily seen in patients who are HIV-positive, particularly in those with low CD4 counts. The clinical presentation includes CNS involvement or peripheral blood and bone marrow involvement.

The clinical evaluation of BL is always an emergency procedure. Bone marrow aspiration and biopsy and lumbar puncture are necessary to diagnose BL, in addition to liver and renal function tests and radiographic staging with Computed Tomography scan (CT) and Positron Emission Tomography (PET) of the chest, pelvis, and abdomen. The Ann Arbor staging system for the extent of disease evaluation is currently widely used. In recent years, however, the Lugano classification has emerged for staging of NHL [17,18].

Morphology and cytogenetics

BL tumor cells are usually monomorphic with very limited pleiomorphism. Importantly, the diagnosis of BL demonstrates cytogenetic characteristics of t(8;14) (q24;q32) and its variant translocation t(2;8) (p12;q24) and t(8;22) (q24;q11), occurring in 90% of cases, or c-MYC rearrangement. The rate of Ki-67 proliferative index is usually >90%, and up to 100% in BL. However, a high Ki-67 by itself does not equate with BL. Therefore, when diagnosing BL, karyotyping and FISH are commonly used to detect MYC translocation [19-21].

Immunophenotype and molecular signature

BL is a subtype of B-cell NHL, for which positive B-cell markers are typically detected, including CD10, CD19, CD20, CD22, and CD79a; BCL6 and monotypic surface IgM with kappa and lambda. BL cells do not usually express CD5 and CD23 or Terminal deoxynucleotidyl Transferase (TdT). Meanwhile, BCL2 is negative in most patients. The over proliferation of B-cells derived from the lymphoid cells' Germinal Center (GC) are separated into blast (centroblast) and centrocyte. The somatic hypermutation express immunoglobulin gene variable (IgV) region transforms B-cells into neoplasm with either BL or diffuses, Large B-Cell Lymphoma (DLBCL) [22].

TREATMENT OPTIONS

Due to the aggressive nature of BL, diagnosis and workup should be completed as soon as possible to begin chemotherapy. Interestingly, different types of chemotherapy protocols are recommended, and the prognosis for this disease is good.

Treatment must be started promptly (ideally within 48 hours after diagnosis) including the prevention of Tumor Lysis Syndrome (TLS). The unavoidable first step of treatment is the application of the prophase, with low-dose cyclophosphamide and prednisone. This pre-phase helps limit the risk of TLS by decreasing the release of cytokines, particularly in case of high tumor burden-a situation that can be lethal given the aggressiveness and chemo-sensitivity of the tumor burden. The anti-CD20 monoclonal antibody rituximab transforms the management of other mature B-cell malignancies [23-25]. Clinical trials have demonstrated that adding rituximab to chemotherapy can improve patients' Overall Survival (OS). An efficacy benefit has also been shown in patients with BL and other aggressive lymphomas. However, in pediatrics, rituximab is given prior to chemotherapy. Because BL expresses CD20 positive markers in their cell surfaces, rituximab has been shown to improve the survival rate in this disease (Table 1).

Chemotherapy

Hyper-CVAD regimen: The MD Anderson Cancer Center developed a hyper- CVAD regimen (hyper-fractionated cyclophosphamide, adriamycin, vincristine, and dexamethasone alternating with methotrexate plus cytarabine), which has been used to treat B-cell aggressive neoplasms in addition to rituximab. This regimen was evaluated prospectively in 31 adult patients with either ALL or BL. The outcomes were excellent. The achieved response rate was 81%, with an overall survival of 89%; Only one induction death was observed [26,27]. The hyper-CVAD regimen is often used in adult patients.

CODOX-M/IVAC regimen: Although BL is highly invasive, it is

Table 1: Treatment results of Rituximab combined with different chemotherapy regimens.

| Reference | Regimen | Patient number | Median age (year) | Complete remission rate (%) | Overall survival % (year) | EFS/PFS, % (year) |
|-----------|--------------------------|----------------|-------------------|-----------------------------|---------------------------|-------------------|
| [26] | Hyper-CVAD | 26 | 58 | 21 (81) | 49 (3) | 61 (3) |
| [27] | R-Hyper-CVAD | 31 | 46 | 24/28 (86) | 89 (3) | 80 (3) |
| [28] | CODOX-M+ IVAC | 41 | 25 | 39 (95) | No report | 92 (2) |
| [25] | R-CODOX-M-IVAC | 25 | 44 | 100 (92) | 84 (2) | 80 (2) |
| [24] | RD-CODOX-M/IVAC | 30 | 52 | 90 | 82 (4) | 78 (4) |
| [29] | CALGB (GMALL type) | 92 | 47 | 68 (74) | No report | No report |
| [30] | GMALL B-NHL 2002 | 105 | 47 | 83 (79) | 67 (3) | 75 (3) |
| [31] | CALGB 10002 (GMALL type) | 105 | 44 | 77 (73) | 79 (2) | 74 (2) |
| [32] | DA-EPOCH+R | 19 | 25 | No report | 100 (7.1) | 95 (7.1) |

chemosensitive. Multiagent chemotherapeutic regimens yielded significant impacts in the treatment of BL. One such regimen is referred to as CODOX-M/IVAC, as demonstrated by Magrath et al. at the National Cancer Institute (NCI) in 1996. This regimen consists of cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with ifosfamide, etoposide and cytarabine, along with intrathecal methotrexate and cytarabine. This regimen was reported in 72 patients, consisting of 39 adults and 33 children, stratified into low- and high-risk groups. The lower risk stratification was described as an extra-abdominal mass or resected abdominal disease with normal LDH, and the patients were given three cycles of treatment. Patients considered to be high-risk were given two cycles each of CODOX-M/IVAC, which yielded favorable outcomes, with an Event-Free Survival (EFS) rate of 92% after two years. According to Evens et al. 25 patients (20 high-risk and 5 low-risk) were enrolled and treated with this regimen, which resulted in 2-year PFS and OS rates of 80% and 84%, respectively. The CODOX-M/IVAC was reported as achieving a better outcome compared with that of children and younger adults [24,25,28].

Cancer and leukemia group B (CALGB): Another short-duration chemotherapy regimen was introduced by the Cancer and Leukemia Group B (CALGB) phase, which involved two multi-institution trial that included 105 patients with BL/BLL with median age of 43 (range 19-79). Patients received one week of cytoreduction, including cyclophosphamide and prednisone with allopurinol (one cycle), and subsequently undertook six cycles of cyclophosphamide, ifosfamide, methotrexate, vincristine, cytarabine, etoposide, glucocorticoids, and intrathecal plus rituximab. Patients also received intrathecal therapy. Nearly 80% completed at least six of the seven planned cycles of therapy. There were seven treatment-related deaths. The rate of complete remission was 83%, with no differences observed related to age. The EFS at two years was 78% and OS was 80%, with a few relapses occurring after two years. Interestingly, similar to the BFM protocol, LMB96 was demonstrated in children and adolescents. Excellent results were obtained in the younger patients who used this regimen [29,30].

Dose-adjusted EPOCH regimen: The dose-adjusted EPOCH regimen includes etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab. Research on the EPOCH and rituximab combination in adult patients with BL demonstrated superior outcomes to children. Good results were reported by Dunleavy et al. who used this standard regimen in patients with BL to confirm the value of adding rituximab, demonstrating better outcomes, particularly for younger patients. They showed an outstanding PFS of 95% and OS of 100% [31].

Hematopoietic stem cell transplantation (HSCT)

Because BL may be cured through combination therapy, Hematopoietic Stem Cell Transplantation (HSCT) has now decreased. Previous studies have evaluated HSCT in patients with BL. A group of 117 patients who received autologous SCT in 1984 and 1994 showed a 72% 3-year OS for those in first time CR. Moreover, 37% of patients exhibited a chemotherapy-sensitive disease, but only 7% had a chemotherapy-resistant disease (retrospective analysis) [32]. Hematopoietic stem cell transplantation is currently of no advantage compared to modern treatment regimens and has no proven value for this disease. The HOVON group examined 27 patients, first using CR with initial dose chemotherapy, including two cycles of cyclophosphamide, doxorubicin, etoposide, mitoxantrone, and prednisone. This was followed by autologous HCT and BEAM conditioning (carmustine, etoposide, cytarabine, melphalan). A 5-year EFS was 73% and estimates OS of 81%, respectively [30-34].

Immunotherapy and experimental agents

Ofatumumab and obinutuzumab GA101: In recent years, people have witnessed the development of B-cell lymphoid malignancy treatment. Several groups have furthered the growth of chemotherapy regimens, with immunotherapy also considered an attractive option. Because BL cells express specific target markers, such as CD19, CD20, CD22, or CD52, much has been written about the improvement of anti-CD20 monoclonal antibodies (such as rituximab) in patients with BL. However, BL patients [35] have also exhibited resistance to rituximab. New studies have thus utilized other CD20-targeting agents, such as ofatumumab and obinutuzumab (GA101). Ofatumumab is a second-generation anti-CD20 monoclonal antibody that sticks to a site and is more effective than rituximab in inducing both cell-mediated and Complement-Dependent Cytotoxicity (CDC). It works by targeting a membrane proximal small-loop epitope on the CD20 molecule. Some studies have shown the effects of ofatumumab in Acute Lymphoblastic Leukemia (ALL) patients, for which promising CD20-positive results were achieved [36,37]. Obinutuzumab is another type of glycoengineered humanized anti-CD20 antibody that has developed potency in B-cell malignancies and has been approved by the FDA for the upfront treatment of Chronic Lymphocytic Leukemia (CLL). Obinutuzumab is more effective than other CD20 monoclonal antibodies due its ability to directly induce cell death. Some studies have reported finding promising preclinical results in ALL cell lines and xenograft, but thus far, no evidence has been found in clinical studies for ALL patients. A

preclinical trial developed has been by Awasth et al. for children and adolescents, which involves rituximab resistant-BL and pre-ALL evaluation of atumumab- and Obinutuzumab-enhanced cell death against BL and pre-ALL [35,36].

Chimeric antigen receptor (CAR T-cell): New studies have demonstrated that clinical trials of an anti-CD19 chimeric antigen receptor CAR T-cell therapy aimed at fighting B-cell lymphoid malignancies, such as CLL and DLBCL [37-40] are being undertaken. This new technology uses gene-modified autologous T-cells with a CD19 antigen specificity that is mainly expressed on the surface of B-cells. Therefore, this approach would be used in BL to improve treatment of advanced or Minimal Residual Disease (MRD). New clinical trials have demonstrated that CAR-T cells can induce complete remission in a patient with refractory BL [41].

Immune-checkpoint (PD-1 - PD-L1): Other highly effective inhibitors for B-cell malignancies are programmed cell-death protein 1 (PD-1) / programmed cell death 1 ligand 1 (PD-L1) immune checkpoint inhibitors. These are the proteins that regulate immune cell activation to maintain self-tolerance and to prevent autoimmunity [42]. Interestingly, these proteins play an important role in controlling T-lymphocyte priming and activation. Several studies have reported on the clinical benefits of the PD-1/PD-L1 antibody in Follicular Lymphoma (FL) patients and DLBCL, as well as Hodgkin Lymphoma (HL) patients treated with nivolumab [43-46]. Other studies have reported that PD-1/PD-L1 are not expressed in BL cells, and hence PD-1/PD-L1 checkpoint inhibitors have not been demonstrated for BL [47,48]. Several papers have further demonstrated that the EBV-Latent Membrane Protein (LMP) can also stimulate PD-L1 expression via AP-1 and JAK-STAT pathways in HL cells with diploids 9p24.1 in both EBV-positive and -negative patients because the spreading of genetic alteration is similar, even though EBV-positive patients are more likely to have greater PD-L1 Immunohistochemistry (IHC) staining scores [45,49]. An ongoing clinical trial was developed using CD19 CAR- T cells and PD-1 knockout engineered T-cells (CD19 CAR and PD-1 knockout engineered T-cell) in patients who exhibit a high risk of relapsed CD19 positive ALL+BL, and thus receive the CD19 CAR and PD-1 knockout engineered T-cell following lymphodepleting chemotherapy. This clinical trial demonstrates the safety, efficacy, and duration response of the CD19 CAR and PD-1 knockout engineered T-cells in patients with a high risk of relapsed CD19 positive malignancies.

Future directions in MYC inhibition

Because most BL patients have an over-expression of the pathogenic MYC proto-oncogene, new experimental biologically targeted agents should be studied, particularly in patients with high-risk and relapsed refractory disease [50]. Direct and indirect MYC inhibitors are, therefore, particularly attractive. Pharmacologic inhibition of MYC is difficult to achieve, however, because of its several functions and targets. Direct inhibitors, such as JQI and THZ1, that target MYC interactions may be useful in this regard. Interestingly, the link between JQI and MYC may also be involved in the dependence of MYC on bromodomain and Bromodomain Extraterminal Inhibitors (BET) protein BRD443 in combination with the PI3K pathway. Experimental studies have shown that mechanistically, the Mammalian Target of Rapamycin (MTOR) or Histone Deacetylase (HDAC) inhibitors may cause tumor regression [51-53]. Moreover, MTOR signaling plays an important role in tumor cell growth and is aberrantly activated in lymphoma [54,55].

Several studies have demonstrated the effectiveness of unique combinations of the HDAC+MTOR and HDAC+BET inhibitors or BL/leukemia, therefore providing us with a new direction by targeting MYC proto-oncogene and associated proteins [56].

New finding therapies

With newly developed technologies, novel drugs have been discovered that could undergo preclinical sensitivity screening using ex-vivo culture methods, with simultaneous testing for leukemia/lymphoma [57]. Related to B-cell lymphoid malignancies, some studies have shown venetoclax to be synergistic with vincristine and dexamethasone in B-precursor ALL expressing TCF3-HLF gene rearrangement. Recently, published studies have unveiled sets of additional recurrently mutated genes in B-cell malignancy patients (ID3, TCF3, and CCND3 occur in BL). Another study has demonstrated that birinapant, a SMAC mimetic inducer of apoptosis and necroptosis, was found to be more effective against highly MRD-resistant patients of B-cell lineage ALL [58,59].

CONCLUSION

BL is an uncommon and highly aggressive form of lymphoma. In the modern era, however, treatment with intensive and different combinations of chemo-immunotherapy can achieve excellent results. Nevertheless, in some relapsed/refractory patients, the prognosis remains poor. Most patients do not achieve second remission despite an intensive salvage treatment, and therefore urgent therapies are required to treat these patients. Several drugs that are currently undergoing clinical trials may provide new ways of treating BL.

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AUTHORS' CONTRIBUTIONS

Issa Hajji Ally wrote the manuscript. Both authors read and approved the final manuscript.

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