17 Adult Burkitt Leukemia/Lymphoma

Pamela Abdayem, Jean-Marie Michot, Valérie Camara-Clayette, Yegor Vassetsky, and Vincent Ribrag

17.1 Introduction

Initially described by Dennis Burkitt in 1958, Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma (NHL). Originating from mature, germinal, or post-germinal center B cells, it often manifests as extra nodal disease or as an acute leukemia. Being the first cancer described containing viral particles (Epstein–Barr virus) and pathologically driven by a genetic translocation, BL largely contributed to the field of tumor immunology and molecular genetics. Despite the recent improvement in disease outcomes with pediatric-inspired chemotherapy protocols, data about the optimal management of elderly or other specific patient groups and relapsed BL remain scarce.

According to the revised 2016 World Health Organization (WHO) classification of hematologic malignancies, BL and Burkitt cell acute lymphoblastic leukemia (L3ALL) are a single entity, a mature B-cell neoplasm with c-MYC overexpression. The 2016 WHO classification also proposes three aggressive B cell neoplasms that resemble BL: "Burkitt-like lymphoma with 11q aberration"; "High-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement," and "High-grade B cell lymphoma, not otherwise specified" [1].

Accounting for 1–3% of all cases of ALL, L3ALL rather than BL is usually considered when patients present with extensive marrow infiltration (greater than 25% blasts) and a low tumor burden disease. Central nervous system (CNS) involvement is equally prevalent in both forms of the disease. L3ALL predominates in children and adolescents and is less common in adults. Unlike the other types of ALL, it is treated similarly to BL with short and intensive chemotherapy protocols.

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17.2 Forms: Endemic, Sporadic, and Immunodeficiency-Related

Three distinct clinical forms of BL/L3ALL have been individualized. With similar histological characteristics and comparable outcomes, each form has specific epidemiologic, genetic, and clinical features.

17.2.1 Endemic Form

In 1958, Dennis Burkitt reported 38 cases of "sarcomas" affecting the jaw and abdomen in children at Mulago hospital in Uganda. This endemic variant accounts for 30–50% of all childhood tumors in equatorial Africa with an estimated incidence of 3–6 cases per 100,000 children per year [2]. It occurs mainly in males (male to female ratio is approximately 2:1) aged 4–7 years.

The prevalence of this disease in tropical regions suggested the involvement of an infectious agent. Yellow fever was initially suspected; Epstein–Barr virus (EBV) was later identified and became the first example of an oncogenic pathogen. In addition, the geographic distribution of BL corresponded with areas holo- or hyperendemic for *Plasmodium falciparum* malaria in the "lymphoma belt of Africa" and in Papua New Guinea/Irianjaya in Asia, making it a polymicrobial disease [3]. The increased EBV load observed during acute malaria infection seems to result not only from an impairment of the EBV-specific T-cell response and polyclonal B-cell activation but also from viral reactivation directly driven by malarial antigens. Chene et al. [4] identified a cysteine-rich inter-domain region 1α (CIDR1α) of the *Plasmodium falciparum* membrane protein 1 that increases B-cell survival and revives the memory compartment where EBV is known to persist, therefore triggering viral replication. *Euphorbia tirucalli*, a herbal remedy used in the "lymphoma belt," might reactivate EBV leading to c-MYC altered expression and increased occurrence of endemic BL, according to preliminary results by Manucci et al. [5]. Similarly, sub-Saharan populations are highly exposed to aflatoxin B1 which acts as a cofactor in EBV-mediated lymphomagenesis [6].

17.2.2 Sporadic Form

The sporadic form is observed in the United States (US) and Western Europe. In the US, it includes 30% of pediatric lymphomas and less than 1% of adult NHLs, with an estimated incidence of three cases per million persons per year in both children and adults [7]. In Europe, the incidence is approximately 2.2 cases per million persons per year [8]. Median age at diagnosis is 11 years and 30 years, among children and adults, respectively [9]. Sporadic BL is most common among Caucasian males with a 3 or 4:1 male to female ratio [7, 10, 11]. Contrary to the endemic form where EBV genome is ubiquitous, EBV infection is detected in approximately 20% of sporadic cases only.

17.2.3 Immunodeficiency-Related Form

This variant is mainly observed in patients with human immunodeficiency virus (HIV) infection and CD4 count higher than 200 cells/μL [12]. The relative risk of developing BL in HIV-positive compared to HIV-negative individuals is 50. BLs represent 30% of HIV-associated lymphomas. Thus, the lifetime risk of developing BL in HIV-positive patients is between 10% and 20%. In contrast with most other HIV-related lymphomas that develop at a stage of profound immunodeficiency, its incidence has not decreased with the use of antiretroviral therapy (ART). Increased aggressiveness of the disease combined with poor health status of HIV-infected patients are responsible for the dismal prognosis of this variant compared to HIV-negative BL [13].

17.3 Pathogenesis

17.3.1 c-MYC

17.3.1.1 Functions of c-MYC

MYC is one of the first described oncogenes; its expression is associated with independent cell growth [14]. MYC acts both as a positive and as a negative regulator of gene transcription [15–17]. It therefore regulates cell cycle transition, cell differentiation, growth, metabolism, protein synthesis, adhesion, migration, and angiogenesis. MYC contributes to genomic instability, triggers telomere aggregation, and controls the balance between stem cell self-renewal and differentiation. It can also drive focus formation and anchorage-independent growth in vitro as well as full tumorigenesis in vivo. Deregulation of *MYC* expression can occur by many mechanisms: retroviral transduction, retroviral promoter or enhancer insertion, chromosomal translocation, gene amplification, and activation of hormones or growth factors, their receptors, second messengers, or transcriptional effectors that converge on MYC expression. Alterations in mechanisms that directly or indirectly stabilize *MYC* mRNA and/or protein can also deregulate expression of this potent oncogene [18].

17.3.1.2 c-MYC in BL

The development of BL relies on the constitutive expression of the *MYC* proto-oncogene located at chromosome 8q24, which encodes the MYC protein transcription factor. The dysregulation of c-MYC, a genetic hallmark of BL, is a consequence of a chromosomal translocation between chromosome 8 at the locus q24 and either chromosome 14 (t(8;14) (q24;q32), 70–80% of cases) or chromosome 22 (t(8;22)(q24;q11), 10–20% of cases), or chromosome 2 (t(2;8)(p12;q24), 2–5% of cases) [19]. *MYC* gene at 8q24 is therefore juxtaposed with one of the immunoglobulin (Ig) loci on chromosomes 14, 22, or 2. Transgenic mice that expressed the MYC gene under the control of the Ig heavy-chain intronic enhancer (Em), emulating the chromosomal translocation found in BL, developed B-cell lymphomas with a latency of 4–6 months [20]. BL cells express activation-induced cytidine deaminase (AID), which mediates both Ig somatic hypermutation and Ig class switch recombination (CSR). Thus, human BLs have somatically mutated Ig variable regions, and *IG/MYC* translocations typically involve Ig switch regions, suggesting that they arise by aberrant CSR [21].

DNA breaks in the involved Ig genes occur through processes that are normal for B cells, namely either attempted Ig V(D)J recombination or Ig class switch recombination. DNA breaks near *MYC* might result from the recruitment of activation-induced cytosine deaminase (AID) [22, 23]. DNA breaks in *MYC* may come to be spatially close to DNA breaks in the IG gene loci in the interphase nucleus, which is a prerequisite for these DNA ends to be joined to form *MYC* translocations. This was observed upon B-cell activation in mice or in HIV-infected individuals where HIV-1 Tat protein induced spatial proximity between the *MYC* and *IGH* loci [24]. Identification of MYC translocation by Polymerase Chain Reaction (PCR) is often impossible due to the variable DNA break sites although a method using the long-range PCR was proposed. Fluorescence in situ hybridization (FISH), standard cytogenetic techniques, and more recently immune-FISH are more accurate diagnostic tools.

DNA break sites on both chromosomes differ between endemic and sporadic BL [25]. In endemic cases, the breakpoint on chromosome 14 involves the heavy chain joining region, while in non-endemic cases, it involves the heavy chain switch region. In endemic cases, the break site on chromosome 8 is usually adjacent to MYC, while in sporadic cases, it often lies in intron 1 within the gene [26].

17.3.2 Beyond c-MYC

High-throughput sequencing approaches identified additional cytogenetic and molecular events cooperating with MYC to induce BL [27–29].

Cytogenetic aberrations include gains in 1q, 13q, 7q, 8q as well as losses in 3, 4p, 4q, 9p and 13q [30]. Poirel et al. [31] showed that +7q and del(13q) were independently associated with a significant inferior event free survival (EFS) in children and adolescents with BL.

Overexpression of MYC likely triggers TP 53-dependent apoptotic pathways, thus increasing the selection for TP 53 inactivating mutations (35% of cases) [32, 33].

Mutations in the CCND3 gene encoding cyclin D3, a D-type cyclin that regulates the G1–S cell-cycle transition, explain the rapidly proliferative character of BL [34]. They are present in 38% and 2.6% of sporadic and endemic tumors, respectively.

All three variants of BL express highly recurrent mutations in the transcription factor TCF-3 gene (10–25%) and/or in its negative regulator ID3 (35–58%) [27–29]. Identification of these mutations, typically absent in diffuse large B-cell lymphoma (DLBCL), might offer a diagnostic solution when DLBCL and BL are difficult to distinguish. TCF-3 has a central role in survival and proliferation [28, 29]. It directly transactivates CCND3, thereby promoting cell-cycle progression. It also transactivates ID3 as well as the related family members ID1 and ID2, thus inducing expression of its own negative regulators.

As for signaling pathways, BL relies on BCR signaling which is mostly "tonic" and antigen-independent. PI3K is the main pathway in opposite to other antigen-dependent pathways such as NF-KB [35, 36]. PI3K activity in BL is also dependent on TCF-3, suggesting a connection between oncogenic activation of this transcription factor in BL and tonic BCR signaling. First, TCF-3 directly upregulates BCR expression. Second, TCF-3 increases BCR signaling by negatively regulating PTPN6, encoding the SHP-1 phosphatase. SHP-1 attenuates BCR signaling by dephosphorylating the ITAM motifs of the CD79A and CD79B signaling subunits of the BCR [29]. Other PI3K signaling triggers include inactivating mutations of PTEN.

17.3.3 EBV

Discovered in the 1960s, EBV is the first recognized human cancer virus. It is present in all cases of endemic BLs and in a minority of sporadic BLs. About 25–40% of BL occurring in HIV-positive patients are EBV-associated. EBV-transformed lymphoblastoid cell lines (LCLs) express several proteins involved in the modulation of oncogenesis pathways such as PI3K and NF-KB [37]. However, a significantly restricted pattern of viral gene products, primarily EBNA1, which is involved in the replication of the EBV genome, is expressed in the BL cells. This may be the result of vigorous selective pressure by T cells that are specific for latent antigens. In the absence of functional T cells, EBV-induced LCLs grow unimpeded, as in the case of posttransplant lymphoproliferative disorder [38].

The adepts of the "hit-and-run" hypothesis argue that EBV contributes to the pathogenesis of most BLs, but malignant cells are obliged to either repress most latent viral gene expression or lose the viral genome completely, because of the incompatibility between c-MYC and EBNA2/LMP1 expression [39] and the immune-selection against EBV transformation–associated proteins [40, 41]. Nevertheless, available evidence suggests that EBV-negative BLs arise independently of EBV involvement. In addition, EBV-positive and EBV-negative cases of BL differ in the number of somatic mutations in their immunoglobulin heavy chain (V_H) genes, in the involvement of antigen selection, as well as in the translocation breakpoints in the *MYC* locus, suggesting distinct cell origins and pathogenesis [42, 43].

17.3.4 HIV

Although HIV does not infect B cells, the increased incidence of BL in HIV-positive individuals could result from both underlying immunodeficiency and direct viral-induced lymphomagenesis. HIV may trigger chronic B-cell activation and dysregulated monoclonal expansion [44]. As mentioned previously,

overexpression of AID in activated B cells triggers DNA breaks leading to the *MYC-IgH* translocation. Another potential mechanism is that HIV-encoded Tat protein induces a sustained *MYC* relocalization next to *IGH* [24] and induces aberrant expression of AID in circulating B cells.

17.4 Clinical Features

17.4.1 Clinical Presentation

The disease is predominant in males, with a median age ranging between 25 and 35 years. Nearly 25% of patients are older than 50. BL often presents as a rapidly growing tumor, with a very short doubling time (24 h) and a quick dissemination to extranodal sites including the bone marrow and the central nervous system (CNS). Primary tumor sites vary between endemic and sporadic forms of the disease. Seventy percent of patients present with advanced stage III or IV disease [45]. Spontaneous tumor lysis syndrome (TLS), with high lactate dehydrogenase (LDH) and uric acid levels, is frequent at diagnosis and often requires early admission into the intensive care unit and potential hemodialysis upon initiation of treatment. Mental neuropathy, resulting from infiltration of inferior dental nerves, is frequently found in BL and L3ALL and generally indicates CNS involvement [46]. Cervical lymphadenopathy might be associated with higher rates of CNS infiltration.

17.4.1.1 Endemic Forms

The facial skeleton, mainly the jaw, is affected in 50% of the cases of endemic BL. In a Ugandan case series, Orem et al. [47] showed a decrease in mandibular presentation and an increase in abdominal presentation with advancing age. At the time of initial presentation, CNS involvement is found in 30–40% of patients, whereas bone marrow involvement is seen in less than 10% of the cases [19].

17.4.1.2 Sporadic Forms

Patients typically present with a rapidly growing abdominal mass and symptoms related to bowel obstruction, gastrointestinal bleeding, or rarely bowel perforation. Bowel intussusception is more common in children. Involvement of the jaw or facial bones occurs in 25% of cases. Lymphadenopathy, if present (10–20% of cases), is generally localized. Bone marrow and CNS involvement is detected in approximately 30% and 15% of cases, respectively, at the time of initial presentation [19].

17.4.1.3 Immunodeficiency-Related Forms

Patients often have signs and symptoms related to the underlying immunodeficiency. Lymph node, bone marrow, and CNS involvement are more common.

17.4.1.4 Leukemic Forms

In L3ALL with CNS involvement, other cranial nerve palsies were described. Blasts are not always detectable in the cerebrospinal fluid (CSF). While anemia is less frequent, thrombocytopenia is present in most patients, and leukocytosis is found in two thirds of the cases but exceeds 50×10^9/l in only 10–20% of the patients. Myelocytes and metamyelocytes are usually found alongside blasts, a rather unusual finding in most other types of acute leukemias.

17.4.2 Diagnosis

Considering the aggressiveness and rapid doubling time of BL, rapid diagnosis is crucial. The latter is based on the pathologic evaluation of involved tissue. Immunophenotyping and cytogenetic identification of c-MYC rearrangement are mandatory. Molecular diagnosis is difficult due to the diverse DNA break sites.

17.4.2.1 Histology

Macroscopically, BL consists of a whitish tumor with necrotic and hemorrhagic foci, compressing and infiltrating adjacent structures. Lymph node

involvement is less frequent and is mainly present in immunodeficiency-related forms.

Microscopically, sheets of cohesive, monomorphic, medium-sized atypical lymphoid cells with basophilic cytoplasm replace normal tissue architecture. Proliferation and apoptotic cell death rates are extremely high (Ki-67+ fraction approaching 100 percent). A classic "starry-sky" pattern is usually observed: the "sky" represented by the background of basophilic tumor cells and the "stars" being the numerous interspersed tangible body macrophages (histiocytes), with a large clear cytoplasm, that have ingested apoptotic cells. At higher power, BL cells have round nuclei with dark nucleoli and resemble the small non-cleaved cells within normal germinal centers of the secondary lymphoid follicle. Macrophages are irregularly shaped with pale nuclei and inconspicuous nucleoli.

Other morphologic variants exist. An important granulomatous reaction might mask the tumor cells in the background. A plasmacytoid appearance, with single centrally placed nucleoli and eccentric cytoplasm, is mostly described in immunodeficient individuals.

17.4.2.2 Immunophenotype

BL cells express surface immunoglobulin of the IgM type and immunoglobulin light chains (kappa more often than lambda), pan-B cell-associated antigens (CD19, CD20, CD22, CD79a), germinal center-associated markers (CD10 and BCL6), as well as HLA-DR and CD43. They lack expression of CD5, B-cell leukemia/lymphoma 2 (BCL2), TdT, and CD23. BCL6 protein staining is in a nuclear pattern and independent of BCL6 gene rearrangement [48].

CD21, the EBV/C3d receptor, is expressed in EBV-positive disease. Adhesion molecules LFA-1 (CD11a/CD18), p150/95 (CD11c), and CD44 are usually absent.

CD5-positive, CD10-negative, and BCL2-positive variants were reported. MYC and BCL6 rearrangements should be sought out in tumors with high BCL2 expression, to rule out diffuse large B-cell lymphoma (DLBCL). Moreover, DLBCLs often lack the expression of CD 10 and have a lower proliferative index (Ki-67 less than 90%).

In regard to the leukemic form, a high correlation was found between L3 morphology and the presence of surface Ig although cases of morphologically L1 or L2 ALL with surface Ig, and cases of morphologically L3ALL without surface Ig have been described, both in children and adults [49–52]. Hoelzer et al. [50] reported poor outcomes in patients with surface Ig and L1 or L2 morphology; this form is probably a subtype of ALL different from L3ALL that requires other therapeutic approaches. Kantarjian et al. [53] also described L3 morphology in only 11 of their 18 cases of mature B-cell ALL.

17.4.2.3 Cytogenetics

Translocation (8;14), between the long arm of chromosome 8, the site of the *MYC* oncogene (8q24), and the immunoglobulin heavy chain gene on chromosome 14 is the most frequent translocation observed in 80% of BLs. Translocation t(2;8) and translocation t(8;22) between 8q24 and kappa light chain on chromosome 2 and lambda light chain on chromosome 22, respectively, are much less frequent. Rearrangements involving *MYC* can be detected both by routine cytogenetics and by FISH using a *MYC* break apart probe that employs two different fluorescent colors which hybridize to both ends of the gene [35]. A few studies reported lack of *MYC* rearrangements in up to 5% of tumors with features typical of BL [54, 55]. Diagnosis of BL in the absence of *MYC* rearrangement is not recommended in the 2016 World Health Organization classification of lymphoid neoplasms [1]. Many of the cases that were previously categorized as BL in the absence of a *MYC* rearrangement are better classified as the new provisional entity "Burkitt-like lymphoma with 11q aberration."

Conventional cytogenetic analysis also revealed additional chromosomal abnormalities that lack prognostic values in 30–40% of patients [56]. Onciu et al. reported additional abnormalities in 81 and 73% of the children and adults, respectively. Of the most commonly observed abnormalities involving chromosomes 1, 6, 13, 17, and 22, only those of chromosome 17 were associated with a poor prognosis in adults [57].

Comparative genomic hybridization (CGH) analysis also showed that L3ALL had higher numbers of cytogenetic changes than BLs, including a high level of genetic amplification [58].

17.4.2.4 Molecular Biology

Two large studies using gene expression profiling (GEP) described a characteristic molecular signature discerning between BL and DLBCL [35, 55]. New approaches such as Nanostring analysis that facilitate the detection of RNA signature might render the use of GEP more attractive in the future for the diagnosis of BL [59].

Next-generation sequencing studies of BL identified mutations in the transcription factor TCF3 (10–25% of cases) or a negative regulator of TCF3, ID3 (35–58% of cases) [38]. Most TCF3 mutations are gain-of-function mutations that block ID3 binding to TCF3. They are rarely found in DLBCL and other B-cell lymphomas, suggesting that TCF3 gain of function is a defining lesion that could be used to diagnose BL in the coming years.

17.4.3 Staging and Pretreatment Evaluation

Zeigler and Magrath developed the earliest staging system for BL in 1974. Nowadays, staging is performed according to the Ann Arbor, or more often the St. Jude (Murphy) systems [19]. As per the Lugano criteria, being a 100% fluorodeoxyglucose-avid lymphoma, current staging of BL must be based on fluorodeoxyglucose positron emission tomography (FDG-PET) scans [60]. CT scans of the neck, chest, abdomen, and pelvis are an acceptable alternative. Unilateral bone marrow aspiration and biopsy are recommended. Lumbar puncture with assessment of CSF by cytology and flow cytometry is also advised.

Pretreatment evaluation should include:

- Complete blood count with differential, renal function, electrolytes, uric acid, and LDH levels.
- Hepatitis B, hepatitis C, and HIV serologies.
- Assessment of cardiac function with echocardiogram or MUGA before the administration of anthracyclines.
- Fertility counselling: while sperm banking for men is performed rapidly, options for women are limited given the urgent need to start treatment.

In case of spontaneous tumor lysis with renal failure at diagnosis, ICU admission and initiation of hemodialysis should be considered before starting treatment, to prevent the high mortality risk associated with worsening of TLS upon initiation of chemotherapy.

17.4.4 Prognosis

Two-year survival rates of 80–90% are reported in prospective trials using modern regimens. However, these excellent rates likely overestimate those achieved in clinical practice, where patients are less "fit."

In 2013, Costa et al. published survival data from the Surveillance Epidemiology and End Results (SEER) database that included 3691 cases of BL diagnosed between 1973 and 2008. The estimated 5-year survival rate improved from 41% to 54% in patients diagnosed from 1973 to 2001, and from to 2002 to 2008, respectively. Survival decreased with age (87%, 60%, 48%, and 33% for patients aged $\leq$19 years, 20–39 years, 40–59 years, and $\geq$60 years, respectively), and advanced stage (hazard ratio 1.90; 95% CI 1.65–2.19) [61].

Other negative prognostic factors include CNS involvement, bone marrow infiltration, presence of t(14;18), del 13q, abnormalities in 1q and 7q, lack of early response to chemotherapy and absence of complete remission (CR) at the end of the treatment [58, 62–65].

HIV-infected patients carry a poorer prognosis that mostly results from their underlying fragility as well as the use of non-optimal doses of chemotherapy [66]. Several studies showed that relapse-free survival (RFS) is identical in HIV-negative and HIV-positive patients after achieving complete remission. Recent antiretroviral

therapies might improve outcomes in this population.

A fairly large number of small series of L3ALL (with 3–10 patients) treated with conventional ALL regimens have been reported, and their results have been uniformly poor with CR rates of only 30–50% and most patients subsequently relapsing in the CNS [56]. Early death from TLS was common. Outcomes in children dramatically improved with the new regimens developed by several groups, especially the St. Jude's group, the German Berlin, Frankfurt, Munster (BFM) group, and the French Société Française d'Oncologie Pédiatrique (SFOP). In L3ALL patients treated "optimally," poor prognostic factors include poor performance status at diagnosis [67], older age, high white blood cell (WBC) counts (>50 × 10^9/l) and hemoglobin <8 g/dl [50]. Elevated LDH levels had borderline significance [50]. CNS infiltration was not associated with poorer prognosis in the SFOP 86 trial, which incorporated higher dose methotrexate (MTX) (8 g/m^2), high-dose cytarabine (Ara C) 3 g/m^2, and cranial irradiation at 24 Gy [68]. In opposite to most other hematological malignancies, p53 mutations have no prognostic value in BL or L3ALL [69].

17.5 Treatment

17.5.1 BL/L3ALL in Children

Initially used in children with BL/L3ALL, classical ALL or lymphoma regimens combining moderate doses of cyclophosphamide (CPM), anthracyclines, vincristine (VCR),and prednisone with CNS prophylaxis failed to achieve CR in advanced disease [68, 70].

The St. Jude's group, French SFOP, and German BFM group succeeded in improving survival rates in children with BL. They initiated treatment with a "pre phase" combining low doses of steroids and chemotherapy (CPM, VCR) to prevent the onset of potentially lethal tumor lysis syndrome. Urate oxidase was given concomitantly. High-dose chemotherapy was started a week later. Treatment protocols consisted of fractionated high doses of CPM (or ifosfamide), intermediate or high dose (HD) MTX and Ara C, and teniposide or etoposide in addition to doxorubicin and VCR. CNS treatment was gradually intensified with HD MTX (at 5 g/m^2 in BFM trials and 8 g/m^2 in SFOP trials), a greater number of triple intrathecal injections (with Ara C, MTX, hydrocortisone), consolidation with etoposide and HD Ara C, and cranial irradiation [64, 70, 71]. These new protocols resulted in 70–75% cure rates in children with advanced disease, regardless of CNS infiltration. For instance, the overall event-free survival (EFS) was 89% at 6 years in 266 pediatric patients with BL treated per BFM protocol [71]. Cure rates exceeded 80% when CNS prophylaxis with HD intravenous MTX (8 g/m^2) and intrathecal chemotherapy was used in the LMB89 protocol [64] (Figs. 17.1, 17.2, 17.3, and 17.4).

17.5.2 General Therapeutic Strategy in Adults

BL/L3ALL is an aggressive disease requiring chemotherapy in all disease stages. Radiotherapy has a very limited role, limited mainly to cases of spinal cord compression or testicular involvement. Similarly, as response to chemotherapy is rapid and disease is inevitably disseminated, there is no role for surgery even in localized disease. Surgical resection of residual masses is not beneficial.

The approaches that showed improved results in children were rapidly proposed to adults. For instance, the SFOP and BFM protocols were applied to adults, with no or minor modifications. The standard of care in BL remains undefined; however, all groups share the same following principles:

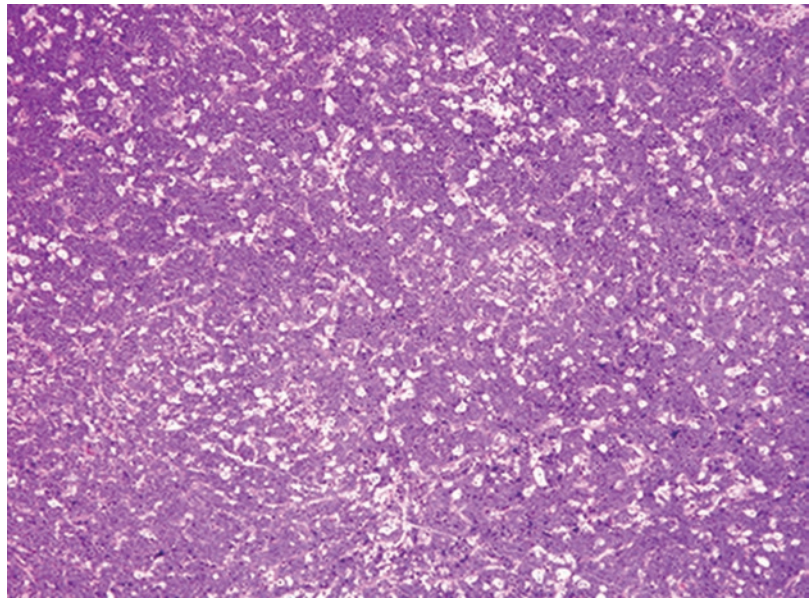

Fig. 17.1 Low-power magnification with the characteristic "starry sky" pattern. (Reproduced with permission from Ioachim HL, Medeiros LJ. Burkitt lymphoma. In: Ioachim's lymph node pathology, 4th edition, Lippincott Williams & Wilkins, Philadelphia 2009)

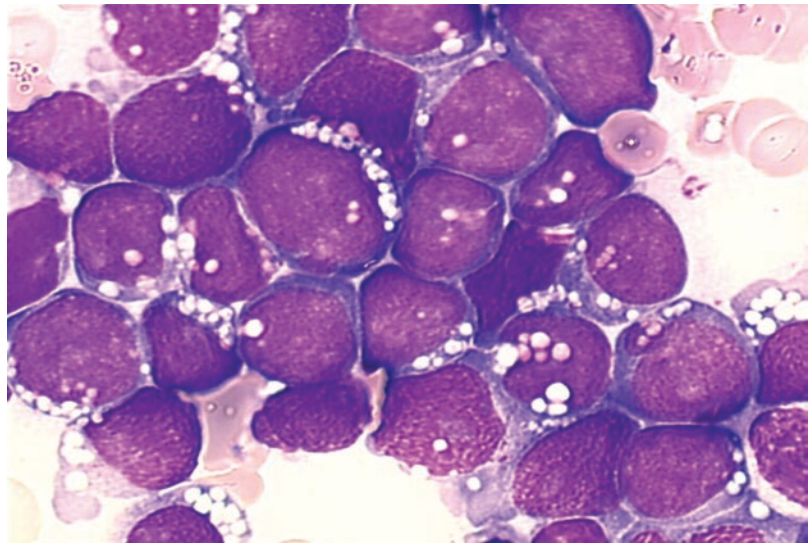

Fig. 17.2 BL cells, with basophilic cytoplasm, round nuclei with coarse chromatin, multiple nucleoli, and several cytoplasmic vacuoles. (Reproduced with permission from Ioachim HL, Medeiros LJ. Burkitt lymphoma. In: Ioachim's lymph node pathology, 4th edition, Lippincott Williams & Wilkins, Philadelphia 2009)

- Referral to expert centers increases remission rates and limits complications.
- Patients should be enrolled in clinical trials whenever possible.
- In case of high tumor burden at diagnosis, a "pre phase" induction therapy with low doses of steroids and chemotherapy reduces the risk of fatal TLS.
- Aggressive CNS-oriented treatment using intravenous (high-dose) as well as regular intrathecal MTX and cytarabine is recommended. With the incorporation of CNS prophylaxis, CNS relapse rates drop from 30–50% to approximately 6–11% [72–74]. Prophylactic whole-brain radiation is no longer used due to its long-term toxicity.
- Systemic treatment must be initiated rapidly and consists of a short intensive course of high-dose, multi-agent cytotoxic chemotherapy. Dose reductions should be avoided.
- Given the high proliferative rate of these tumors, chemotherapy must be re-

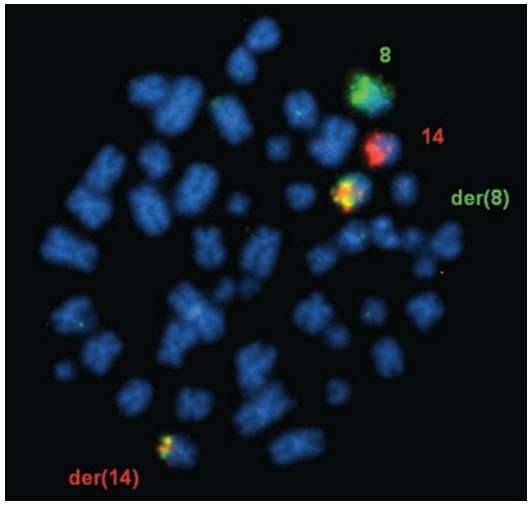

Fig. 17.3 Fluorescence in situ hybridization showing t(8;14), a hallmark of BL

administrated upon hematologic recovery rather than at a predefined schedule.
- TLS should be anticipated with ICU admission and "preventive" hemodialysis of patients presenting with renal failure and high uric acid levels. Rasburicase administration and aggressive hydration are mandatory.
- Rituximab is a standard of care and should be added to all treatment regimens [65].
- As most relapses occur within 1 year of diagnosis, prolonged maintenance treatment is not needed.

Toxicity remains one the major challenges in the treatment of BL. Unlike children and young adults who generally tolerate intensive therapy, older and/or immunosuppressed patients develop

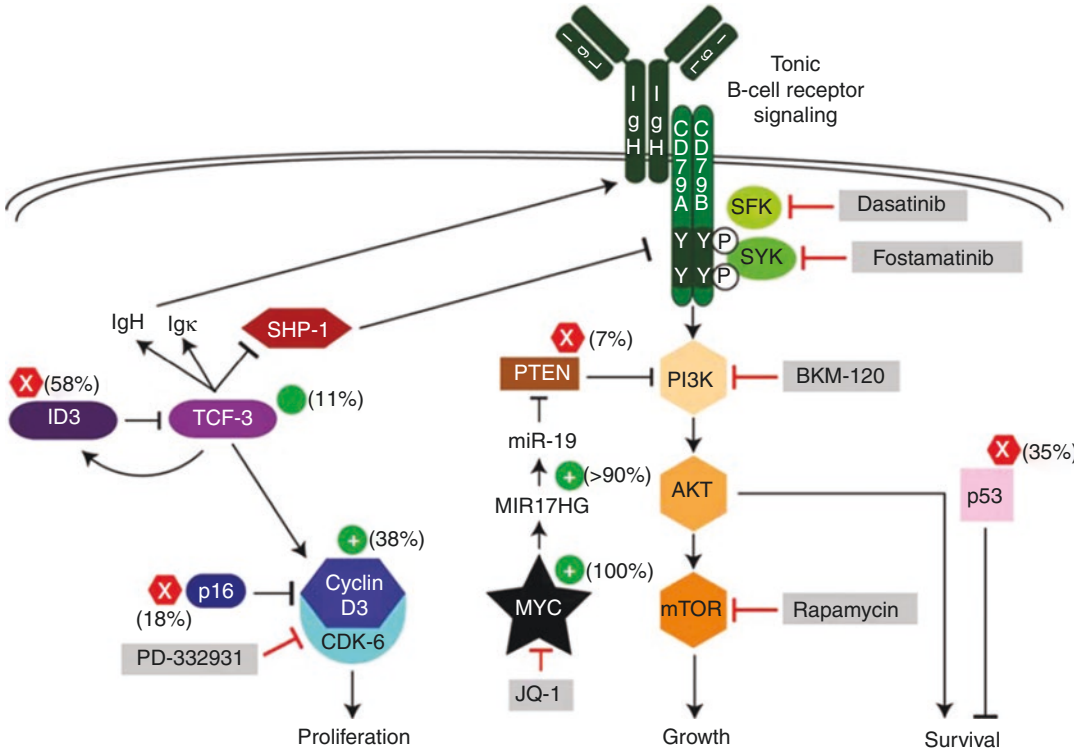

Fig. 17.4 Recurrent oncogenic pathways in BL. Gain-of-function mutations are indicated by + signs and loss-of-function mutations by X signs. Potential drugs to block these pathways are highlighted in gray. (From Schmitz et al. [29])

more treatment-related side effects. Dose reductions are often necessary and affect response rates. These patients, who are usually excluded from clinical trials, have reduced quality of life and shortened survival (Tables 17.1, 17.2, 17.3, and 17.4).

Table 17.1 Clinical presentations of BL/L3ALL

	Endemic	Sporadic	Immunodeficiency-related
Incidence	3–6 per 10^5 children/year	2–3 per 10^6 subjects/year 30% of pediatric NHLs 1% of adult NHLs	30 % of HIV associated NHL, CD4+ >0.2 × 10^9/l
Age	Children > adults Mainly males 4–7 years	Children > adults	Adults
Localization	Extranodal	Extranodal	Frequently extranodal (gut, bone marrow)
	Jaw (50%)	Mainly the gut Jaw (25%)	
Bone marrow infiltration	<10 %	30%	20–60%
CNS involvement	30–40%	15%	20–30%
EBV	>90%	20%	20–40%
c-Myc	Identical in all types	80% t(8;14),	15% t(2;8), 5% t(8;22)

Table 17.2 Diagnosis and management of laboratory and clinical tumor lysis syndrome

Metabolic abnormality	Laboratory TLS[a]	Clinical TLS[b]	Prevention	Management
Hyperuricemia	Uric acid >8.0 mg/dl (475.8 µmol/l) in adults or above the upper limit of the normal range for age in children	Acute kidney injury	(1) Intravenous hyperhydration (2500–3000 ml/m^2 per day in the patients at highest risk) (2) Loop diuretic agent (furosemide) after optimal state of hydration, to achieve a target urine output of at least 2 ml/kg/h (3) Allopurinol or rasburicase[e] (4) Avoid urinary alkalization[f]	– Hyperhydration – Rasburicase – Hemodialysis
Hyperkalemia	Potassium >6.0 mmol/l	Cardiac dysrhythmia or death		– Oral sodium polystyrene sulfonate, insulin and glucose, beta-agonists – Calcium gluconate and cardiac monitoring – Low potassium intake – Frequent monitoring – Hemodialysis
Hyper-phosphatemia	Phosphorus >4.5 mg/dl (1.5 mmol/l) in adults or >6.5 mg/dl (2.1 mmol/l) in children	Cardiac dysrhythmia or death		– Phosphate binders – Limit phosphorus intake – Hemodialysis[c]
Hypocalcemia	Corrected calcium <7.0 mg/dl (1.75 mmol/l) or ionized calcium <1.12 mg/dl (0.3 mmol/l)	Cardiac dysrhythmia or death, seizure, neuromuscular irritability		– Avoid hyperphosphatemia – If symptomatic, calcium supplementation at the lowest dose required to relieve symptoms[d]

Adapted from Cairo and Bishop [75]

[a]Laboratory TLS requires the simultaneous presence of two or more metabolic abnormalities within 3 days before initiation of therapy or up to 7 days afterward

[b]Clinical TLS is defined by the presence of laboratory TLS with clinical manifestations, increased creatinine level, seizures, cardiac dysrhythmia, or death

[c]Continuous venovenous hemodiafiltration more effectively reduces phosphate levels compared with conventional hemodialysis [76]

[d]Excessive calcium supplementation increases the calcium–phosphate product and the rate of calcium phosphate crystallization, particularly if the product is greater than 60 mg^2 per square deciliter

[e]Uric acid may take 2 days or more to decrease with allopurinol. Rasburicase is more effective than allopurinol

[f]Decreases calcium phosphate solubility

Table 17.3 Patients characteristics in selected regimens for adult Burkitt lymphoma/leukemia

Regimen	Author (year)	Number of patients	HIV status	Older patients	Median age, years (range)	Stage III/IV (%)	Risk category	Rituximab
LMBA-02	Ribrag[a] (2016)	260[b]	Negative	Age ≥ 60 years: 23%	47	62% CNS(+): 25%	Group B[c]: 48% Group C[c]: 52%	Yes
GMALL-B-ALL/ NHL2002	Hoelzer[d] (2014)	363	Unknown	Age > 55 years: 27%	42 (16–85)	71% CNS(+): 10% BM(+): 42%	CNS(+)[e]	No
CODOX-M/ IVAC UKLG LY06 Trial	Mead[f] (2002)	52	Negative	Age ≥ 60 years: 0%	35 (16–60)	61%	LR[g]: 23% HR[g]: 77%	No
CODOX-M/ IVAC MRC/NCRI LY10 Trial	Mead[h] (2008)	128 58 BL 70 DLBCL	Negative	Age ≥ 60 years: 10%	37 (17–76)	73% CNS (+): 12% BM(+): 44%	LR[g] 24% HR[g] 76%	No
R-CODOX M/ IVAC AMC 048 Trial	Noy[i] (2015)	34	Positive (100%)	–	42 (19–55)	74% CNS(+): 0%	LR[j]: 6% HR[j]: 94%	Yes
CALGB 9251	Rizzieri[k] (2004)	92[l]	Negative	Age ≥ 60 years: 21%	47 (17–78)	99% CNS(+): 5% BM(+): 63%	Cohort 1[l]: 57% Cohort 2[l]: 43% CNS(+)	No
CALGB 10 002	Rizzieri[m] (2014)	105	Negative	Age ≥ 60 years: 27%	43 (19–79)	49% CNS(+): 14%	CNS(+)[n]	Yes
Hyper-CVAD	Thomas[o] (1999)	26	?	Age ≥ 60 years: 46%	58 (17–79)	CNS(+): 21%	CNS(+)[p]	No
R-Hyper-CVAD	Thomas[q] (2006)	31	Negative[r]	Age ≥ 60 years: 29%	46 (17–77)	CNS(+):7%	CNS(+)[p]	Yes
(R)-Hyper-CVAD	Cortes[s] (2002)	13	Positive (100%)	Age ≥ 35 years: 77%	43 (32–55)	CNS(+):23%	CNS(+)[p]	Yes[s]
DA-EPOCH-R	Dunleavy[t] (2013)	30[u]	Positive (37%)	Age ≥ 40 years: 40%	33 (15–88)	67% CNS(+): 3% BM(+): 13%	LR[v] 17% IR[v] 73% HR[v] 10%	Yes

Table 17.3 (continued)

Regimen	Author (year)	Number of patients	HIV status	Older patients	Median age, years (range)	Stage III/IV (%)	Risk category	Rituximab
RA-DA-EPOCH-R	Dunleavy[w] (2015–ongoing)	77	Positive (26%)	Age ≥ 40 years: 55%	45 (19–78)	64% CNS(+): 10%	LR[x] 14% HR[x] 86%	Yes

[a]Ribrag et al. [65].
[b]Randomized phase 3 study. Patients assigned to two groups: group 1 receiving chemotherapy alone and group 2 receiving chemotherapy with rituximab
[c]Group B: absence of BM or CNS involvement. Group C: Presence of BM or CNS involvement; patients further stratified into five groups according to age and CNS status. Group C patients received MTX 8000 mg/m^2, triple IT injections and enforced consolidation with HD Ara-C and VP-16. Cranial RT was delivered to patients with CNS (+) disease
[d]Hoelzer et al. [77]
[e]CNS(+) patients received more IT injections as well as cranial irradiation. Mediastinal irradiation was recommended in patients with mediastinal tumor (<7.5 cm) at diagnosis
[f]Mead et al. [78]
[g]Low-risk patients had normal LDH, WHO performance status 0–1, Ann Arbor stage I–II and ≤1 extranodal site. All other patients were high risk. LR patients received three cycles of modified CODOX-M while HR patients were given four cycles of alternating modified CODOX-M and IVAC. In LY06 trial, CNS prophylaxis in LR patients included HD IV MTX (6.7 g/m^2) along with IT injections of MTX and Ara-C. HR patients were additionally given HD intravenous Ara-C. In LY-10 trial, MTX dose was reduced to 3 g/m^2 in all patients and 1 g/m^2 in those older than 65 years
[h]Mead et al. [79]
[i]Noy et al. [80]
[j]LR patients were those with stage I disease, <10 cm and normal LDH or intra-abdominal disease only and total resection and normal LDH after surgery. They received three cycles of rituximab and CODOX-M. All other patients were considered HR and received R-CODOX-M/IVAC in an R-CODOX-M/IVAC/R-CODOX-M/IVAC sequence for a total of four cycles
[k]Rizzieri et al. [81]
[l]Patients divided into two cohorts. Cohort 1 included 52 patients receiving IT chemotherapy and cranial irradiation. Cohort 2 included 40 patients who received less IT injections. Cranial irradiation was performed exclusively in HR cohort 2 patients. CNS(+) patients received weekly triple IT injections until CSF clearance then 4 weekly doses followed by cranial RT
[m]Rizzieri et al. [82]
[n]CNS (+) patients received additional triple IT injections twice weekly until CSF clearance then monthly for four treatments, followed by cranial radiation. Those with gonadal disease received RT to the testes during systemic therapy
[o]Thomas et al. [83]
[p]All patients received alternated IT MTX and Ara-C on days 2 and 7 of each course of HD MTX and Ara-C. If there was CNS involvement, IT therapy was increased to twice weekly until CSF clearance. The IT therapy then alternated MTX and Ara-C weekly for four doses (including planned IT days 2 and 7 if course given). The program was then resumed for prophylaxis until completion of chemotherapy. No prophylactic cranial irradiation was administered. Therapeutic RT was given if indicated, e.g., for cranial nerve palsies or intracranial mass
[q]Thomas et al. [84]
[r]Ten patients with HIV-related BL were reported separately
[s]The protocol was modified to include rituximab [85].
[t]Dunleavy et al. [86]
[u]Of the 30 patients, 19 were HIV-negative and were treated with DA-EPOCH-R. Eleven were HIV-positive and received SC-EPOCH-RR (lower-dose short-course combination with a double dose of rituximab)
[v]LR: resected stage I or abdominal stage II cancer. HR: central nervous system involvement, at least 25% blasts in bone marrow, or both characteristics. IR: not in either of the other risk groups
[w]Dunleavy et al. [87]
[x]LR: Normal LDH, ECOG P.S. 0–1, stage I or II disease and maximum tumor size <7 cm. These patients received three cycles without IT prophylaxis. HR patients received six cycles with IT prophylaxis days 1 and 5 on cycles 3–6

Table 17.4 Patient outcomes in selected regimens for adult Burkitt lymphoma/leukemia

Regimen	Author (year)	ORR (%), CR (%)	EFS or PFS (%)	OS (%)	Grade 3–5 toxicities (%)
LMBA-02	Ribrag[a] (2016)	–	75% in the rituximab arm vs. 62% in the control arm at 3 years $p = 0.024$	83% vs. 70% at 3 years $p = 0.011$	Infections: 17% vs. 15% Non-hematologic toxicity: 17% Neurotoxicity: <1% Mucositis: 9%
GMALL-B-ALL/NHL2002	Hoelzer[b] (2014)	CR: 88% 84% in patients older than 55 years	75% 60% in patients older than 55 years	80% 62% in patients older than 55 years	Neutropenia: 58% at cycle A1[c] Infections: 38% at cycle A1[c] Mucositis: 29%
CODOX-M/IVAC UKLG LY06 Trial	Mead[d] (2002)	ORR: 86.5% CR: 76.5% CR in LR: 83% CR in HR: 74%	64.6% at 2 years HR: 59.5% at 2 years	72.8% at 2 years HR: 69.9% at 2 years	Myelosuppression: 100% Mucositis: 42% Thrombocytopenia: 66% Diarrhea: 8%
CODOX-M/IVAC MRC/NCRI LY10 trial	Mead[e] (2008)	–	64% at 2 years 85% LR 49% HR	67% at 2 years 88% LR 52% HR	Neutropenia: 99% Febrile neutropenia: 80% Thrombocytopenia: 86% Mucositis: 45% Neuropathy: 8% Toxic deaths: 8%
R-CODOX-M/IVAC AMC 048	Noy[f] (2015)	–	69% at 1 year	69% at 2 years	All toxicities: 79% Hematologic: 59% Infectious: 41% Metabolic: 18% Mucositis: 0% Toxic deaths: 3%
CALGB 9251	Rizzieri[g] (2004)	ORR 85% CR 74% No significant differences between the two cohorts	52% CH1 vs. 45% CH2 at 3 years	54% vs. 50%	Myelosuppression: 100% Infection: 55% Mucositis: 51% Neuropathy Sensory neuropathy: 9% Motor neuropathy: 18% Toxic deaths: 8%
CALGB 10 002	Rizzieri[h] (2014)	CR 83% Compared to CALGB 9251 improvement in CR EFS OS with addition of Ritux and filgrastim	78% at 2 years	80% at 2 years	Febrile neutropenia or infection: 93% Mucositis: 69% Renal insufficiency: 10% Neurologic: 25% Pulmonary toxicity: 18% Toxic deaths: 7%

Table 17.4 (continued)

Regimen	Author (year)	ORR (%), CR (%)	EFS or PFS (%)	OS (%)	Grade 3–5 toxicities (%)
Hyper-CVAD	Thomas[i] (1999)	CR 81%	–	49% at 3 years	Myelosuppression: 100% Febrile neutropenia: 86% Induction deaths: 19%
R-Hyper-CVAD	Thomas[j] (2006)	CR 86%	80% at 3 years	89% at 3 years	Myelosuppression: 100% No induction deaths
(R)-Hyper-CVAD	Cortes[k] (2002)	CR 92%	–	mOS: 12 m 48% at 2 years	Myelosuppression: 100% Fever/infections: 35% of cycles
DA-EPOCH-R	Dunleavy[l] (2013)	–	95% at 86 months for DA-EPOCH-R 100% at 73 months for SC-EPOCH-RR	100% at 86 months for DA-EPOCH-R 90% at 73 months for SC-EPOCH-RR	Grade 4 neutropenia: 46% of cycles Fever and neutropenia: 19% of cycles Mucositis 5% of cycles No toxic deaths Toxicity lower in the SC-EPOCH-RR group
RA-DA-EPOCH-R	Dunleavy[m] (2015-ongoing)	–	87% at 25 months 84% over 40 No significant difference according to risk, age, and HIV status	88% at 25 months 83% over 40 No significant difference according to risk, age, and HIV status	Same as above Toxic deaths: 7% (infection)

[a]Ribrag et al. [65]
[b]Rates decrease in the following cycles
[c]Hoelzer et al. [77]
[d]Mead et al. [78]
[e]Mead et al. [79]
[f]Noy et al. [80]
[g]Rizzieri et al. [81]
[h]Rizzieri et al. [82]
[i]Thomas et al. [83]
[j]Thomas et al. [84]
[k]Cortes et al. [85]
[l]Dunleavy et al. [86]
[m]Dunleavy et al. [87]

17.5.3 Chemotherapy Protocols

In 2016, Ribrag et al. [65] published the results of a randomized, controlled, open-label, phase 3 trial, of rituximab and chemotherapy (LMB regimen) versus chemotherapy alone in 260 adult patients with BL/L3ALL. With a median follow-up of 38 months, 3-year EFS and overall survival (OS) were significantly improved in the rituximab group without added toxicities.

Apart from rituximab, there is no current standard of care in BL/L3ALL due to the lack of randomized clinical trials and the heterogeneity of single-arm trials. Three main treatment approaches are available.

17.5.3.1 Intensive Short Duration Combination Chemotherapy

Magrath Regimen CODOX-M/IVAC

CODOX-M (CPM, VCR, doxorubicin, and HD-MTX) with IVAC (ifosfamide, Ara C, etoposide, and intrathecal MTX), also called the Magrath regimen, is one of the most widely used chemotherapy protocols outside of a clinical trial [78, 79, 88]. Developed in the 1980s, this regimen uses a risk-adapted approach based on disease bulk of 10 cm or greater, elevated LDH, poor performance status, and advanced stage. One case series and three prospective trials have been reported on the use of CODOX-M/IVAC in patients with newly diagnosed BL [78, 79, 88, 89]. Chemotherapy doses were slightly different between the studies. CNS prophylaxis consisted of intrathecal cytarabine and methotrexate. Patients experienced severe toxicities that required prolonged hospitalization, antibiotics and transfusion support. Two-year OS ranged from 67% to 92%, although among adults, the rate was approximately 75%. In a retrospective analysis, addition of rituximab to CODOX-M/IVAC in 40 adult patients, most of them having high-risk disease, resulted in an overall response rate (ORR) of 90% compared to 88% in patients without rituximab (no statistically significant difference). In all patients, progression-free survival (PFS) and OS were 68% and 71%, respectively. Furthermore, significantly fewer relapses were reported among patients receiving rituximab compared with those receiving chemotherapy alone [90].

Lymphome Malin B (LMB) Protocol

The SFOP adopted the already successful risk-adapted LMB89 pediatric regimen in adults with a median age of 33 years and mostly advanced disease. EFS and OS at 2 years were 65% and 70%, respectively [91]. Toxicity was important and treatment-related mortality was significant. As mentioned previously in the only randomized trial by Ribrag et al. [65], addition of rituximab to this regimen significantly improved EFS and OS. Patients were stratified according to severity of disease into group B (no CNS or BM involvement) or group C (all other patients).

The German Adult ALL Group Experience

GMALL-B-ALL/NHL2002 remains the largest published multicenter prospective international trial for BL. Three hundred sixty three patients in 98 centers received six cycles of HD MTX, HD Ara C, CPM, etoposide, ifosfamide, steroids, and intrathecal therapy along with eight doses of rituximab [77]. Doses were reduced in patients older than 55 years. CR rates were excellent at 88%, OS and PFS were 80% and 71% at 5 years, respectively. Patients with CNS involvement received 24 Gy of radiation and those with bulky mediastinal disease received 36 Gy of mediastinal radiation. In patients older than 55 years (27%), OS and PFS were 62% and 60%, respectively.

The Cancer and Leukemia Group B (CALGB) Experience

The CALGB (study 9251) adapted the German adult ALL protocol by replacing teniposide with etoposide [81]. Subsequent studies (CALGB 10002) have evaluated this regimen in combination with rituximab and filgrastim support in 105 adults [82]. CR rates, 4-year EFS and OS were 83%, 74%, and 78%, respectively.

17.5.3.2 ALL-Like Therapy with a Stepwise Induction, Consolidation, and Maintenance Therapy Lasting at Least 2 Years from Diagnosis

Hyper CVAD

Hyper-CVAD is a regimen developed by the MD Anderson Cancer Center for ALL using fractionated CPM, VCR, doxorubicin, and dexamethasone alternating with HD MTX and HD Ara C [53]. Following successful outcomes in ALL, this protocol was tested in BL. In combination with rituximab, R-hyper-CVAD induced CR in 86% of patients. OS at 3 years was 89%, and EFS 80% [84]. No treatment-related deaths were observed despite significant toxicity.

17.5.3.3 Infusional Chemotherapy with Dose-Adjusted EPOCH Plus Rituximab

Dose-adjusted etoposide, VCR, and doxorubicin administered as a 96-h continuous infusion with oral prednisone and bolus dose-escalated CPM is mostly used in AIDS-related BL. Dose adjustments are based on nadir neutrophil counts during the previous cycle. Dunleavy et al. treated 17 patients (median age 25 years) with sporadic BL with DA EPOCH, rituximab and intrathecal chemotherapy for 6–8 cycles. After a median follow-up of 86 months, freedom from progression and OS were 95% (95% CI 75–99%) and 100% (95% CI 82–100%), respectively [86]. These results might be the consequence of prolonged exposure to anthracyclines etoposide and VCR which may inhibit DNA repair and favor apoptosis by enhancing genotoxic stress and impeding microtubule-dependent protein transport. Conversely, the small sample of adults, the small number of patients with central nervous system involvement, and the wide confidence intervals are major limitations. This regimen could be a valid option in older or less fit patients given its good toxicity profile. Nevertheless, larger studies are needed before recommending its use in all patients with sporadic BL. Indeed, the Hemato Oncology Foundation for Adults in the Netherlands (HOVON) group, the United Kingdom Cancer Research group, and the Swiss Group for Clinical Cancer Research (SAKK) are currently conducting a randomized phase 3 study (HOVON 127) comparing R-CODOX-M/IVAC to dose-adjusted R-EPOCH in high-risk BL patients.

17.5.4 Evaluation of Response

Assessment of response should be done 1 month after the completion of planned therapy (or sooner, if refractory disease is suspected). History, physical examination, laboratory studies (CBC, LDH levels, biochemical profile), and post-treatment CT scan are recommended.

17.5.5 Disease Surveillance

There are no randomized data comparing schedules of follow-up. History, physical examination, CBC, serum chemistries, and LDH are recommended every 3–4 months during the first year, every 6 months during the second year, and then annually.

Most relapses occur during the first year after treatment and are usually symptomatic. The benefit of imaging in routine surveillance is therefore uncertain. Younger patients may be at risk for second malignancies; care should be taken to limit exposure to radiation.

17.5.6 Relapsed and Refractory BL

Relapsed disease should be confirmed by biopsy. Patients have an extremely poor prognosis and must be enrolled in clinical trials whenever possible. Best supportive care is a valid option.

In pediatric series, second-line chemotherapy followed by intensification with autologous hematopoietic stem cell transplantation (HSCT) was effective in 40% of the cases. The former series are biased, since they mostly include “fit”

patients who received sub-optimal first-line treatment. Drugs used for salvage chemotherapy include HD MTX and HD Ara C, and/or etoposide and cisplatin.

Outcome of adult BL/L3ALL patients who had PR or relapsed after first-line intensive protocols (SFOP, BFM, or German ALL trials) is dismal [67, 77].

Fit patients who received suboptimal regimens in first-line may respond to dose-intensive regimens.

17.5.7 Role of Hematopoietic Stem Cell Transplantation (HSCT)

In opposite to other aggressive lymphomas with high-risk features at presentation, there is lack of solid data regarding the efficacy of high-dose chemotherapy followed by HSCT both at first CR [67] and relapse. An observational study conducted by the Center for International Blood and Marrow Research (CIBMTR), reported decreased rates of ASCT during 1985 and 2007. At the time, rituximab was not a standard of care; however, a subset of patients achieved long-term disease control with a 5-year OS of 83% and 53% for ASCT at first and second remission, respectively [92].

In patients with relapsed disease, 2-year PFS after autologous SCT is around 30–40%. These relatively good results, however, were mostly reported in selected series of patients that had received sub-optimal first-line therapy, and who were able to reach ASCT. In fact, Cremer et al. [93] showed in a single-center retrospective study that aggressive salvage therapy is ineffective in patients who relapse after induction with a short-intensive chemo-immunotherapy protocol.

Allogeneic SCT may be considered in relapsing patients with a sibling or matched related donor who may not be eligible for or may have previously received an autologous SCT. Five-year PFS is around 27% and treatment-related morbidity is high [92]. Disease status at transplant and chemosensitivity is the most significant prognostic factors [94].

17.6 Treatment for Specific Demographics

17.6.1 HIV-Infected Patients

During an 8-year period, the National Cancer Institute of Italy declared 46 (35%) cases of BL among 131 cases of HIV-associated NHL [13]. As mentioned previously, unlike other types of HIV-associated lymphomas, BL usually develops at a stage when immune functions are still preserved. It is considered an AIDS-defining malignancy. Bone marrow infiltration is found in 20–60% of cases. HIV-infected patients are often excluded from clinical trials; data regarding treatment efficacy and survival are scarce. In HIV-associated BL, chemotherapy results in CR rates of 20–45% and median survival of 3–6 months, approximately [95, 96]. Outcomes are less favorable than in HIV-negative BL, with a CR rate of 40% vs. 65% ($p = 0.03$) [13]. The difference may result from the higher incidence of deaths from opportunistic infections as well as the use of less dose-intensive regimens in immunocompromised individuals.

With the concurrent use of active antiretroviral therapy, HIV-associated BL and sporadic BL treated with dose-intensive protocols have comparable outcomes. In a retrospective study by Wang et al., 14 HIV-positive adults were treated with different protocols. Outcomes were compared with those of 24 HIV-negative patients with BL who had similar characteristics and were treated concomitantly (13 with CODOX-M/IVAC; 11 with other regimens). Of the 8 patients who received CODOX-M/IVAC (Magrath regimen), 5 achieved a CR (63%). The 2-year EFS rate was 60%. Long-term EFS was not adversely affected by HIV status ($p = 0.88$). CODOX-M/IVAC was associated with improved EFS ($p = 0.05$), in all patients, regardless of HIV status. Treatment-related adverse events were equally prevalent in HIV-positive and -negative patients [97]. These results suggest that HIV-infected patients with BL have better outcomes when treated with dose-intensive regimens. Furthermore, the addition of rituximab to modified CODOX-M/IVAC (intensified treatment of CNS disease if present at diagnosis along with

preventive measures against mucositis, hematologic and neurologic toxicities) did not increase toxicity in a population of 34 HIV-positive adults with BL. Estimated PFS at 1 year was 69% and OS at 1 and 2 years was 72% and 69%, respectively [80]. Similarly, HIV-infected patients who received DA-EPOCH-R had favorable outcomes with CR, 2-year PFS and OS rates of 82%, 66%, and 70%, respectively. Treatment-associated deaths occurred in 10% of patients and may be minimized by sequential rather than concurrent administration of rituximab in those with a CD4 count less than 50/μL [98].

As in HIV-negative patient, CNS prophylaxis is mandatory. There are possible interactions between chemotherapy agents and anti-retroviral therapy, particularly with HD methotrexate. Temporary interruption of ART is recommended in this case.

In conclusion, HIV-infected patients with acceptable CD4 counts and without advanced AIDS symptoms should be treated similarly to HIV-negative patients with dose-intensive short chemoimmunotherapy protocols.

17.6.2 The Elderly

Most clinical trials excluded older adults. Of 25 patients over the age of 60 years who received hyper CVAD with or without rituximab, those who tolerated the treatment had a survival benefit comparable to younger patients [84]. Nevertheless, most studies showed a poor tolerance of hyper CVAD in older adults [99].

A comprehensive geriatric assessment is important to assess comorbidities and functional status in the elderly patient. It leads to the elaboration of a "customized" treatment plan.

Treatment options include:

- EPOCH: Less toxic than conventional therapy with promising results in a younger population [86].
- Standard CHOP chemotherapy with rituximab and intrathecal therapy. Two-year progression-free survival is likely less than 30% with this approach [100].

17.6.3 Patients with Cardiac Dysfunction

Anthracyclines are contraindicated in patients with a baseline left ventricular ejection fraction below 30%. Non-anthracycline-containing regimens should be used in this setting. Chemotherapy protocols requiring intravenous fluid hydration may also be difficult to administer. Pegylated liposomal doxorubicin allows higher cumulative doses with equivalent efficacy and less cardiac toxicity.

17.7 Future Perspectives

Despite the improvement in CR and survival rates with the use of intensive chemotherapy, the treatment of BL remains challenging, particularly in special "vulnerable" populations (elderly, immunocompromised patients, etc.) as well as in resource-poor environments where the disease is endemic and access to adequate chemotherapy and supportive care is difficult [47]. Therefore, the development of new treatment protocols that are more affordable and better tolerated is crucial. These new protocols may target the following pathways:

17.7.1 TCF3 Pathway Activation

In opposite to other lymphoma types, mutations in TCF3/ID3 genes are detected in more than two thirds of sporadic and HIV-related BLs and in 40% of EBV-positive cases and may be used for diagnostic purposes in difficult situations. Moreover, TCF3 acts as a lineage-survival oncogene and activates the pro-survival PI3-K pathway in BL. Agents that block this transcription factor are yet to be developed [29].

17.7.2 PI3K Pathway

Preclinical studies showed a potential benefit of blocking the PI3K pathway, an essential pervasive pro-survival mechanism in BL cell lines. The

PI3K-targeting agents used in these studies have proven their efficacy and tolerability in the treatment of other neoplasms. Potential candidates for future clinical trials include:

- BKM-120 that targets all of the catalytic isoforms of PI3K [29].
- Rapamycin or its analogs that may be used to block the mTORC1 kinase complex, activated by PI3K signaling [29].
- Inhibitors of SYC (e.g., fostamatinib) or SRC-family kinases (e.g., dasatinib) that target BCR-proximal kinases and thus bloc PI3K in an important fraction of BL lines [29].

17.7.3 Cyclin-Dependent Kinase Inhibitors

In BL, pairing of cyclin D3 with CDK-6 results in an active kinase. Knockdown of either subunit is toxic for these cells [29]. PD 0332991, a CDK-4/6 inhibitor initially blocks BL cell-cycle progression at the G1–S phase transition, as expected. However, unexpectedly, significant apoptosis is induced by the continuous exposure of BL cells to this agent. The association of increased MYC expression by the t(8;14) translocation with a complete G1 block likely triggers a checkpoint response that results in apoptosis. In BL xenografts, response to PD 0332991 is spectacular with virtual disappearance of tumor cells by day 10 of treatment [29]. Targeting the cyclin D3-CDK-6 appears to be beneficial and should be evaluated in clinical trials.

17.7.4 Targeting MYC Expression

Suppression of MYC remains challenging because of both the diverse mechanisms driving its aberrant expression and the challenge of disrupting protein-DNA interactions.

Bromo and extra-terminal (BET) family inhibitors are small molecules that prevent the binding of the BET family of chromatin adaptors to chromatin, a process usually required for MYC expression. Thus, BL cell lines are killed following the downregulation of MYC expression. Significant antitumor activity of BET inhibitors was observed in xenograft models of BL and acute myeloid leukemia. These preclinical studies support further clinical investigation of BET inhibition in relapsed BL.

Antisense oligonucleotides directed at several different sites of human c-Myc mRNA reduced proliferation of HL-60 and Raji cells in vitro [101]. In a murine model of BL, antisense oligonucleotides delayed tumor onset by 3–6 days and reduced total tumor mass by 40–65%, compared with controls [102].

Human mitochondrial peptide deformylase (HsPDF) and mitochondrial sirtuin SIRT 4 are additional candidates that could be targeted in MYC-overexpressing cancers.

17.7.5 Other Potential Candidates

Additional novel therapeutic agents include:

- Monoclonal antibodies directed at common B-cell antigens such as CD22 and HLA-DR.
- Chimeric antigen receptor (CAR) T-cell therapy against B-cell antigens is particularly effective in childhood ALL and might therefore be beneficial in relapsed/refractory BL.
- Selective serotonin re-uptake inhibitors (SSRIs) cause apoptosis of lymphoma cells without affecting normal germinal center B cells. The underlying mechanism is still unclear but is probably independent of the serotonin transporter [103, 104].
- Proteasome inhibitors may result in apoptosis of BL cell lines [105].
- Blockade of EBV-related viral proteins EBNA-1 and EBNA-2, detected in 20–50% of sporadic and HIV-related BL, limits cell growth and increases apoptosis of EBV-immortalized cells in vitro [106, 107].
- Targeting epigenetic modifications with DNA methyltransferase inhibitors (decitabine or 5-azacytidine) or histone deacetylase inhibitors (depsipeptide, MS-275, or suberoylanilide hydroxamic acid) [108].

17.8 Conclusion

BL is a highly aggressive, chemo-sensitive NHL that requires diagnosis and treatment in expert centers. Nowadays, rapid establishment of a short intensive course of chemoimmunotherapy, with CNS-oriented therapy and aggressive prevention and treatment of tumor lysis syndrome yields excellent outcomes in young "fit" patients. Despite the improvement in CR and survival rates, many challenges remain, particularly in the treatment of certain patient groups such as immunocompromised and elderly individuals as well as the treatment of relapsed/refractory disease. Targeting PI3K pathway, MYC and TCF3 expression, and cell cycle kinases are among many therapeutic options to be tested in future clinical trials.

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