Advances in the Diagnosis and Treatment of Childhood and Adolescent B-Cell Non-Hodgkin Lymphoma

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Abstract: Burkitt lymphoma and diffuse large B-cell lymphoma represent the majority of mature B-cell non-Hodgkin lymphomas in children, adolescents, and young adults. Although they are characterized by specific clinical and biological nuances, the 2 diseases share significant clinicopathologic overlap and are treated with the same chemotherapy regimens in pediatrics. Modern-day chemotherapy protocols achieve overall event-free survival rates of nearly 90%. The addition of the anti-CD20 monoclonal antibody rituximab to backbone chemotherapy holds great promise for improving long-term curative outcomes while diminishing acute and long-term toxicities. However, in the contemporary era, the long-term survival for patients with relapsed or refractory disease is meager. The role of hematopoietic stem cell transplantation in children, adolescents, and young adults with relapsed/refractory disease is currently being defined. Meanwhile, novel humoral and cellular immunotherapies, as well as agents targeting specific molecular pathways that drive lymphomagenesis, are exciting developments that are being evaluated in clinical trials.

Introduction

Mature B-cell non-Hodgkin lymphomas (B-NHLs) account for more than half of the NHLs occurring in children, adolescents, and young adults (CAYA). Burkitt lymphoma (BL) is the most common, representing approximately 40% of NHL in CAYA throughout the world, and diffuse large B-cell lymphoma (DLBCL) accounts for nearly 20%. Primary mediastinal B-cell lymphoma (PMBL) is much less common and accounts for approximately 2%.[1] Other rarely occurring mature B-NHLs in CAYA include follicular lymphoma, nodal marginal zone lymphoma, rare variants of DLBCL (the T cell– and histiocyte-rich large B-cell lymphoma, *ALK*–positive DLBCL, and DLBCL arising in the setting of lymphomatoid granulomatosis or human herpesvirus-8-associated multicentric Castleman disease), and those B-NHLs that occur almost exclusively in the setting of immunodeficiency (primary central nervous system [CNS] lymphoma, primary effusion lymphoma, plasmablastic lymphoma, and posttransplant lymphoproliferative disease).[2] Sub-Saharan Africa has

Table 1. Clinical Characteristics of Children and Adolescents with DLBCL and PMBL vs Burkitt Lymphoma[a]

	DLBCL Variant						
	Centroblastic	Immunoblastic	T Cell-/ Histiocyte-Rich	DLBCL, NOS	All DLBCL	PMBL	BL
No. of patients	186	17	20	21	244	33	924
Male:female	1.86:1	2.4:1	4:1	2.5:1	2:1	1.06:1	4.7:1
Age, median, y (range)	11.5 (1.9-19.7)	12.9 (3.7-16.2)	10.9 (6.6-17.4)	14.2 (1.1-17.3)	11.4 (1.4-17.9)	14.7 (1.4-17.9)	8.6 (0.7-19.2)
Stage I, St Jude	24%	0%	20%	9%	21%	0%	9%
Stage II, St Jude	37%	29%	40%	19%	35%	0%	22%
Stage III, St Jude	37%	59%	35%	62%	41%	97%	41%
Stage IV, St Jude	2%	12%	5%	9%	4%	3%	28%[b]
Bone marrow	0%	6%	5%	5%	1%	3%	25%
CNS	2%	6%	5%	5%	3%	0%	10%
Mediastinal	11%	23%	25%	24%	14%	100%	8%
Lung	3%	12%	5%	14%	5%	36%	2%
Liver, focal	4%	12%	10%	9%	6%	3%	12%
Spleen, focal	4%	12%	15%	9%	6%	9%	3%
Kidney	2%	6%	5%	14%	4%	24%	13%
Skin	0%	0%	10%	0%	1%	0%	1%
Bone	8%	0%	5%	14%	8%	3%	7%
Soft tissue	3%	0%	10%	0%	3%	3%	3%
Pleural effusion	3%	0%	5%	5%	3%	39%	14%
Pericardial effusion	3%	12%	0%	0%	3%	36%	2%
Ascites	5%	12%	5%	19%	6%	6%	24%
B-symptoms	13%	12%	25%	24%	14%	36%	17%
LDH ≥500 U/L	12%	24%	10%	24%	14%	30%	46%
Immunodeficiency	4%	12%	5%	14%	6%	0%	1%

BL, Burkitt lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; NOS, not otherwise specified; PMBL, primary mediastinal (thymic) large B-cell lymphoma, y, years.

[a] Data derived from multicenter studies in the Berlin-Frankfurt-Munster NHL database. Patients registered from March 1990 to December 2002.

[b] Including cases with more than 25% French-American-British L3 blasts in the bone marrow (B-cell acute lymphocytic leukemia).

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a unique epidemiology of childhood cancer. Endemic BL is the most common pediatric malignancy in this region, representing up to one-third to one-half of all pediatric oncologic diagnoses. This review will focus on the common mature B-NHL only—BL, DLBCL, and PMBL—and will not discuss the rare B-NHL of childhood or B-cell lymphoblastic lymphoma.

BL and DLBCL have considerable clinical and biological overlap in children. Both are considered aggressive mature B-NHLs, and respond similarly to treatment. In the contemporary era, pediatric mature B-NHL patients are enrolled in the same treatment protocols throughout the world. However, there are some notable clinical differences. The biggest clinical distinction is that DLBCL rarely involves the CNS or bone marrow, and is stage I/II in approximately half of patients. BL, on the other hand, is advanced (stage III/IV) in approximately 70% of patients. Similarly, as a measure of disease burden, lactate dehydrogenase (LDH) is significantly elevated in a small minority of patients with DLBCL. In contrast, nearly half of children with BL have severely elevated LDH levels. Data from the Berlin-Frankfurt-Munster (BFM) experience reflect some of the clinical distinctions (Table 1).

Pathology and Biology

There are important biological nuances that distinguish BL from DLBCL. The defining characteristic of BL is a

translocation of the *C-MYC* oncogene on chromosome 8 with the immunoglobulin genes on chromosomes 14, 22, or 2. The classic histology shows intermediate-sized cells with round nuclei and scant cytoplasm with lipid vacuoles that are best appreciated on touch preparations or aspirate smears. BL has one of the highest proliferation rates of any malignancy and usually reveals numerous mitotic figures and apoptotic bodies that can be seen engulfed in scattered macrophages, portraying the characteristic "starry sky" appearance on low-power histology.[3] Endemic BL refers to the epidemiologic subtype that occurs in the holoendemic malaria belt of sub-Saharan Africa and is virtually always associated with Epstein-Barr virus infection. On the other hand, sporadic BL, which occurs everywhere else in the world, is associated with Epstein-Barr virus in approximately 30% of cases.[4]

The classic histology of DLBCL is described as a diffuse infiltrate of medium- to large-sized cells that efface the lymph node architecture. However, there are pitfalls in relying solely on histology owing to the potential for overlap in both the morphologic and immunophenotypic appearance of BL and DLBCL. Although there are no defining cytogenetic abnormalities for DLBCL, another confounding factor is that 5% to 10% of pediatric DLBCL cases carry a *C-MYC* translocation.[5]

The immunophenotypic signature of both diseases can be identical in children. They share expression of mature B-cell antigens CD20 and CD19, and notably lack expression of terminal deoxynucleotidyl transferase—an antigen expressed by the immature B-cell lymphoblastic lymphoma. Both BL and DLBCL usually express the antigens CD10 and BCL6, which are associated with germinal center derivation. Although BL classically expresses the proliferation antigen Ki-67 at higher rates than DLBCL (often >99%), it is not uncommon for DLBCL to have equally high proliferation rates. One distinguishing protein can be BCL2, which is expressed in about 40% of DLBCL; it is rarely expressed in BL.[5]

Landmark gene expression profiling (GEP) studies have recently established an extensive biological definition of B-NHL. By comparing the GEP of more than 200 cases of B-NHL in adults with a core group of 8 prototypical cases of BL, Hummel and colleagues were able to produce a molecular definition of BL that extended the spectrum of the World Health Organization (WHO) criteria.[6] Dave and colleagues focused on comparing the GEP of BL vs DLBCL. In doing so, they established a unique and accurate method of distinguishing between the 2 types of B-NHL on a genomic level. *C-MYC* and its target genes as well as a subgroup of germinal center B-cell genes were more highly expressed in BL. In contrast, DLBCL exhibited a higher expression of major-histocompatibility class I genes and nuclear factor κB target genes; DLBCL cases clustered into the 2 well-established subtypes, activated B cell–like (ABC) and germinal center B cell–like (GCB).[7] It is important to note that the GCB subtype accounts for the vast majority of pediatric DLBCL.

The aforementioned genomic research was performed on adult B-NHL specimens. However, GEP studies in pediatric B-NHL have highlighted similar findings.[8,9] In the study by Klapper and colleagues, although morphologic diagnoses of pediatric BL were confirmed by molecular studies, 31% of pediatric DLBCL cases were reclassified molecularly as BL (mBL). Interestingly, some of the reclassified cases of mBL had atypical features such as BCL2 expression or lower Ki-67 index.

In the gray area that exists between BL and DLBCL arises another disease entity, formerly known as Burkitt-like lymphoma or atypical Burkitt lymphoma. This entity refers to mature B-NHL with a morphologic appearance of BL, but lacking the characteristic *C-MYC* translocation. In the current version of the WHO classification of lymphoid neoplasms, this diagnosis is called *B-cell lymphoma, unclassifiable* (with features intermediate between DLBCL and BL).[2] Ultimately though, in the current era in which pediatric patients with mature B-NHL receive uniform therapies with similar outcomes, precise molecular classification of the diagnosis has not become integrated into standard clinical care.

PMBL has a predilection for adolescents and young adults and historically has been thought of as a variant of DLBCL.[10] However in the past decade, definitive evidence has come forth establishing PMBL as a distinct diagnosis.[11] Classic morphology is described as large-sized malignant cells within a tumor microenvironment characterized by the presence of sclerosis. Morphologically, PMBL appears to be in a gray zone between DLBCL and classic Hodgkin lymphoma. Similar to Hodgkin lymphoma, PMBL is frequently CD30 positive, which is an uncommon finding in DLBCL. Another important distinction is that PMBL is predominantly located within the thymus, whereas DLBCL arising in the mediastinum tends to affect mediastinal lymph nodes. There also exists a gray-zone diagnostic entity called B-cell lymphoma, unclassifiable (with features intermediate between DLBCL and classical Hodgkin lymphoma), which serves to cloud the differential diagnosis even further.

Staging and Risk Assessment

The major determinants for risk stratification in mature B-NHL of childhood are rooted in the original Murphy stage of the clinical presentation (Table 2). The French-American-British/Lymphomes Malins B (FAB/LMB) approach has risk-stratified pediatric B-NHL into 3 groups and built the treatment platform upon that. The

Table 2. Murphy's Staging

Stage 1
- A single tumor (extranodal) or a single anatomical site (nodal) with exclusion of the mediastinum or abdomen
Stage 2
- A single tumor (extranodal) with regional involvement - Two or more nodal areas on the same side of the diaphragm - Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm - A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
Stage 3
- Two single tumors (extranodal) on opposite sides of the diaphragm - Two or more nodal areas above and below the diaphragm - All primary intrathoracic tumors (mediastinal, pleural, thymic) - All extensive primary intraabdominal disease, unresectable - All paraspinal or epidural tumors, regardless of other tumor sites
Stage 4
- Any of the above with initial central nervous system and/or bone marrow involvement

From Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol*. 1980;7(3):332-339.

BFM group has incorporated the LDH level at original presentation into the staging classification to determine risk stratification (Figure 1). In the previous FAB96 study, Cairo and colleagues recently reported clinical variables that are associated with a significantly inferior event-free survival (EFS); these include advanced stage, elevated LDH, primary mediastinal involvement, and combined bone marrow/CNS disease.[12] Additionally, one of the most important prognostic indicators to guide treatment decision is the patient's response to therapy. Further studies are needed to determine whether specific higher-risk cytogenetic findings, such as deletion of 13q, gain of 7q, and complex cytogenetics require and/or benefit from an intensification of the therapeutic approach.[13,14]

Treatment

There has been a dramatic improvement in long-term curative outcomes in pediatric mature B-NHL over the past 3 decades (Figure 2). EFS rates have essentially doubled from the late 1970s to the contemporary era.[15] Since the turn of the century, clinical trials have focused on establishing risk-stratified therapy to diminish acute and long-term toxicities for patients with favorable prognoses and to intensify regimens for those with a higher risk for treatment failure.[16,17] International collaboration in large-scale clinical trials has resulted in the modern day FAB/LMB chemotherapy backbone that has served to improve the curative rates dramatically.

FAB/LMB backbone chemotherapy protocols were established based upon the 3 risk-stratification groups in Figure 1. Low-risk group A patients with fully resected stage I or abdominal stage II disease are treated with 2 cycles of cyclophosphamide, vincristine, prednisone, and doxorubicin (COPAD) without intrathecal chemotherapy. This yields excellent outcomes, with 98.3% 4-year EFS.[18] FAB group B intermediate-risk therapy was established by Patte and colleagues in 2007, ultimately demonstrating equivalent EFS rates of 91% despite reduced total doses of cyclophosphamide and deletion of maintenance cycles.[17] Group B backbone chemotherapy consists of a low-dose COP reduction (cyclophosphamide 300 mg/m^2, vincristine, and prednisone), followed by 2 induction cycles (COPAD plus methotrexate 3 g/m^2) and 2 consolidation cycles (cytarabine 500 mg/m^2 plus methotrexate 3 g/m^2), each with intrathecal chemotherapy given throughout. Even patients with group C high-risk disease—defined as having CNS involvement and/or greater than 25% bone marrow involvement—achieve long-term EFS rates of 79% with the FAB/LMB backbone bolstered by the addition of high-dose methotrexate (8 g/m^2 for CNS-positive patients) during induction and cytarabine (12,250 mg/m^2/cycle) plus etoposide for 2 cycles of intensification followed by 4 cycles of maintenance chemotherapy.[16] Intrathecal chemotherapy is delivered with greater frequency in the group C patients, especially in those with CNS involvement.

The BFM chemotherapy backbone is similar to the FAB/LMB regimen, with the notable difference being the incorporation of ifosfamide into the regimens. Low-risk patients also receive only 2 cycles of chemotherapy, with lower doses of doxorubicin and cyclophosphamide (compared with FAB/LMB) compensated for by the addition of ifosfamide, etoposide, and intermediate-dose methotrexate (1 g/m^2). Intermediate-risk patients are further risk-stratified by the LDH level and receive 4 to 5 cycles of chemotherapy. The difference from the FAB/LMB regimen, again, is the addition of ifosfamide and etoposide in exchange for slightly lower doses of doxorubicin and cyclophosphamide. Finally, the high-risk patients also receive ifosfamide with lower total doses of doxorubicin, cyclophosphamide, and etoposide compared with the FAB/LMB group C regimen. Table 3 depicts a summary of FAB/LMB vs BFM backbone chemotherapy.

CD20 antigen expression is present in greater than 98% of cases of pediatric mature B-NHL and potentially may be an important target in the incorporation of novel therapeutic agents with modern chemotherapy

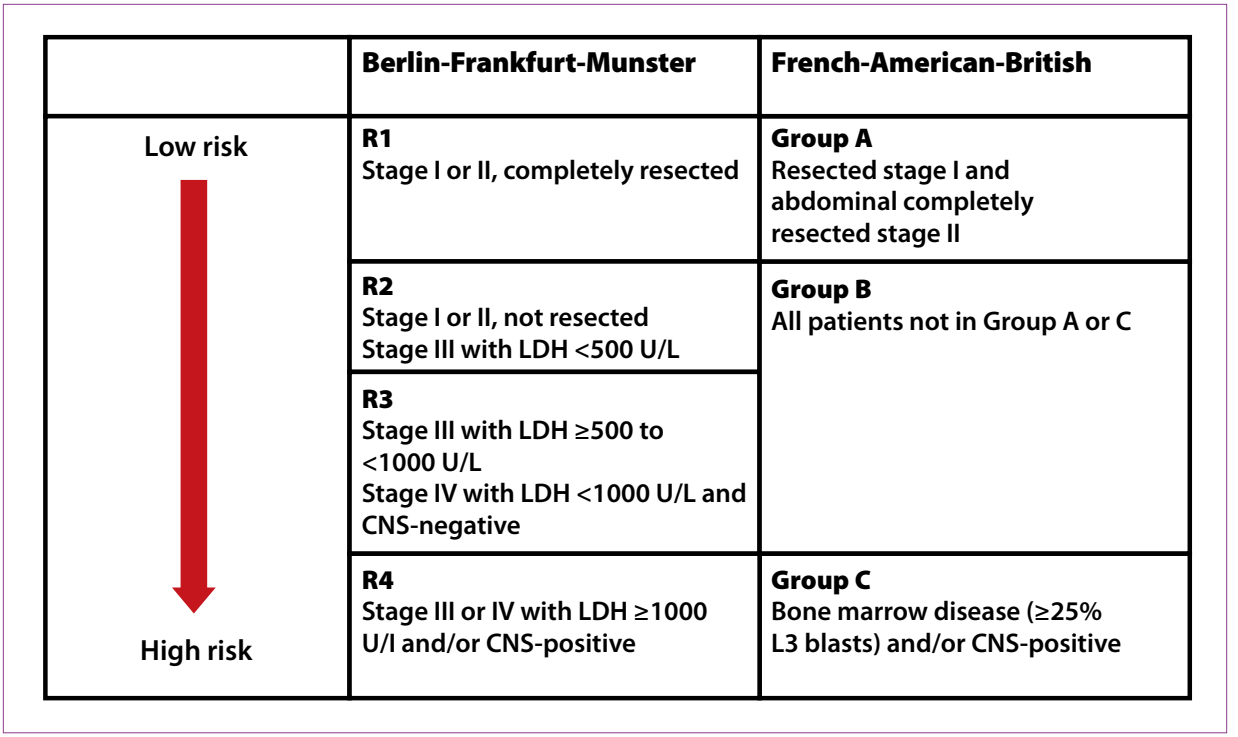

Figure 1. Risk stratification groups for pediatric B-cell non-Hodgkin lymphoma.

CNS, central nervous system; LDH, lactate dehydrogenase.

From Waxman I, Hochberg J, Cairo MS. Lymphoma. In: Kliegman RM, Stanton B, St. Geme J, Schor NF, Behrman RE, eds. *Nelson Textbook of Pediatrics*. 19th ed. New York, NY: Elsevier Inc; 2011:1739-1745.

Table 3. Comparison of Chemotherapeutic Regimens and Dose Between FAB and BFM Treatment Regimens for BL

	BFM	FAB	BFM	FAB	BFM	BFM	FAB
Group	**R1**	**Group A**	**R2**	**Group B**	**R3**	**R4**	**Group C**
Definition	Resected	Resected	Not resected, I, II, III, LDH <500	Not resected, I, II, III, IV, CNS-neg	III, LDH 500-999, IV plus B-ALL, LDH <1000, CNS-neg	LDH >1000 and/or CNS-pos	B-ALL IV, CNS-pos
No. of courses	2	2	4	4	5	6	8
MTX g/m², infusion	1, 4 h, × 2	—	1, 4 h, × 4	3, 3 h, × 4	5, 24 h, × 4	5, 24 h, × 4	8, 4 h (CNS-pos; 24 h), × 3 (4)
Dox mg/m²	50	120	100	120	100	100	240
CP g/m²	1.4	3	2.4	3.3	2.4	2.4	6.8
Ifo g/m²	4	—	8	—	8	8	8
Eto mg/m²	200	—	400	—	900	1400	2500

B-ALL, B-cell acute lymphocytic leukemia; BFM, Berlin-Frankfurt-Munster; BL, Burkitt lymphoma; CNS, central nervous system; CP, cyclophosphamide; Dox, doxorubicin; Eto, etoposide; FAB, French-American-British; h, hours; Ifo, ifosfamide; LDH, lactate dehydrogenase; MTX, methotrexate.

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protocols.[19] Rituximab (Rituxan, Genentech/Biogen Idec) is a type 1, chimeric monoclonal antibody targeting the CD20 antigen. Combining rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in adults with DLBCL resulted in 3-year EFS of 79% vs only 59% for those receiving CHOP without rituximab.[20] Additionally, rituximab has been combined with chemotherapy in the treatment of both adult and

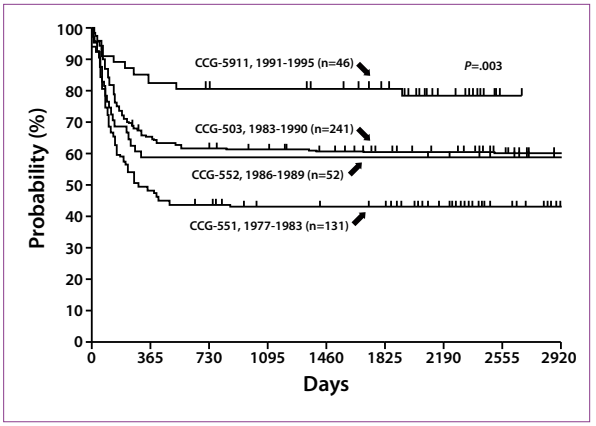

Figure 2. Comparison of EFS by CCG study among 470 disseminated Burkitt and Burkitt-like lymphoma patients from CCG studies -551, -503, -552, and -5911. CCG-5911 vs all other studies (CCG-551, -503, and -552), 4-year EFS (80 ± 6% vs 54 ± 2%, *P*=.003).

CCG, Children's Cancer Group; EFS, event-free survival.

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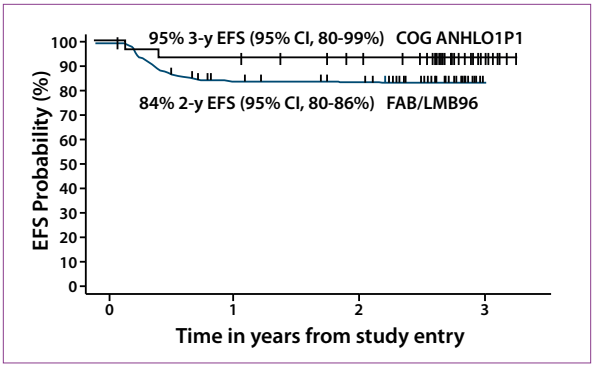

Figure 3. Product-limit estimate of probability of EFS in all stage III/IV pilot patients on study compared with all stage III/IV patients treated on FAB/LMB 96 without rituximab.

EFS, event-free survival; FAB, French-American-British; OS, overall survival.

From Goldman S et al. *Leukemia.* 2013;27(5):1174-1177.[24]

pediatric PMBL as well as children with relapsed/refractory B-NHL, with excellent outcomes.[21-23]

The most recent Children's Oncology Group (COG) ANHL01P1 pilot study for mature B-NHL integrated rituximab into the standard FAB/LMB backbone chemotherapy, with outstanding results. Not only did the study show that it was safe to combine rituximab with FAB/LMB chemotherapy, the chemoimmunotherapeutic approach produced phenomenal results. The probability of EFS at 3 years for 45 patients with advanced (stage III/IV) group B intermediate-risk disease was 95% (Figure 3).[24] Meanwhile, rituximab combined with the group C regimen yielded a 3-year EFS of 90% in 40 patients (Figure 4).[25] The BFM evaluated the efficacy of rituximab differently, as they utilized a 1-week window of a single dose of rituximab (375 mg/m^2) prior to initiation of standard frontline BFM chemotherapy. Despite the short observation period of 1 week, 37 of 87 evaluable patients (42%) demonstrated a significant response.[26]

Current clinical trials in pediatric mature B-NHL are focusing on the rituximab plus FAB/LMB chemoimmunotherapy regimen. Several collaborative groups throughout the world are participating in the Intergroup Trial for Children or Adolescents With B-Cell NHL or B-AL: Evaluation of Rituximab Efficacy and Safety in High Risk Patients (NCT01595048). This trial will evaluate FAB/LMB backbone chemotherapy with and without rituximab in a randomized fashion to measure the efficacy of rituximab in a larger cohort. Another multicenter clinical trial designed by the CAYA NHL and Hodgkin Lymphoma Translational Research and Treatment Consortium (CANTREAT) is titled REBOOT ABLY (Reduced Burden of Oncologic Therapy in Advanced B-Cell Lymphoma) in Children, Adolescents and Young Adults With CD20+ Mature B-Cell Lymphoma (NCT01859819). This trial asks the question whether the addition of rituximab will enable dose reductions of cytotoxic chemotherapy. Finally, the German NHL BFM 04 trial is evaluating their chemotherapy platform following the incorporation of the aforementioned rituximab window into the initial phase of the treatment regimen.

It is important to note that children with PMBL did not fare as well as those with BL or DLBCL in the aforementioned FAB/LMB chemotherapy protocols, with 5-year EFS reaching only 66%.[11] PMBL, similarly to DLBCL, rarely presents as stage IV disease, indicating that the inferior response to therapy has more to do with the disease biology than the extent of disease. Fortunately, recent data have shown that EFS rates of 93% can be achieved in CAYA using dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (EPOCH-R) without radiotherapy.[21,23] The aforementioned Intergroup B-NHL trial is also evaluating EPOCH-R in a prospective fashion for CAYA with PMBL. An important nuance in the response to treatment in PMBL is that the mediastinal mass may persist on imaging studies in a significant number of patients, even with utilization of ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT).

The response to chemotherapy is paramount for prognostic implications in BL and DLBCL. Although the role of FDG-PET in FDG-avid NHL in adults has been established by the Lugano classification for initial evaluation, staging, and response assesment, there is a paucity of data to determine its precise role in pediatric/adolescent mature B-NHL. Therefore, in mature B-NHL in CAYA, disease response based upon standard imaging with CT

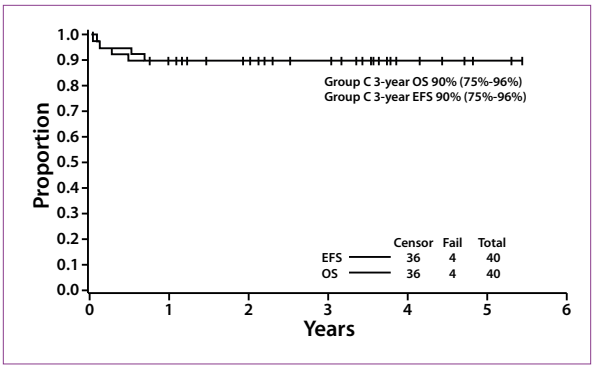

Figure 4. Probability of EFS and OS in children and adolescents with BM and/or CNS disease with de novo mature B-cell non-Hodgkin lymphoma (B-NHL) treated with rituximab and FAB Group C1 Chemotherapy Pilot on COG ANHL01P1 as determined by Kaplan–Meier method.

BM, bone marrow; CNS, central nervous system; EFS, event-free survival; FAB, French-American-British; OS, overall survival; 01P1, ANHL01P1 protocol.

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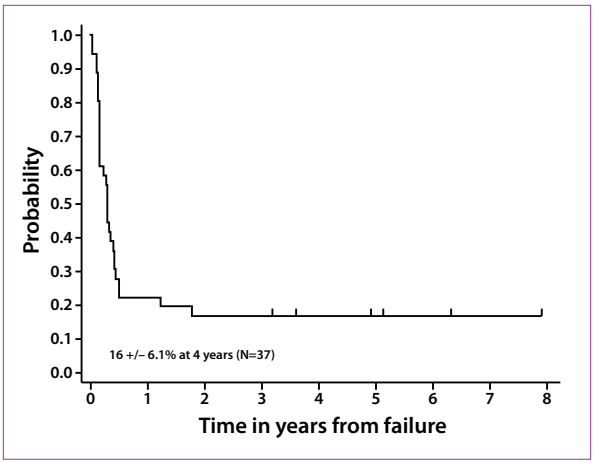

Figure 5. Survival probability after progression/recurrence. The probability of 4-year survival of patients with persistent, progressive, or recurrent disease, excluding those experiencing toxic deaths or secondary neoplasms, was 16% ± 6.1%.

From Cairo MS et al. *Blood.* 2007;109(7):2736-2743.[16]

provides valuable information. On the FAB/LMB protocol, failure to achieve at least a 20% reduction in disease burden with the first week of reduction-phase chemotherapy is a poor prognostic indicator and requires intensification of the treatment regimen.[17] Additionally, failure to achieve complete remission (CR) by the completion of the first consolidation cycle is associated with poor long-term survival and is another indication for intensification of therapy. FDG-PET may one day provide an additional role in staging and response evaluation in BL and DLBCL in CAYA and improve the identification of patients at risk for treatment failure, but prospective evaluations of the role of FDG-PET in CAYA are still needed.

Relapsed and Refractory Disease

Alongside the encouraging improvement in overall curative rates, a major challenge has surfaced in the management of patients with relapsed/refractory mature B-NHL. As outcomes on up-front protocols have improved dramatically for the vast majority of patients, salvaging those patients with relapsed/refractory disease has become inordinately difficult. Long-term data for patients who relapsed after treatment on the United States collaborative group CCG (Children's Cancer Group) protocols revealed overall survival (OS) of only 12%.[15] British data demonstrated that only 3 of 26 (11.5%) patients with relapsed/refractory B-NHL survived; of note, all 3 had been treated in an era with less intense up-front protocols. All patients who relapsed after the modern FAB backbone (UKCCSG 9003 protocol) died.[27] On the recent international FAB/LMB 96 protocol, shorter 1-year probability of OS for all patients with relapsed/refractory mature B-NHL was 28%.[28] Data from the FAB/LMB 96 high-risk study revealed a 16% probability of 4-year OS for those with progressive or recurrent disease (Figure 5).[16] In a smaller cohort from Austria/Germany, of 9 children with refractory/relapsed mature B-NHL, all but 1 died of progressive disease.[29] Meanwhile, in the contemporary cohort of COG group C patients receiving rituximab-based chemoimmunotherapy, 3-year EFS and OS were identical (at 90%), demonstrating that none of the patients with relapsed/refractory disease were successfully salvaged (Figure 4).[25] These extremely low rates of long-term survival reflect the enormity of the challenge in curing patients with relapsed/refractory disease, especially in the rituximab era.

Combination chemotherapy using ifosfamide, carboplatin, and etoposide (ICE) has been established in the setting of relapsed/refractory lymphomas in CAYA.[30] More recently, rituximab was combined with ICE for children with relapsed/refractory B-NHL, with encouraging results. Of 20 evaluable patients, there were 12 responders—7 CR and 5 partial remissions (PR). In DLBCL, 3 of 6 patients achieved CR (no PR). Among the 14 patients with relapsed/refractory BL, there were 4 CR and 5 PR.[22] Although the rituximab/ICE combination proved capable of inducing response in a significant number of patients, it has failed to provide long-term cures. Rather, it serves to provide a bridge to definitive therapy utilizing hematopoietic stem cell transplantation (HSCT).

Hematopoietic Stem Cell Transplantation

It is very challenging to interpret reports on outcomes for patients with relapsed/refractory B-NHL who undergo HSCT. Dismal outcomes are found in the contemporary

literature despite autologous HSCT (autoHSCT) and allogeneic HSCT (alloHSCT). On the other hand, large registry data analyses that include patients dating back 20 years ago sometimes project optimism that may not be relevant in the modern era. Philip and colleagues reported on the French experience with 27 cases of relapsed mature B-NHL from 1984 to 1987. Twelve patients received conventional chemotherapy without HSCT; all of them died. Fifteen patients received an HSCT (14 auto, 1 allo), and their probability of OS was 27%.[31] Ladenstein and colleagues reported on European transplant registry data utilizing autoHSCT for relapsed/refractory B-NHL spanning the years 1979 to 1991. Continuous CR was achieved in 39% of patients, but the authors emphasized in the discussion that among patients originally treated with the more intensive LMB 86/89 protocols (in which high-dose methotrexate and cytarabine were given), there were no long-term survivors despite autoHSCT.[32] Data from Memorial Sloan Kettering on a smaller cohort of 5 patients with relapsed/refractory BL and 4 with DLBCL recapitulates these poor outcomes.[33]

There is 1 prospective trial evaluating the use of autoHSCT in CAYA with lymphoma; the data for patients with NHL include BL, DLBCL, lymphoblastic lymphoma, and anaplastic large-cell lymphoma (ALCL). Unfortunately, the report does not delineate the NHL subtypes of the patients who ultimately survived. The 3-year EFS for patients with NHL was less than 30%. Of the 30 children enrolled with NHL, only 10 proceeded to receive high-dose chemotherapy plus autoHSCT, and ultimately only 7 survived. The NHL patients enrolled in the study included 5 with ALCL, which can have very promising outcomes with autoHSCT when relapse occurs more than 1 year after the original diagnosis.[34] Nonetheless, 1 finding that was consistently reported by all of the above studies was the importance of performing HSCT in patients with chemosensitive disease. Patients receiving HSCT in either CR or PR had statistically superior outcomes compared with patients with stable, progressive, or refractory disease.

The retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) registry data analysis examined outcomes for CAYA receiving either autoHSCT or alloHSCT for refractory and relapsed NHL between 1990 and 2005. For 35 patients with DLBCL treated with autoHSCT, the probability of 5-year EFS was 52%. For 17 patients with BL receiving autoHSCT, the EFS was only 27%. Interestingly, there was no statistically significant difference in EFS for patients receiving alloHSCT, despite the transplant-related mortality rates between autoHSCT and alloHSCT being comparable.[35] The authors discussed some of the challenges in interpreting retrospective registry data, stating that although they deliberately started the cohort analysis in 1990 with the goal of capturing mostly those patients treated with contemporary high-intensity chemotherapy regimens, there is a lack of details in registry data regarding front-line regimens. Furthermore, patients were more likely to receive autoHSCT in the earlier years of the cohort, a period more likely to coincide with less intensive up-front chemotherapy regimens, and perhaps a higher likelihood of being salvaged with HSCT. Nonetheless, as the largest analysis of HSCT in childhood and adolescent NHL, the information is valuable.

Ultimately, the likelihood of achieving long-term curative outcomes for children with relapsed/refractory mature B-NHL with autoHSCT is low. With that background understanding, and the promise of current advances in alloHSCT in CAYA with hematologic malignancies, it is important to consider whether a graft-versus-lymphoma (GVL) effect can be optimized in mature B-NHL via alloHSCT. Although the retrospective CIBMTR data would argue against it, extrapolation from the adult experience with DLBCL[36,37] as well as the evident GVL benefit in lymphoblastic lymphoma and ALCL serve as motivation to continue to pursue definitive answers.[35,38,39] In the cohort of patients reported by Satwani and colleagues utilizing autoHSCT followed by a reduced-intensity alloHSCT, there were 8 patients with relapsed/refractory mature B-NHL. Although the numbers are low, 5 of 8 achieved long-term CR (1.9-8.8 years).[40]

Long-term survival in mature B-NHL patients with relapsed or refractory disease in the modern era is meager. In the absence of targeted therapies with curative potential, novel approaches to therapy are desperately needed. In this setting, nonstandard approaches including the use of alloHSCT in hopes of driving a GVL effect may be indicated. Ultimately, clinicians must make a critical assessment of the individual patient's risk profile, prior therapies received, and the lymphoma's sensitivity to chemotherapy to determine which patients may gain curative benefit from HSCT.

New Directions

As shown in the review of the literature on relapsed/refractory disease, there is a dire need to develop novel targeted therapies. One must also consider the significant acute and long-term toxicities associated with the intensity of group C FAB/LMB chemotherapy; ideally the development of novel targeted agents will enable a focus on diminishing toxicity. New therapies under development range from humoral and cellular immunotherapies to agents targeting specific molecular pathways such as Bruton's tyrosine kinase (BTK) and phosphoinositide 3-kinase (PI3K) inhibitors.

Obinutuzumab is a novel anti-CD20 monoclonal antibody that recently has demonstrated encouraging success in preclinical studies as well as large-scale clinical

trials in adults. Obinutuzumab is a fully humanized type II antibody, in contrast to the chimeric human-mouse nature of rituximab. It was specifically glycoengineered to create bisected, afucosylated Fc region carbohydrates, resulting in enhanced affinity for the human Fcγ receptor IIIa on effector cells.[41] Although this modification results in less antibody-associated complement-dependent cytotoxicity, it enhances antibody-dependent cellular cytotoxicity, and has an added benefit of enhancing direct cell death (apoptosis) of target cells.[41] Preclinical data have been well established for both chronic lymphocytic leukemia (CLL) and mature B-NHL.[42-44] Additionally, in vitro and in vivo models have established superior cancer-cell death with obinutuzumab in comparison to rituximab, as well as efficacy in rituximab-resistant models.[45]

Clinical trials in adults with CLL and indolent B-NHL also have demonstrated the exciting potential of obinutuzumab. A landmark phase 3 study in patients with CLL established superior treatment outcomes in more than 700 patients with previously untreated CLL receiving obinutuzumab/chlorambucil vs rituximab/chlorambucil.[46] Phase 1 and 2 data also have been established in adults with indolent and aggressive mature B-NHL (including patients with DLBCL).[47-49] Phase 2 data in adults with relapsed/refractory DLBCL showed a 32% overall response rate with obinutuzumab monotherapy.[47] Obinutuzumab also has been safely combined with standard chemotherapy regimens in adults with relapsed/refractory follicular lymphoma, resulting in greater than 90% response rates, with an acceptable safety profile.[50] Based upon the encouraging data in adults with mature B-NHL, including patients who previously had received rituximab-based regimens, obinutuzumab potentially can play an important role in mature B-NHL in CAYA as well.

Other monoclonal antibodies that are in development for B-NHL include agents targeting CD19. A recent trial in adults with refractory/relapsed B-NHL receiving the maytansinoid immunoconjugate SAR3419 achieved reduction in tumor size in 74% of patients, including 7 out of 15 patients whose disease was refractory to rituximab.[51] Blinatumomab is another anti-CD19 monoclonal antibody; it is a bispecific T-cell engager that directs an effector CD3-positive cytotoxic T cell in close proximity to the CD19-positive tumor cell. Blinatumomab has achieved favorable results in studies of both B-NHL and B-cell acute lymphoblastic leukemia (ALL).[52,53]

Cellular immunotherapy targeting B-NHL is another novel development offering great promise. T cells modified with chimeric antigen receptors (CARs) targeting CD19 have generated excitement, with initial excellent results in treating relapsed/refractory CLL and ALL.[54,55] Preclinical data for CAR immunotherapy in BL shows promise,[56] while small cohorts of adults with mature B-NHL have been treated with anti-CD20 CAR T cells.[57] Meanwhile, clinical trials evaluating the safety and efficacy of anti-CD19 CAR immunotherapy for CAYA with mature B-NHL are underway.

Finally, targeted therapy that aims at disrupting cell-signaling pathways that drive lymphomagenesis represent another area of development in novel therapeutic agents. Ibrutinib is a BTK inhibitor and has shown extraordinary potential in adults with CLL, mantle cell lymphoma, and DLBCL.[58-61] Because BTK plays an important role in the B-cell antigen receptor signaling cascade, this targeted agent has great potential. Another important pathway in B-NHL lymphomagenesis is mediated through PI3K. The PI3K inhibitor idelalisib has demonstrated an objective response in phase 2 data evaluating adults with relapsed indolent mature B-NHL,[62] as well as significantly improved outcomes in combination with rituximab in adults with relapsed CLL.[63] Ultimately, great promise lies in these novel targeted agents and the potential to combine them in hopes of both decreasing the incidence of relapses and enabling reductions in the doses and toxicity of traditional chemotherapy. Continued efforts to enhance the understanding of B-NHL biology in CAYA will be critical in improving outcomes for those patients whose disease fails to respond to contemporary chemoimmunotherapy-based regimens.

Conclusion

Mature B-NHL in CAYA is a group of diseases with one of the best prognoses in all of pediatric oncology. However, for the subset of patients whose disease fails to respond to modern therapy, long-term curative outcomes are elusive. Advances in the understanding of B-NHL biology, alongside developments in humoral and cellular immunotherapy and targeted inhibitors of critical molecular pathways, hold the potential to improve overall curative outcomes. One potential tool to improve earlier identification of high-risk patients is evaluation for minimal residual disease (MRD). Although different technologies have been utilized to assess for MRD, Shiramizu and colleagues have been using polymerase chain reaction technology to evaluate for molecular levels of disease.[64] Although it is too early to determine the significance of MRD in CAYA with B-NHL, extrapolating from the preliminary data as well as the experience in acute leukemias and lymphoblastic lymphoma, there could be immense potential to identify high-risk patients through this methodology. The future of cancer therapeutics lies in the ability to combine multimodality treatments that optimize curative outcomes and minimize toxicities. With the already well-established outcomes using standard chemotherapy, there are exciting frontiers to explore with regards to combining targeted immunotherapy and molecular pathway blockade.

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