Novel Therapies Potentially Available for Pediatric B-Cell Non-Hodgkin Lymphoma

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ABSTRACT

Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and primary mediastinal B-cell lymphoma are the most common aggressive pediatric mature B-cell non-Hodgkin lymphomas (B-NHLs). Despite excellent survival with current chemotherapy regimens, therapy for Burkitt lymphoma and DLBCL has a high incidence of short- and long-term toxicities. Patients who experience relapse generally have a very poor prognosis. Therefore, novel approaches using targeted therapies to reduce toxicities and improve outcomes in the relapse setting are needed. The addition of rituximab, a monoclonal antibody against CD20, to upfront therapy has improved survival outcomes for high-risk patients and may allow decreased total chemotherapy in those with low-risk disease. Antibody–drug conjugates have been combined with chemotherapy in relapsed/refractory (R/R) NHL, and multiple antibody–drug conjugates are in development. Additionally, bispecific T-cell–engaging antibody constructs and autologous CAR T-cells have been successful in the treatment of R/R acute leukemias and are now being applied to R/R B-NHL with some successes. PD-L1 and PD-L2 on tumor cells can be targeted with checkpoint inhibitors, which restore T-cell–mediated immunity and antitumor responses and can be added to conventional chemotherapy and immune-directed therapies to augment responses. Lastly, trials of small molecule inhibitors targeting cell signaling pathways in NHL subtypes are underway. This article reviews many of the targeted therapies under development that could be considered for future trials in R/R pediatric mature B-NHL.

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As a group, lymphomas are the third most frequent malignancy in pediatric patients. Mature B-cell non-Hodgkin lymphomas (B-NHLs) constitute approximately 60% of all pediatric NHL diagnoses and 7% of all pediatric cancers. Most pediatric B-NHLs are Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and primary mediastinal B-cell lymphoma (PMBCL). Each is highly aggressive and has its own unique biology.^{1–5} Additionally, there are rare subtypes, including pediatric-type follicular lymphoma, pediatric marginal zone lymphoma, primary central nervous system (CNS) lymphoma, and posttransplant lymphoproliferative disorder.

Sporadic Burkitt lymphoma accounts for up to 80% of pediatric B-NHL in developed nations.^{3,5} Burkitt lymphoma is a germinal center mature B-NHL with a phenotype that includes expression of CD10, CD19, CD20, CD22, surface IgM in >90% of cases, and proliferation marker Ki67 in >90% of cells. Nearly all constitutively express the MYC oncogene due to translocations with the immunoglobulin heavy chain [t(8;14)(q24;q32)] in 80% of cases, or the kappa light chain [t(2;8)(p11;q24)] or lambda light chain [t(8;22)(q24;q11)] in 15% and 5%, respectively. Additionally, MYC-positive cases frequently have a mutation in one of the genes in the ID3-TCF-CCND3 pathway, which may account for a second hit in Burkitt lymphoma pathogenesis.⁶ MYC-negative Burkitt-like lymphoma with 11q aberrations is a provisional entity in the 2016 WHO lymphoid classification.

DLBCL accounts for 10% to 20% of pediatric B-NHL.^{2,3,5} Phenotypically, DLBCLs often express light chain–restricted surface IgG as well as B-cell markers CD19, CD20, CD22, CD79a, PAX-5, and occasionally CD30, which is a non-specific marker of activation. Expression of the proliferation marker Ki-67 is lower than in Burkitt lymphoma, usually <90%. In addition, one-third express the MYC transcription factor, which plays an important role in tumor pathogenesis and development,⁷ and two-thirds express the antiapoptosis protein BCL2. Coexpression of these 2 proteins occurs in approximately 10% of germinal center DLBCL and is associated with worse prognosis.⁸ Gene expression profiling has demonstrated that most pediatric DLBCLs are the germinal center B-cell subtype (GCB) rather than the activated B-cell subtype (ABC) more commonly seen in adults. This difference in

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underlying biology somewhat limits the ability to extrapolate the results of mature B-NHL trials in adults to pediatric patients.

PMBCL accounts for only 3% of pediatric NHL diagnoses, and unlike Burkitt lymphoma and DLBCL, it is a thymic B-cell lymphoma.^{2-4,9} Phenotypically, PMBCL expresses B-cell markers, including CD19, CD20, CD22, and CD79a, but not surface immunoglobulin. It has a unique gene expression profile and genomic changes that overlap with classic Hodgkin lymphoma, including constitutive activation of the NF- κ B and JAK-STAT pathways, immune evasion via downregulation of MHC I and II, and alterations in the 9p24 locus resulting in PD-L1 and PD-L2 expression.

Current Therapies Combine Monoclonal Antibodies With Chemotherapy

The International Pediatric NHL Staging System¹⁰ is based on the Murphy (St. Jude) criteria¹¹ and allows for allocation of pediatric patients with Burkitt lymphoma and DLBCL into risk groups based on disease stage with or without resection in the French-American-British (FAB)/Lymphome Malins B (LMB) protocols and with the additional incorporation of lactate dehydrogenase level in the Berlin-Frankfurt-Münster (BFM) protocols. In the pre-rituximab era, risk-stratified, response-based, multiagent chemotherapy included higher doses and additional cycles of chemotherapy for patients with higher-stage disease and resulted in cure rates ranging from 79% to 98% (Table 1).

The addition of immunotherapy has increased survival in patients with higher-stage disease. Rituximab is a chimeric murine/human monoclonal antibody with a

high affinity against CD20 on B cells that functions through complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity (ADCC). The addition of rituximab to standard chemotherapy improved 3-year event-free survival (EFS) rates from 59% (95% CI, 54%–64%) to 79% (95% CI, 75%–83%) ($P<.0001$) in adults with DLBCL.¹² In a phase II window study of pediatric patients with newly diagnosed B-NHL, rituximab monotherapy demonstrated a response rate of 41.4% (95% CI, 31%–52%) measured 5 days after administration.¹³ Rituximab was shown to be safe when combined with standard chemotherapy in a Children's Oncology Group (COG) pilot study, and resulted in 3-year EFS rates of 95% (95% CI, 80%–99%) for intermediate-risk FAB group B (stage III/IV) patients¹⁴ and 90% (95% CI, 76%–96%) for high-risk group C patients. In this study, outcomes were comparable for patients with and without CNS involvement.^{15,16} Most recently, the European Intergroup/COG Inter-B-NHL 2010 trial, which randomized high-risk patients with Burkitt lymphoma and DLBCL to chemotherapy with or without rituximab, was terminated early due to an increased 1-year EFS rate of 94.2% (95% CI, 88.5%–97.2%) in the rituximab arm compared with 81.5% (95% CI, 73.0%–87.8%) in the control arm.¹⁷ Based on the outcomes after the addition of rituximab in higher-stage NHL, it could be inferred that that rituximab should be added to standard chemotherapy backbones for patients with lower-stage disease as well, although this has not been investigated in a clinical trial.

Despite excellent EFS with current chemotherapy regimens, patients with Burkitt lymphoma and DLBCL have a high incidence of grade 3–4 oral mucositis,

Table 1. Outcomes for Current Chemotherapy Regimens in Pediatric Burkitt Lymphoma and DLBCL

Group	Definition	Trial	EFS
BFM R1	Stage I/II resected disease	BFM95 ²⁰	3-y: 94% $\pm$ 4%
BFM R2	Stage I–III, LDH <500 μ /L	BFM95 ²⁰	3-y: 94% $\pm$ 2%
BFM R3	Stage III, LDH 500–999 μ /L Stage IV + B-ALL, LDH $<1,000$ μ /L	BFM95 ²⁰	3-y: 85% $\pm$ 4%
BFM R4	Stage III/IV with LDH $>1,000$ μ /L or CNS+	BFM95 ²⁰	3-y: 81% $\pm$ 3%
FAB Group A	Stage I/II resected disease	FAB/LMB96 ¹⁰⁰	4-y: 98.3% (95% CI, 94–99.5)
FAB Group B	Stage I–IV, CNS–, BM $<25\%$	FAB/LMB96 ¹⁸	4-y: 93.4% (95% CI, 90–96)
FAB Group C, CNS–	Stage IV, CNS–	FAB/LMB96 ¹⁸	4-y: 85.6%
FAB Group C, CNS+	CNS+	FAB/LMB96 ¹⁰¹	3-y: 75 $\pm$ 4.5%
FAB Group C, CNS+	CNS+	COG-ANHL01P1 ¹⁵	4-y 93.3% (n=15)
Advanced	Stage III/IV with LDH $>2\times$ ULN, any stage IV	Inter-B-NHL 2010 ¹⁷	3-y: 82.3 (95% CI, 75.7–87.5) (without rituximab)
			3-y: 93.9 (95% CI, 89.1–96.7) (with rituximab)

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; B-NHL, B-cell non-Hodgkin lymphoma; BFM, Berlin-Frankfurt-Münster; BM, bone marrow; CNS, central nervous system; EFS, event-free survival; FAB, French-American-British; LDH, lactate dehydrogenase; ULN, upper limit of normal.

hematologic toxicities, and infections, which often result in prolonged hospitalizations. In addition, other long-term effects of current chemotherapy regimens include risk of infertility, secondary malignancies, and late cardiac toxicity due to high cumulative doses of alkylators, topoisomerase II inhibitors, and anthracyclines. Novel approaches to reduce both acute and long-term toxicities are needed. The FAB/LMB96 trial demonstrated that for patients with intermediate-risk B-NHL who had an early response to therapy and achieved a complete remission (CR) after their first consolidation course, the cumulative cyclophosphamide dose could be safely reduced and the maintenance 1 phase could be omitted.¹⁸ The FAB/LMB96 trial also replaced CNS irradiation with high-dose methotrexate and had similar outcomes to the prior LMB89 trial.^{18,19} The NHL-BFM95 trial demonstrated that reducing high-dose methotrexate dose and infusion rate reduced the incidence of grade III/IV mucositis.²⁰ High-dose methotrexate is not used in adult DLBCL and could be a future target for replacement by a less toxic agent. The most recent NHL-BFM and Scandinavian NOPHO pediatric B-NHL trial (B-NHL 2013) is testing whether rituximab can be substituted for anthracyclines in patients with limited-stage disease (R1, R2 stage 1 and II) without compromising survival, as well as analyzing the survival impact of adding rituximab to chemotherapy for patients with higher-stage disease (ClinicalTrials.gov identifier: NCT03206671). A recently closed clinical trial from the New York Medical College is investigating whether the addition of rituximab and liposomal cytarabine to the FAB Group B backbone can safely reduce the cumulative anthracycline dose and number of intrathecal injections for a subset of patients (NCT01859819).²¹

Rituximab has been added to chemotherapy for PMBCL as a substitute for mediastinal radiation,^{22,23} thus reducing the risk of cardiotoxicity and breast cancer. In a phase II trial of 51 adults with PMBCL, the addition of rituximab to dose-adjusted etoposide/doxorubicin/cyclophosphamide + vincristine/prednisone (DA-EPOCH) increased EFS from 70%²⁴ to 93%.²³ In pediatric PMBCL, chemotherapy regimens successful in pediatric Burkitt lymphoma and DLBCL have resulted in EFS of only approximately 66%.²⁵ Therefore, the adult strategy of DA-EPOCH-R was applied to pediatric patients with PMBCL in a prospective trial of 47 patients but resulted in a 2-year EFS rate of only 72% (95% CI, 57%–84%).²⁶ In a retrospective review of 156 patients, including 38 pediatric patients, treated with DA-EPOCH-R at 24 academic centers, 3-year EFS was 86% (95% CI, 80.3%–91.5%).²⁷ Although pediatric EFS rates are less than those seen in adults, the DA-EPOCH-R regimen (without radiation) has fewer acute toxicities, including less stomatitis, enteritis, febrile neutropenia, and infections, compared with other pediatric B-NHL chemotherapy backbones,^{17,23}

and has been adopted as the standard therapy for this group of patients.

Relapsed B-NHL

Relapsed pediatric B-NHL has a very poor prognosis with survival rates ranging from 27% to 36%.^{28–30} Common chemotherapy salvage approaches include rituximab + ifosfamide/carboplatin/etoposide (R-ICE) or rituximab + high-dose cytarabine/etoposide (R-CYVE). These salvage regimens have CR rates of 35% to 47% and are usually followed by either autologous or allogeneic hematopoietic stem cell transplantation (HSCT). In a prospective COG study of relapsed B-NHL, only 7 of 20 patients were alive and disease-free, and 5 of the 6 patients who underwent HSCT (4 autologous, 2 allogeneic) were survivors.²⁹ In a retrospective study in the United Kingdom and Ireland, only 9 of 27 patients survived, all of whom received HSCT (8 autologous, 1 allogeneic) in CR.²⁸ Similarly, in a retrospective study of 33 patients in France, 5-year survival for patients in CR at the time of transplant was 75% (95% CI, 46.8%–91.1%) compared with 33.3% (95% CI, 9.7%–70%) for patients who underwent HSCT following only a partial response (PR).³⁰ Additionally, this study found no difference in survival based on type of transplant. Therefore, although HSCT in CR remains standard, relapse post HSCT is common, and it is unclear whether autologous or allogeneic HSCT provides superior disease control.^{31,32} Two smaller trials have shown promising results using myeloablative autologous HSCT followed by reduced-intensity conditioning allogeneic HSCT.^{30,33,34} There are no case series of relapsed pediatric PMBCL; however, in adult patients with relapsed PMBCL, even with allogeneic HSCT progression-free survival is only 34%.³⁵ Therefore, novel strategies are needed for pediatric patients with relapsed mature B-NHL, especially for those who experience relapse posttransplant. Although there are many agents being developed for B-NHL in adults (Table 2), relatively few are being tested in pediatric patients. Selection of novel therapies for pediatric clinical trials will likely be derived from clinical trials that are successful in adults (Table 3).

Monoclonal Antibodies

Multiagent chemotherapy with rituximab has become the standard of care for most intermediate- and high-risk pediatric mature B-NHL. A number of next-generation monoclonal antibodies have also been investigated but have had limited success in improving survival outcomes. Obinutuzumab, a type II monoclonal antibody with greater in vitro ADCC and direct cell death than rituximab,³⁶ did not improve outcomes in adults newly diagnosed with DLBCL randomized to receive either rituximab or obinutuzumab in conjunction with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP).³⁷ A pediatric

Table 2. Novel Agents and Targets in Non-Hodgkin Lymphoma

Class	Medication	Target
Antibody drug conjugate	Inotuzumab ozogamicin	CD22
	Pinatuzumab vedotin	CD22
	Brentuximab vedotin	CD30
	Polatuzumab vedotin	CD79b
	Denintuzumab mafodotin	CD19
	Debio 15621	CD37
Monoclonal antibody	Rituximab	CD20
	Obinutuzumab	CD20
	Ofatumumab	CD20
	Veltuzumab	CD20
T-cell engagers	Blinatumomab	CD19
	Mosunetuzumab	CD20
	REGN1979	CD20
	RG6026	CD20
CAR T-cells	CTL019 (tisagenlecleucel)	CD19
	KTE-C19 (axicabtagene ciloleucel)	CD19
	Lisocabtagene maraleucel	CD19
	MB-106	CD20
	PBCAR0191	CD19
Checkpoint inhibitors	Nivolumab	PD-1
	Ipilimumab	CTLA-4
	Pembrolizumab	PD-1
	Pidilizumab	PD-1/DLL1
Cell signaling inhibitors	Ibrutinib	BTK
	Acalabrutinib	BTK
	Buparlisib	PI3K
	Copanlisib	PI3K
	Idelalisib	PI3K
	IPI-145	PI3K
	Temsirolimus	mTOR
	Everolimus	mTOR
	Bortezomib	26S proteasome
	Venetoclax	BCL-2
	Navitoclax	BCL-2
	Lenalidomide	IRF4
	EPZ-6438	EZH2
	GSK2816126	EZH2
	CPI-1205	EZH2

phase II trial combining obinutuzumab + ifosfamide/carboplatin/etoposide (ICE) is ongoing (ClinicalTrials.gov identifier: NCT02393157). In a clinical trial that closed early due to slow accrual, the second-generation

anti-CD20 human monoclonal antibody ofatumumab resulted in 2 patients with PR and 2 patients with stable disease among 11 enrolled patients.³⁸ Similar response rates were seen when ofatumumab was combined with lenalidamide.³⁹ No difference was seen in EFS for patients with R/R DLBCL randomized to either ofatumumab or rituximab in addition to cisplatin/cytarabine/dexamethasone (DHAP).⁴⁰ The slow onset of effect, lack of improved outcomes using monoclonal antibodies against the same antigen, and fact that most patients with R/R B-NHL have previously received CD20-directed therapy at initial diagnosis have limited the enthusiasm for future clinical trials using next-generation monoclonal antibodies in pediatric B-NHL.⁴¹

Antibody–Drug Conjugates

The conjugation of monoclonal antibodies to agents that are cytotoxic at nanomolar concentrations allows increased tumor-specific drug delivery, higher intracellular drug concentrations, and increased potency compared with traditional chemotherapy.^{42,43} Approximately 30% of DLBCL⁴⁴ and 80% of PMBCL⁴⁵ express CD30, a member of the tumor necrosis factor receptor superfamily and an inducible marker of activation.⁴⁴ Brentuximab vedotin (Bv) is a monoclonal anti-CD30 antibody conjugated with monomethyl auristatin E (MMAE) with established pediatric safety data.^{46–48} In an adult phase II study of 44 patients with R/R CD30+ DLBCL, there was an overall response rate (ORR) of 44% (95% CI, 29.5%–50.8%) with 8 CRs (15%) and 13 PRs (27%).⁴⁹ This study also showed a similar ORR of 31% (95% CI, 18.7%–45.1%) in patients with undetectable CD30 expression by conventional immunohistochemistry, with 6 (12%) CR and 10 (19%) PR,⁵⁰ suggesting a cytotoxic mechanism that is independent of CD30 expression. A phase II study of Bv in adults with R/R PMBCL showed no CRs and a PR in only 2 of 15 patients.⁵¹

Inotuzumab ozogamicin (IO) is a humanized anti-CD22 IgG4 conjugated with the cytotoxic antibiotic calicheamicin and demonstrated only modest responses (2 CRs, 2 PRs) in the phase I trial of 26 adult patients with R/R DLBCL.⁵² However, CR rates were 30% to 50% in subsequent studies that combined IO with rituximab.^{53,54} The higher-than-expected incidence of cytopenias and sinusoidal obstruction syndrome (SOS) suggests off-target activity of the drug. IO was very well tolerated in the prospective phase II trial of 49 pediatric patients with R/R CD22+ acute lymphoblastic leukemia (ALL); however, in this study, the incidence of SOS in patients who underwent allogeneic HSCT was 40% (4 of 10 patients) (ClinicalTrials.gov identifier: NCT02981628). Similarly, in a retrospective review of 51 pediatric patients with R/R ALL who received IO, no cases of SOS occurred while patients were receiving the drug; however, 11 of

Table 3. Recent Adult Clinical Trials Using Novel Therapies for DLBCL

Category	Medications	Target	Phase	Diagnosis	No. Treated	CR n (%)	PR n (%)
ADC combinations	Inotuzumab ⁵²	CD22	I	R/R DLBCL	26	2 (7.7%)	2 (7.7%)
	Inotuzumab + rituximab ⁵³	CD22 + CD20	I/II	R/R DLBCL	42	21 (50%)	10 (23.8%)
	Inotuzumab + rituximab ⁵⁴	CD22 + CD20	II	R/R DLBCL	63	9 (14.3%)	19 (30.2%)
	Inotuzumab + rituximab ¹⁰²	CD22 + CD20	III	R/R DLBCL	166	26 (16%)	42 (25%)
	Polatuzumab ⁵⁶	CD79b	I	R/R DLBCL	25	4 (16%)	10 (40%)
	Polatuzumab + rituximab ⁵⁶	CD79b + CD20	I	R/R DLBCL	9	2 (22.2%)	5 (55.5%)
	Polatuzumab + rituximab ⁶⁰	CD79b + CD20	II	R/R DLBCL	39	8 (20.5%)	13 (33.3%)
	Obinutuzumab + CHOP ³⁷	CD20	III	DLBCL	706	248 (35.1%)	329 (46.6%)
	Polatuzumab + obinutuzumab ⁵⁷	CD79b + CD20	Ib/II	R/R DLBCL	21	6 (28.6%)	5 (23.8%)
	Pinatuzumab + rituximab ⁶⁰	CD79b + CD20	II	R/R DLBCL	42	11 (26.2%)	14 (33.3%)
	Polatuzumab + bendamustine + rituximab ⁵⁸	CD79b + CD20	II	R/R DLBCL	40	23 (57.5%)	5 (12.5%)
	Polatuzumab + bendamustine + obinutuzumab ⁵⁸	CD79b + CD20	Ib/II	R/R DLBCL	27	11 (40.7%)	5 (18.5%)
	Polatuzumab + R-CHP or G-CHP ⁵⁹	CD79b	Ib/II	DLBCL	66	51 (77.3%)	8 (12.1%)
Immunotherapy	Blinatumomab ⁶⁶	CD19	II	R/R DLBCL	21	4 (19%)	5 (23.8%)
	Mosunetuzumab ⁶⁷	CD20	I/Ib	R/R DLBCL	73	13 (17.8%)	11 (15%)
	REGN1979 ⁶⁹	CD20	I	R/R DLBCL	19	8 (42.1%)	3 (15.8%)
CAR T-cells	Axicabtagene ciloleucel ⁷³	CD19	II	R/R DLBCL	77	38 (49%)	25 (32%)
	CTL019 (tisagenlecleucel) ⁷²	CD19	Ila	R/R DLBCL	93	48 (52%)	37 (40%)

Abbreviations: ADC, antibody–drug conjugate; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; G-CHP, obinutuzumab/cyclophosphamide/doxorubicin/prednisone; NR, not reported; PR, partial response; R-CHP, rituximab/cyclophosphamide/doxorubicin/prednisone; R/R, relapsed/refractory.

21 patients (52.4%) who subsequently underwent allogeneic HSCT developed SOS during transplant.⁵⁵

CD79B, a component of the B-cell antigen receptor, is expressed on most B-cell–derived malignancies.⁵⁶ Polatuzumab vedotin is a CD79B-directed monoclonal antibody conjugated with MMAE and induces cell death by microtubule inhibition, antibody-mediated opsonization, and ADCC.⁴³ In the adult phase I trial of 25 patients with R/R DLBCL treated at the recommended phase II dosing, there were 4 CRs and 10 PRs.⁵⁶ Polatuzumab vedotin has subsequently been combined with rituximab,⁵⁶ obinutuzumab,⁵⁷ and bendamustine and rituximab or obinutuzumab⁵⁸ for patients with R/R DLBCL. In the latter study,⁵⁸ with a mean follow-up of 30 months, 9 of 19 responders remained event-free. In previously untreated adult patients, polatuzumab combined with cyclophosphamide/doxorubicin/prednisone and either rituximab or obinutuzumab had an 89% ORR, a 77% CR rate, and a 24-month progression-free survival of 83% (95% CI, 73–93).⁵⁹

Pinatuzumab vedotin is an anti-CD22 ADC conjugated to MMAE. In the ROMULUS trial, adults with R/R B-NHL were randomized to rituximab and either pinatuzumab vedotin or polatuzumab vedotin with comparable outcomes⁶⁰; however, polatuzumab vedotin was

chosen for further development due to longer durations of response and fewer toxicities.⁶⁰ Because immunotherapy has improved outcomes in both adult and pediatric B-NHL trials, ADCs may show increased efficacy in patients with prior exposure to naked monoclonal antibodies.

T-Cell Engagers

Bispecific T-cell-engaging antibody constructs simultaneously bind to tumor-specific surface antigens and CD3, a component of the T-cell receptor complex on cytotoxic T lymphocytes (CTLs) which results in CTL activation, formation of cytolytic synapses, and tumor cell lysis.⁶¹ Blinatumomab is a CD19/CD3 bispecific antibody that is active in adults⁶² and children^{63,64} with R/R ALL and was superior to chemotherapy in the relapse setting in adults.⁶⁵ Blinatumomab was also active in a small trial in adults with heavily pretreated R/R DLBCL, in which 4 of 18 evaluable patients had a CR and 5 a PR.⁶⁶ Mosunetuzumab is a full-length, fully humanized CD20/CD3 bispecific IgG1 antibody that induced CR in 13 of 73 adults with R/R DLBCL,⁶⁷ including 4 of 16 patients who had received prior CAR T-cell therapy.⁶⁸ REGN1979 is a CD20/CD3 bispecific IgG4 modified to reduce Fc binding. In a phase I trial in heavily pretreated adults with R/R

DLBCL, 5 of 7 patients without prior CAR-T exposure achieved CR compared with CR in 3 of 12 patients with prior CAR T-cell therapy.⁶⁹ A large phase II study of REGN1979 in R/R DLBCL is ongoing (ClinicalTrials.gov identifier: NCT03888105). Safety and efficacy data for blinatumomab are known for pediatric patients with R/R ALL^{63,64}; however, neither mosunetuzumab or REGN1979 have been used in children, nor are there published bispecific antibody data in pediatric NHL.

CAR T-Cell Therapy

CAR T-cells are autologous T cells engineered to express single-chain variable fragment antigen recognition moiety, a transmembrane linker, and a CD3 ζ intracellular activation domain that triggers cytotoxic effect.⁷⁰ CAR T-cells bind specific tumor surface antigens in a human leukocyte antigen-independent manner that combines the specificity of monoclonal antibodies with the cytotoxic effector function of CTLs and has the potential for in vivo expansion and persistence. Tisagenlecleucel is a second-generation CD19 CAR-T with an intracellular 4-1BB costimulatory domain designed to provide improved cytokine production, proliferation, and CAR-T persistence, and is highly active in children with R/R ALL.⁷¹ In a phase II trial of tisagenlecleucel for R/R DLBCL, 40% of patients achieved CR and the 2-year relapse-free survival was estimated to be 65% for all patients and 79% for those who achieved CR.⁷² A phase II trial of tisagenlecleucel for pediatric R/R NHL is ongoing (ClinicalTrials.gov identifier: NCT03610724). Axicabtagene ciloleucel is a CD19 CAR-T with a CD28 costimulatory domain and has been shown to have activity in adults with R/R DLBCL. In a phase II trial of 101 adults who received axicabtagene ciloleucel, those with R/R DLBCL had a 49% CR rate.⁷³ At a median follow-up of 15.4 months, CR was sustained in 40% of all patients (including those with PMBCL and transformed follicular lymphoma). Clinical trials using lisocabtagene maraleucel, a CD19 CAR-T with a 4-1BB costimulatory domain⁷⁴; MB-106, a third-generation CD20 CAR-T with intracellular 4-1BB and CD28 domains⁷⁵; and PBCAR0191, an allogeneic CD19 CAR-T cell designed for “off the shelf” use⁷⁶ are in early-phase trials in adults. Severe cytokine-release syndrome and neurotoxicity have the potential to limit the therapeutic application of CAR-T therapies, and novel constructs are being designed to reduce these toxicities while maintaining cytolytic activity.⁷⁷ Early pediatric trials in relapsed CD19+ B-NHL are also ongoing.^{78,79}

Targeted Therapies

A number of cell-signaling inhibitors are being tested in early-phase clinical trials. ABC DLBCL acquires mutations that result in chronic BCR signaling. Ibrutinib, a selective

covalent inhibitor of Bruton tyrosine kinase (BTK), inhibits BCR signaling and is active in adults with ABC DLBCL, but much less so in GCB DLBCL.^{80,81} Although most pediatric DLBCL is the GCB type, ibrutinib is currently being combined with chemotherapy in pediatric patients with R/R mature NHL (ClinicalTrials.gov identifier: NCT02703272). A number of ongoing clinical trials in adults are combining chemotherapy with either ibrutinib or the second-generation BTK inhibitor acalabrutinib, which has greater selectivity and potency.⁸² Another potential signaling target is the phosphoinositide 3-kinase (PI3-K pathway), which appears to be active in preclinical studies of Burkitt lymphoma⁸³; however, data showing efficacy of PI3-K inhibitors in aggressive B-NHL are lacking.⁸⁴ The antiapoptotic protein BCL2 is overexpressed in a subset of patients with DLBCL and is associated with inferior prognosis. Venetoclax is a BCL2 inhibitor that is active in adults with R/R DLBCL⁸⁵ and may function as a chemosensitizing agent.^{86,87} Lenalidomide is an oral immune-modulating medication that targets the E3 ubiquitin ligase cereblon and preclinically exhibited synergy with rituximab.⁸⁸ It has also been found to be effective in adult-type ABC DLBCL when combined with rituximab and R-CHOP; however, these subtypes are rarely found in pediatric patients.^{89–91} Bortezomib is a proteasome inhibitor that targets the NF- κ B pathway and can induce apoptosis in tumor cells that continuously express NF- κ B. A meta-analysis showed that the bortezomib-containing regimens did not prolong survival in patients with ABC DLBCL.⁹² Although a number of drugs targeting cell signaling pathways exist, enthusiasm is limited by slow onset of effect and the knowledge that each pathway is active in only a subset of pediatric NHL. Therefore, development of a clinical trial of any individual agent would be limited to the relevant NHL subtype.

Checkpoint Inhibitors

Expression of PD-L1 and PD-L2 on malignant cells and cells in the tumor microenvironment results in exhaustion of PD-1-expressing tumor-infiltrating T cells and is a mechanism of tumor evasion in the host immune response.⁹³ Checkpoint inhibitors are monoclonal antibodies that interrupt PD-1 receptor-ligand interactions and restore T-cell-mediated immunity and antitumor responses. Abnormalities in 9p24.1 are common in PMBCL and lead to overexpression of PD-L1 and PD-L2.⁴ Nivolumab is a fully humanized IgG4 anti-PD-1 antibody. In a phase II trial of adults with R/R PMBCL, the combination of nivolumab with Bv resulted in a 43% complete metabolic response rate.⁹⁴ Pembrolizumab is a humanized IgG4 monoclonal antibody targeting PD-1. The combined results of a phase Ib trial for R/R NHL and a phase II trial for R/R PMBCL showed an ORR rate of approximately 50%, with 18% achieving CR.⁹⁵ The COG

and National Clinical Trials Network are collaborating in a phase III clinical trial randomizing patients with newly diagnosed PMBCL to chemotherapy with or without pembrolizumab.

Although <20% of patients with DLBCL have 9p24.1 alterations, PD-L1 expression in adults with DLBCL is associated with nongerminal center immunophenotype and inferior outcomes.⁹⁶ Although the response rate of 8% in adults with R/R DLBCL treated with nivolumab was disappointing,⁹⁷ the combination of pembrolizumab with R-CHOP in 30 adults with newly diagnosed DLBCL resulted in a 77% CR rate, which compared favorably with historical controls.⁹⁸ The addition of a checkpoint inhibitor is thought to augment the ADCC effect of rituximab. Given that PD-L1 expression was associated with improved progression-free survival in this cohort and the fact that none of the 19 patients with tumor PD-L1 expression have experienced disease relapse, a biomarker-driven approach to therapy may be appropriate. Checkpoint inhibitors are currently being used to augment conventional chemotherapy as well as immune-directed therapies for the treatment of hematologic malignancies.

Future Directions and Challenges in Clinical Trial Design

Advancing treatment of pediatric mature B-NHL is challenging. Although children with newly diagnosed Burkitt lymphoma and DLBCL have an excellent prognosis, current therapies have a high incidence of grade III/IV infection, hematologic toxicities, and mucositis, and novel approaches to reduce both acute and long-term toxicities are needed. Although several recent studies have attempted to reduce cumulative doses of anthracyclines for lower-risk patients (ClinicalTrials.gov identifier: NCT03206671)²¹ and reduce the total number of chemotherapy cycles for patients with low-risk disease,¹⁷ deescalation or substitution of current medications with new ones has

been met with resistance due to a lack of effective salvage regimens.⁴¹ As a result, more attention has been focused on improving outcomes for patients with R/R disease.

Development and execution of clinical trials for children with R/R B-NHL is logistically challenging for several reasons. Selection of novel agents for R/R pediatric NHL is based on results from adult studies in ABC DLBCL (Table 3) and may not be applicable to pediatric NHL due to differences in driving mutations, signaling pathways, and mechanisms of immune evasion. Pediatric trials combining histologic subtypes will likely focus on agents that target shared surface antigens rather than intracellular signaling pathways that are specific to each NHL subtype. R/R pediatric NHL is often rapidly progressive, and novel agents should have a rapid onset of effect and be immediately available without requiring significant production time. Finally, it is estimated that there are <100 R/R B-NHL cases per year in the United States and Europe combined,⁹⁹ and testing even a single new agent in the relapsed setting will require an international collaboration to enroll a sufficient number of patients. However, through international collaboration between adult and pediatric oncology groups and specific focus on the adolescent and young adult population, we can begin to overcome some of the challenges related to testing new agents for the treatment of R/R NHL and expand our use of targeted and immunomodulating medications for this disease.

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