

Adolescent and young adult lymphoma: collaborative efforts toward optimizing care and improving outcomes

Justine M. Kahn,¹ Nmazuo W. Ozuah,² Kieron Dunleavy,³ Tara O. Henderson,⁴ Kara Kelly,⁵ and Ann LaCasce⁶

¹Division of Pediatric Hematology/Oncology/Stem Cell Transplantation, Columbia University Medical Center, New York, NY; ²Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA; ³Department of Hematology/Oncology, George Washington University, Washington, DC; ⁴Department of Pediatrics, Section of Hematology, Oncology and Stem Cell Transplantation, University of Chicago, Chicago, IL; ⁵Department of Pediatrics, Roswell Park Cancer Institute and Women and Children's Hospital, University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, NY; and ⁶Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Lymphomas are responsible for approximately 20% to 25% of annual cancer diagnoses in the adolescent and young adult (AYA) population. In 2006, the National Cancer Institute and the Lance Armstrong Foundation developed a joint Adolescent and Young Adult Oncology Progress Review Group (AYAO-PRG) to formally address the unique cancer burden of patients age 15 to 39 years. As part of their recommendations, the AYAO-PRG identified 5 imperatives for improving outcomes of AYAs with cancer. Broadly, the recommended areas of focus included research, awareness and education, investigational infrastructure, care delivery, and advocacy. In response to the challenges highlighted by the AYAO-PRG, the Lymphoma Research Foundation held the first AYA Lymphoma Research Foundation Symposium on 2 October 2015. At this symposium, clinicians and basic scientists from both pediatric and adult disciplines gave presentations describing the state of the science and proposed a collaborative research agenda built on the imperatives proposed by the AYAO-PRG. The following review presents an in-depth discussion of lymphoma management across pediatric and adult oncologic disciplines, focusing on Hodgkin lymphoma, mature B-cell lymphomas, and anaplastic large cell lymphoma.

Introduction

With ~70 000 new diagnoses annually, cancer in the adolescent and young adult (AYA) population (age 15-39 years) has been a national public health challenge for decades.¹⁻³ Despite therapeutic advances, improvements in the survival of AYAs trail behind those observed in children and older adults.⁴⁻⁶ Lymphomas are responsible for ~20% to 25% of annual cancer diagnoses in AYAs, and studies suggest that lymphoma-related mortality is higher in AYAs than it is in younger children and older adults.^{6,7} These disparities are particularly striking in the setting of overall excellent outcomes and continued diagnostic and therapeutic advances in both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

In 2006, the National Cancer Institute and the Lance Armstrong Foundation developed a joint AYA Oncology Progress Review Group (AYAO-PRG) to formally address the unique cancer burden of AYAs.^{8,9} As part of their recommendations, the AYAO-PRG identified 5 imperatives for improving outcomes of AYAs with cancer: research, awareness and education, investigational infrastructure, care delivery, and advocacy.

The imperatives highlighted by the AYAO-PRG provided the framework for the first Lymphoma Research Foundation AYA Symposium, held on 2 October 2015. As an initial step toward establishing an AYA-specific lymphoma research agenda, clinicians and basic scientists from pediatric and adult disciplines presented the state of the science in their respective fields. The following summary of the symposium

provides an in-depth comparison of pediatric and adult approaches to lymphoma management focusing on Hodgkin lymphoma (HL), mature B-cell lymphomas, and anaplastic large cell lymphoma (ALCL).

HL

Epidemiology

Approximately 10 000 new cases of HL are diagnosed in the United States annually. Nodular sclerosis is the most common histologic subtype of classical HL in Europe and North America. The incidence of HL in AYAs is ~37 per million in patients age 15 to 19 years and ~50 per million in patients age 20 to 29 years. Overall, HL accounts for 16% of cancers in patients between the ages of 15 and 24 years.

Staging and risk stratification

Both adults and children with HL are staged according to the Ann Arbor Staging system with Cotswold modification.¹⁰ In a large retrospective analysis of children and adolescents with intermediate-risk HL, 4 conditions were predictive of reduced event-free survival (EFS): stage IV disease, large mediastinal adenopathy, albumin <3.5, and fever.¹¹ These findings are currently undergoing prospective evaluation. In adults, the International Prognostic Score is used to identify patients with advanced-stage disease who might benefit from intensified therapy.¹² The European Organisation for Research and Treatment of Cancer and the German Hodgkin Study Group both categorize limited-stage HL (stages I and II) into favorable or unfavorable based on the presence or absence of bulky mediastinal disease, elevated erythrocyte sedimentation rate, and/or B-symptoms. In general, survival in HL varies by risk group, with 5-year survival reaching 95% in low-risk patients, and ranging from 70% to 80% in high-risk patients.¹³

Biological features of HL

The tumor microenvironment in HL is primarily composed of reactive, nonneoplastic cells, with malignant Hodgkin Reed-Sternberg cells comprising a small percentage of classical HL tissue samples.¹⁴ Immunohistochemistry and gene-expression profiling of pretreatment whole-tissue biopsies have identified prognostic biomarkers that, although not well validated, have been used to stratify risk in some patients.¹⁵ By using NanoString technology (digital expression profiling on formalin-fixed paraffin-embedded tissue), a 23-gene outcome predictor was generated by using samples from adults enrolled on the Eastern Cooperative Oncology Group E2496 trial.¹⁶ These predictors were not associated with outcome in a cohort of children with intermediate-risk disease, raising questions about whether pediatric and adult HL have distinct biologic characteristics.¹⁷ Currently, there are not enough data to determine whether such differences are clinically meaningful. In a large retrospective study of pediatric patients, Cleary et al¹⁸ reported that the most common histologic subtypes in childhood HL were mixed cellularity and lymphocyte predominant. In a post hoc analysis of AYA patients treated on 2 German Hodgkin Study Group protocols, the predominant histologic subtype was nodular sclerosing.¹⁹ Taken together, these studies suggest the possibility that the distribution of histologic subtypes in HL varies by age.

Pediatric therapeutic approach

Risk-adapted combined modality therapy has resulted in outstanding survival outcomes in pediatric HL. Today, cooperative

group trials focus primarily on maintaining survival while reducing long-term treatment sequelae.²⁰⁻²² Because of gonadal and cardiac toxicity, pediatric regimens have shifted away from traditional MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) or ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) over the past 2 decades (Table 1).²² Traditionally, the standard approach of the Deutsche Arbeitsgemeinschaft für Leukämieforschung and German Society of Pediatric Oncology and Hematology-Hodgkin's Disease (GPOH-HD) was to use OPPA-COPP (vincristine, procarbazine, prednisone, and doxorubicin-cyclophosphamide, vincristine, procarbazine, and prednisone). Because of its association with male infertility, procarbazine was replaced with etoposide and dacarbazine in the GPOH-HD-2002 trial.²³ Outcomes after OEPA-COPDAC (vincristine, etoposide, prednisone, and doxorubicin-cyclophosphamide, vincristine, prednisone, and dacarbazine) in boys were comparable to outcomes after OPPA-COPP in girls. Thus OEPA-COPDAC is now widely used in Europe, Latin America, and in parts of North America. In North America, ABVE-PC (doxorubicin, bleomycin, vincristine, and etoposide-prednisone and cyclophosphamide) is the most commonly used therapeutic regimen for low- and intermediate-risk patients. BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has proved to be an effective regimen in children and adolescents with high-risk HL (Table 1).²⁴

The omission of involved-field radiation therapy (IFRT) in children with HL was originally restricted to early-stage disease. Recent studies have investigated AVPC (doxorubicin, vincristine, prednisone, and cyclophosphamide), VAMP (vinblastine, doxorubicin, methotrexate, and prednisone), and OEPA with and without IFRT (Table 1). Early-response evaluation with risk-based therapy was successfully tested in a trial with intermediate-risk patients on the Children's Oncology Group (COG) AHOD0031 study. This protocol omitted radiation therapy (RT) in rapid early responders who achieved complete remission (CR) after 4 cycles of ABVE-PC (Table 1). Slow early responders received augmented chemotherapy with 2 cycles of DECA (dexamethasone, etoposide, cytarabine, and cisplatin) plus IFRT.²⁵ Analyses revealed that IFRT (vs no IFRT) significantly improved 4-year EFS (IFRT, 89.3%; no IFRT, 77.9%; $P = .019$) in children with bulky stage I or II disease who also had anemia at the time of diagnosis.²⁶

Adult therapeutic approach

Similar to the pediatric approach, risk-adapted therapy in adults with HL aims to minimize late effects and maximize cure. In adults, ABVD remains the backbone of therapy for most patients with HL. For early-stage nonbulky HL, the current approach is 2 to 4 cycles of ABVD plus 20 Gy IFRT.²⁷ For bulky disease, standard protocols include 4 to 6 cycles of chemotherapy plus 30 Gy IFRT. In advanced-stage HL, dose-intensive BEACOPP is an effective regimen that, compared with ABVD, has better progression-free survival (PFS) but worse overall survival (OS) (PFS, 81%; OS, 68%) due to excessive toxicity (Table 2).²⁸

One of the most consistent predictors of survival in both pediatric and adult HL is interim response to chemotherapy, as measured by fluorodeoxyglucose positron emission tomography (FDG-PET).²⁹ The Cancer and Leukemia Group B (CALGB) 50604 study (NCT01132807) demonstrated the prognostic significance of early response after 2 cycles of ABVD (PET2) in early-stage HL. Patients who were PET2-negative received 4 additional cycles of ABVD without RT and had a 3-year PFS of 92%. Those who were

Table 1. Pediatric HL trials

Reference	Trial acronym	Stage	Risk	Treatment	EFS		OS	
					Survival	%	Survival	%
94	CCG-P9426	I, IIA, IIIA		ABVE × 4 + IFRT	8-y	86	8-y	97
23	GPOH-HD-2002	I, IIA (treatment group 1)		OEPA × 2 (M); OPPA × 2 (F)	3-y	90	3-y	97.9
		IIIB, IIE, IIIA (treatment group 2)		OEPA × 2, COPDAC × 2 (M); OPPA × 2, COPP × 2 (F)	3-y	91.1 (M); 87.7 (F)		
95	CCG 5942	IIIE, IIIBE, IIIB, IV (treatment group 3)		OEPA × 2, COPDAC × 4 (M); OPPA × 2, COPP × 4 (F)				
		IA, IB, IIA	Low	COPP/ABV × 4 ± IFRT	10-y	83.5		92.5
96		IA, IB, IIA (with adverse features), IIIB, III	Intermediate	COPP/ABV × 6	10-y (IFRT)	91.2		97.1
		IV	High	COPP/ABV, CHOP, etoposide/cytarabine × 2	10-y (no IFRT)	82.9		95.9
97	COG-AHOD0431	IA, IIA (no bulk)		AVPC × 3 ± IFRT	4-y	79	4-y	99.6
98	Stanford, Dana-Farber, and St. Jude Consortium	IA, IIA (no bulk)		VAMP × 4 ± IFRT	2-y	90.8	2-y	100
22	P9425	IB, IIA/IIIA1 (with large mediastinal adenopathy) or IIIA2	Intermediate	ABVE-PC × 3	5-y	84	5-y	95
24	COG-59704	IIIB, IIIB, IV	High	RER; IFRT SER; ABVE-PC × 2 + IFRT				
		IIIB/IIIB (with bulk), IV	High	BEACOPP × 4; RER (F); COPP/ABV × 4; RER (M); ABVD × 2 + IFRT; SER; BEACOPP × 4 + IFRT	5-y	93	5-y	97
25	COG-AHOD0031	IB, IA/IIA (with bulk), IIIB, IIIA, IVA		ABVE-PC × 2 RER; ABVE × 2 ± IFRT; SER; ABVE-PC × 2 ± DECA × 2 + IFRT	4-y	All 85 RER 86.9 SER 77.4	4-y	All 97.8 RER 98.5 SER 95.3
24	AHOD0831	IIIB, IVB	Very high	ABVE-PC × 2 RER; ABVE-PC × 2 + RT (bulk only) SER; ABVE-PC × 2 + ifosfamide/vinorelbine + ABVE-PC × 2 + RT (bulk and PET2-positive sites)	4-y	80.2	4-y	95.9

ABV, doxorubicin, bleomycin, and vinblastine; CCG, Children's Oncology Group; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; COPDAC, cyclophosphamide, vincristine, prednisone, and dacarbazine; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; F, female; GPOH, German Society of Pediatric Oncology and Hematology; M, male; RER, rapid early responder; SER, slow early responder.

Table 2. Adult HL trials

Reference	Trial acronym	Stage	Risk	Treatment	PFS			OS		
					Study arm	Survival	%	Study arm	Survival	%
99	UK RAPID	IA, IIA (early)		ABVD × 3-4 ± IFRT	RT	3-y	94.6			
30	CALGB-50604	I and II (no bulk)	Low	ABVD × 4 (if PET2 negative) ABVD × 2 plus BEACOPP × 2 + IFRT (if PET2 positive)	No RT	3-y	90.8			
27	GHSG HD6	IA, IIA (no bulk)	Low	ABVD × 4-6 cycles	ABVD	12-y†	87	ABVD	12-y	94
28, 100	HD2000	Early (nonbulky)	Unfavorable	20 Gy subtotal nodal RT ± 2 cycles of ABVD ABVD × 4 + 30 Gy IFRT BEACOPP × 2, ABVD × 2, 30 Gy IFRT	RT ± ABVD	12-y†	92	RT ± ABVD	12-y	87
101	GHSG HD15	IIB (advanced, with bulky disease), III, IV		COPP-EBV-CAD escBEACOPP × 8		10-y	69			85
						10-y	75			84
						10-y	76			86
						5-y*	84.4			91.9
						5-y*	89.3			95.3
						5-y*	85.4			94.5
31	SWOG S0816	Advanced		Interim PET-directed after ABVD × 2 ABVD × 4 (PET negative)		2-y	64			
						2-y	82			
102	RATHL	Advanced	Unfavorable	escBEACOPP × 6 (PET positive) ABVD × 2		3-y	85.7			97.2
						3-y	84.4	AVD		97.6
						3-y	67.5	BEACOPP		87.7

AVD, doxorubicin, vinblastine, and dacarbazine; COPP-EBV-CAD, cyclophosphamide, vincristine, procarbazine, and prednisone-epirubicin, bleomycin, and vinblastine-cyclophosphamide, doxorubicin, and dexamethasone; escBEACOPP, escalated BEACOPP; GHSG, German Hodgkin Study Group; RATHL, Response Adapted Therapy in Advanced Hodgkin Lymphoma; SWOG, Southwest Oncology Group.

*Freedom from treatment failure.

†Freedom from disease progression.

Table 3. Pediatric NHL trials

Reference	Trial acronym	Stage	Treatment	EFS		OS	
				Survival	%	Survival	%
B-cell NHL (BL, DLBCL, PMBCL)							
103	FAB LMB96	I and II (localized disease)	COPAD × 2	4-y	98.3		
			COP, COPADM 1-2, CYM, M1	4-y	91.9		
			COP, COPADM 1-2, CYM, no M1	4-y	92.5		
104	FAB LMB96	III and IV (advanced CNS negative)	COP, COPADM 1-2, CYVE, M1-M4	4-y	90		
			COP, COPADM 1-2, mini-CYVE, M1	4-y	80		
105	FAB LMB96	All advanced, including CNS positive	COP, COPADM1+2, CYVE 1+2, M1, M2, M3, M4, CNS-positive patients received 13 IT injections plus an additional course of high-dose methotrexate between CYVE cycles	4-y	79	4-y	82
106	NHL-BFM 95	I, II (R1, resected)	A, B	3-y	94		
		I, II (R2, not resected), III (LDH <500 U/L)	VA, B, A, B	3-y	94		
		III (R3, LDH 500 to <1000 U/L)	V, AA, BB, CC, AA, BB	3-y	85		
		IV (LDH <1000 U/L, CNS negative)					
		III, IV (R4, LDH ≥1000 U/L and/or CNS positive)	V, AA, BB, CC, AA, BB, CC	3-y	81		
104	FAB LMB96	PMBCL		5-y	66	5-y	73
66	NHL-BFM 04	PMBCL	DA-EPOCH-R	2-y	92	2-y	92
T-cell NHL (ALCL)							
83,107	NHL-BFM 90	I, II-r I-, II-nr, III, IV	Prophase: dexamethasone, cyclophosphamide, ifosfamide, doxorubicin, high-dose methotrexate (5 g/m ²) vs methotrexate (0.5 g/m ²), cytarabine, etoposide ± vinblastine	2-y	75		

All medications are part of systemic therapy unless otherwise indicated. Treatment course A: dexamethasone, vincristine, ifosfamide, cytarabine, etoposide, methotrexate (1 g/m²), and intrathecal methotrexate (12 mg) + intrathecal cytarabine (30 mg) + intrathecal prednisolone (10 mg); intrathecal doses adjusted for age in patients <3 years. Treatment course B: dexamethasone, vincristine, cyclophosphamide, doxorubicin, methotrexate (1 g/m²), and intrathecal methotrexate (12 mg) + intrathecal cytarabine (30 mg) + intrathecal prednisolone (10 mg); intrathecal doses adjusted for age in patients <3 years. Treatment courses AA and BB are the same as A and B, respectively, with the following dose adjustments: methotrexate (5 g/m²) and intrathecal methotrexate (6 mg) + intrathecal cytarabine (15 mg) + intrathecal prednisolone (5 mg); intrathecal doses adjusted for age in patients <3 years. Treatment course CC: dexamethasone, vindesine, cytarabine, etoposide, intrathecal methotrexate (12 mg) + intrathecal cytarabine (30 mg) + intrathecal prednisolone (10 mg).

COP, cyclophosphamide, vincristine, and prednisone; COPAD, cyclophosphamide, vincristine, prednisone, and doxorubicin; COPADM, cyclophosphamide, vincristine, prednisone, doxorubicin, and high-dose methotrexate (8 g/m²); CYM, cyclophosphamide, high-dose cytarabine, and high-dose methotrexate; CYVE, cytarabine, high-dose cytarabine (3 g/m²), etoposide (200 mg/m²), and dexamethasone; LDH, lactate dehydrogenase; LMB, Lymphoma Malins de Burkitt; M1, COPADM plus intrathecal methotrexate, cytarabine, and hydrocortisone; M2, cytarabine and etoposide; M3, cyclophosphamide, vincristine, prednisone, and doxorubicin; M4, cytarabine and etoposide; mini-CYVE, cytarabine, high-dose cytarabine (2 g/m²), etoposide (100 mg/m²), and dexamethasone; NR, not resected; R, resected; R1, stage I + II resected; R2, stage I + II not resected, stage III: LDH <500 U/L; R3, stage III: LDH 500 to <1000 U/L, stage IV: BM⁺ and LDH <1000 U/L; R4, stage III + IV: LDH ≥1000 U/L and/or CNS⁺; V, dexamethasone, and cyclophosphamide.

PET2-positive had a 2-year PFS of 65% despite receiving augmented therapy with 2 cycles of escalated BEACOPP in addition to RT.³⁰ The prognostic importance of interim disease response also holds true for patients with advanced-stage disease.³¹

Traditional chemotherapeutic approaches consistently fall short in patients with primary refractory or relapsed HL. Brentuximab vedotin, an anti-CD30 antibody conjugate,³² and programmed cell death protein 1 (PD-1) inhibitors (nivolumab and pembrolizumab)³³ have demonstrated remarkable activity in relapsed or refractory HL and are currently under investigation as part of first-line therapy (NCT02181738). Roemer et al³⁴ recently reported that alterations in chromosome 9p24.1 and PD ligands (PD-L1 and PD-L2) are associated with reduced PFS, suggesting the potential benefit of checkpoint blockade in patients with these alterations.

Future perspectives

In both children and adults with HL, the goal of treatment is to maintain high cure rates while safely reducing overall treatment

burden. Interim disease assessment with risk-adapted therapy has allowed for the omission of RT in a substantial proportion of both adults and children with chemotherapy-sensitive HL. Although both pediatric and medical oncologists seek to improve the therapeutic index in HL, consortium groups largely continue to work in parallel rather than in tandem toward this goal. Different approaches to risk stratification and response criteria render comparisons across consortia and across age groups challenging. Collaborative studies investigating age-related differences in prognostic biomarkers, biology of disease control, host immune response, and susceptibility to long-term toxicities are overdue.

Mature B-cell NHL

Epidemiology

Together, diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL) comprise about 95% of mature B-cell lymphoma diagnoses annually. DLBCL makes up ~30% to 35% of NHL in patients older than age 15 years and ~18% in younger children.³⁵ BL makes up

~40% of NHL in children age 1 to 14 years and ~20% of NHL in patients age 15 to 19 years. In patients older than 20 years, ~5% of NHL is BL. The incidence of NHL increases with age, with 15 cases per million in AYAs age 15 to 19 years, 22 cases per million for those age 20 to 24 years, and 40 cases per million for those age 25 to 29 years.³⁶

Staging and risk stratification

In adults, the Ann Arbor Staging System is used to describe disease stage at diagnosis and the International Prognostic Index (IPI) further characterizes risk. The IPI remains the strongest clinical predictor of outcome in adults. In children, the St. Jude/Murphy classification system has been updated to the International Pediatric NHL Staging System, which incorporates new histologic entities.³⁷

Biological features of BL and DLBCL

Age-related biological differences in NHL subtypes have been well described in children and adults; however, they have not been fully characterized in AYAs. BL is divided into 3 clinico-epidemiologic subtypes: endemic, sporadic, and immunodeficiency-associated. The hallmark of BL in both adults and children is translocation of MYC (8q24) with an immunoglobulin locus on chromosome 14 (85% of cases), 2, or 8.³⁸ In DLBCL, the frequency of MYC rearrangement depends on the method of detection. Frequency ranges from 5% to 10% using fluorescence in situ hybridization but is near 35% using immunohistochemistry.³⁹ In a small study by Gualco et al,⁴⁰ rearrangements were histologically identified in 37% of pediatric DLBCL patients (n = 6). Recently, mutations in ID3, TCF3, and cyclin D3 were shown to cooperate with MYC in BL. These mutations present possible therapeutic targets, particularly for patients who cannot tolerate conventional chemotherapy.⁴¹

DLBCL is biologically and clinicopathologically heterogeneous across age groups. The 2 main molecular subtypes of DLBCL are germinal center B-cell (GCB) and activated B-cell (ABC) DLBCL. GCB lymphoma is the predominant subtype in children and is associated with excellent outcomes.⁴² It is characterized by co-expression of CD10 and BCL6 with variable expression of BCL2. Approximately 30% of adults with GCB DLBCL have translocations involving BCL2, which is associated with favorable outcomes.⁴³ The ABC subtype of DLBCL is more common in older adults and is associated with inferior survival.⁴⁴ Chronic activation of B-cell receptor and MYD88 signalling in ABC DLBCL is characteristic, and leads to constitutive activation of the nuclear factor κ B pathway.⁴⁵ Primary mediastinal B-cell lymphoma (PMBCL) makes up ~10% of DLBCL cases in children and older adults and up to 50% of cases in AYAs.⁴⁶ It affects younger adults and has favorable survival. In contrast to other DLBCL subtypes, PMBCL lacks surface immunoglobulin expression, and BCL2, BCL6, and MYC rearrangements are rare.^{46,47}

In children, DLBCL is a clinically aggressive disease characterized by MYC translocation (37%), low BCL2 expression, and high proliferation rates. Translocations involving BCL2 are infrequent, and up to 84% of cases overexpress MYC.⁴⁸ A large proportion of adults with DLBCL have high protein expression of both MYC and BCL2, an entity termed “double-expresser” DLBCL. Double-expresser DLBCL is associated with poor outcomes after standard therapy.⁴⁹ The presence of both MYC and BCL2 or BCL6 rearrangements constitutes another distinct subgroup of aggressive double-hit lymphomas.⁵⁰ Recently recategorized in the updated World Health

Organization Classification of Lymphoid Malignancies as “high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,” this form of DLBCL is a highly proliferative disease with an aggressive course and poor outcome.⁴⁶ Double-expresser and double-hit lymphomas seem to be uncommon in AYAs.

Pediatric therapeutic approach

In the United States, the current treatment approaches for pediatric BL and DLBCL are based on modifications of 2 successive French Society of Pediatric Oncology, French-American-British (FAB) Lymphomes Malins B (LMB), and Berlin-Frankfurt-Münster (BFM) cooperative group trials.⁵¹ The treatment backbones are largely similar in their emphasis on the importance of central nervous system (CNS)-directed therapy with high-dose methotrexate, high-dose cytarabine, and intrathecal methotrexate in patients with advanced disease or CNS involvement. The BFM therapy includes ifosfamide with lower doses of doxorubicin, cyclophosphamide, and etoposide. Despite different risk group stratification and varied therapeutic approaches, outcomes across protocols are comparable (long-term survival near 80%) (Table 3).^{51,52}

In 2010, Meinhardt and colleagues⁵³ demonstrated the activity of first-line rituximab followed by standard chemotherapy for the treatment of mature B-cell NHL in children, and the COG piloted the addition of rituximab to an FAB/LMB96 chemotherapy backbone (ANHL01P1).⁵⁴ This was further evaluated in an Intergroup trial for children and adolescents with B-cell NHL or B-cell acute lymphoblastic leukemia, which randomly assigned patients with high-risk NHL to receive either rituximab plus standard of care or standard of care only. Results suggested superiority of the rituximab arm.⁵⁵

Although relapse in pediatric BL and DLBCL is infrequent, survival after disease recurrence is poor. There is no standard therapeutic approach for relapsed B-cell NHL in pediatrics although salvage chemotherapy with autologous hematopoietic cell transplantation is often used. Novel therapies, including chimeric antigen-receptor T-cell therapy, are currently being investigated.⁵⁶

Adult therapeutic approach

Estimated 5-year survival in adults with DLBCL varies by IPI score. In adults with an IPI score of 0, OS is reported to be near 94% vs 50% in those with an IPI score ≥ 3 .⁵⁷ Early studies report survival ranging from 40% in patients over age 40 years up to 89% in all ages after the addition of rituximab.⁵⁸ For the past 4 decades, CHOP-based therapy has been the de facto standard for treatment of adult DLBCL. The most notable improvement in outcomes came with the addition of rituximab to the CHOP backbone (R-CHOP).⁵⁹ Except for the French regimen R-ACVBP (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), attempts to intensify R-CHOP have been unsuccessful. Récher et al⁶⁰ reported superior efficacy of R-ACVBP vs R-CHOP in younger DLBCL patients who had low-intermediate IPI scores. Compared with R-CHOP, however, R-ACVBP was associated with more treatment-related toxicities; thus, at present, R-CHOP remains the standard approach for adults worldwide.⁶¹

Optimal therapy for PMBCL is a subject of debate. The MabThera International Trial (MInT) demonstrated comparable EFS in patients with low-risk DLBCL and PMBCL who received R-CHOP. In the study, the majority of patients with PMBCL required RT.⁶²

Table 4. Adult NHL trials

Reference	Trial acronym	Phase	Risk	Regimen	EFS		PFS		OS	
					Survival	%	Survival	%	Survival	%
BL										
108			Low	Modified CODOX-M/IVAC × 3 + intrathecal chemotherapy	2-y	83				81
			High	Modified CODOX-M/IVAC × 4	2-y	65				73
67				CODOX-M/IVAC ± rituximab	3-y	74* [†] ; 61 [†]				
71			Low	DA-EPOCH-R		95				100
69		II	Low	Hyper-CVAD with high-dose methotrexate, high-dose cytarabine + rituximab	3-y	80				88-89
									4-y	75 [‡] ; 76 [§]
DLBCL										
109		III		R-CHOP-14 vs R-CHOP-21			2-y	75 vs 75	2-y	83 vs 81
60		III		R-ACVBP vs R-CHOP			3-y	87 vs 73	3-y	92 vs 84
110	CALGB-50303			R-CHOP vs DA-EPOCH-R	3-y	81 vs 79			3-y	85 vs 85
PMBCL										
62, 111	MInT			R-CHOP	3-y	78			3-y	89
64				DA-EPOCH-R		93				100

CODOX-M/IVAC, cyclophosphamide, vincristine, and doxorubicin-methotrexate/ifosfamide, etoposide, and cytarabine; MInT, MabThera International Trial.

*Rituximab.

[†]No rituximab.

[‡]Age >60 y.

[§]Age <60 y.

In patients who had PMBCL with high-risk features, Soumerai et al⁶³ reported an unacceptably high rate of primary refractory disease after R-CHOP. For DLBCL, early studies suggested increased efficacy with the infusional regimen DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), which was subsequently trialed in PMBCL.^{63,64} A phase 2 trial of DA-EPOCH plus rituximab (DA-EPOCH-R) for PMBCL obviated the need for RT and demonstrated 5-year EFS of 93% and OS of 97%.⁶⁵ Woessmann et al⁶⁶ reported similar outcomes with this regimen in the pediatric NHL-BFM 04 trial. The ongoing Intergroup Trial ANHL1131 (NCT01595048) is investigating both the efficacy and long-term cardiac risks of DA-EPOCH-R in children and adolescents with PMBCL.

Several chemotherapy regimens are used to treat adult BL. The most common therapeutic approach in the United States is CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, and methotrexate/ifosfamide, cytarabine, and etoposide) plus rituximab.^{67,68} Though this regimen is associated with favorable outcomes, survival in pediatric BL remains superior. To reduce the incidence of treatment-related toxicities in patients with comorbidities, Corazzelli and colleagues⁶⁹ modified the CODOX-M/IVAC regimen by adding rituximab and liposome-encapsulated cytarabine to increase antitumor activity while de-intensifying CNS prophylaxis. Despite high actual dose intensity, 93% CR rates, and fair tolerability, the modified regimen was associated with 49% PFS in patients older than age 60 years vs 93% PFS for patients younger than age 60 years (Table 4). Reduced CNS-directed therapy did not increase CNS failure rate (3% to 4%). Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with methotrexate and high-dose cytarabine

is effective for BL, although it, too, is associated with significant treatment-related toxicities.⁷⁰ Dunleavy et al⁷¹ reported excellent outcomes from a single-center study of low-risk BL patients treated with reduced-intensity DA-EPOCH-R (Table 4). For low-risk patients, the current standard is CODOX-M/IVAC.⁷² At present, a multicenter study of DA-EPOCH-R is ongoing in the United States (NCT00001337), and a randomized study of DA-EPOCH-R vs CODOX-M/IVAC is ongoing in Europe.

Future perspectives

To date, no prospective studies have investigated whether AYAs would benefit from pediatric- or adult-like therapy for mature B-cell NHL. Future studies will likely focus on treatment de-intensification and on incorporation of targeted therapies whenever possible. The clinical significance of double-hit disease, MYC overexpression, and MYC translocation in AYAs remains unknown. Similarly, the molecular profile of mature B-cell NHL in this population has been understudied. Identification of genetic markers and establishment of age-associated prognostic factors are needed.

Mature T-cell NHL

Epidemiology

ALCL is a clinically aggressive T-cell NHL with bimodal age distribution. It accounts for ~15% of NHL in children and ~2% of NHL in adults.⁷³ Systemic ALCL is subdivided into 2 groups on the basis of the presence or absence of an abnormal form of the anaplastic lymphoma kinase (ALK) protein⁷⁴ on the lymphoma cell surface. In North America and Europe, ALK⁺ ALCL accounts for ~7% of NHL and ALK⁻ ALCL accounts for ~5%.

Table 5. Summary table of pediatric and adult therapeutic approaches in HL, BL, DLBCL, PMBCL, and ALCL

	Pediatric approach	Adult approach
HL		
Stage I/II (non-bulky)	ABVE × 2-4 ± RT; VAMP × 4 ± RT; OEPA × 2 ± RT	ABVD × 4-6 with risk-adapted use of RT
Stage I/II (bulky)	ABVE-PC × 4 ± RT; OEPA × 2, plus COPDAC × 2 ± RT	ABVD × 4-6 plus RT in most cases
Stage III/IV	ABVE-PC × 4-5 plus RT in most cases; OEPA × 2, plus COPDAC × 4 ± RT	ABVD × 6
BL		
Low risk	COPAD × 2	R-CODOX-M × 3, DA-EPOCH-R, or rituximab, or R-hyper-CVAD
High risk	FAB LMB96 protocol + rituximab*	R-CODOX-M/IVAC or R-hyper-CVAD
DLBCL	Burkitt-like therapy	R-CHOP × 6
PMBCL	DA-EPOCH-R × 6	DA-EPOCH-R × 6
ALCL	ALCL 99 protocol†	CHOEP × 6

CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; R-CODOX-M, rituximab plus cyclophosphamide, vincristine, and doxorubicin-methotrexate; R-CODOX-M/IVAC, rituximab plus cyclophosphamide, vincristine, and doxorubicin-methotrexate/ifosfamide, etoposide, and cytarabine; R-hyper-CVAD, rituximab plus hyper-CVAD.

*R-CHOP (rituximab plus cyclophosphamide, vincristine, and prednisone) prophase → 2 cycles of induction with R-COPADM × 2 → 2 cycles of maintenance with rituximab plus CYM plus intrathecal chemotherapy.

†Cyclophosphamide-dexamethasone prophase followed by 6 alternating cycles of course A (dexamethasone, high-dose methotrexate, ifosfamide, cytarabine, and etoposide) and course B (dexamethasone, high-dose methotrexate, cyclophosphamide, and doxorubicin) chemotherapy.

Staging and risk stratification

Clinical features associated with poor outcomes in ALCL include elevated lactate dehydrogenase and skin, mediastinal, or visceral organ involvement. The ALK⁺ subtype predominates in children, and although young patients often present with advanced disease, 5-year OS in this population exceeds 70%.^{75,76}

Biological features of ALCL

The first pathologic descriptions of ALCL were based on identification of large, multinucleated anaplastic (hallmark) cells. These cells are characterized by cytologic atypia and strong CD30 expression.⁷⁷ The ALK translocation t(2;5)(p23;q25) results in the fusion of nucleophosmin and ALK genes leading to activation of a tyrosine kinase domain with unregulated cell proliferation.⁷⁸ The lymphohistiocytic variant of ALK⁺ ALCL (~10%) is characterized by large numbers of benign histiocytes with fewer large neoplastic cells. The small cell variant (~5% to 10%) is characterized by predominance of small neoplastic cells and rare hallmark cells and is associated with worse outcomes in pediatrics.^{79,80} ALK positivity, an independent predictor of survival in ALCL, decreases in frequency with increasing age. In a study of 70 adults with ALCL, median age of ALK⁺ patients was 30 years, which was significantly younger than that of patients with ALK⁻ ALCL. At present, relative incidence of ALK⁺ vs ALK⁻ disease in the AYA population are not known.

Pediatric therapeutic approach

Therapy for pediatric ALCL has evolved over the past 2 decades, with different consortia taking different approaches. The LSA₂-L₂ (cyclophosphamide, vincristine, methotrexate, daunorubicin, prednisone, cytarabine, thioguanine, asparaginase, hydroxyurea, and carmustine) regimen, developed at Memorial Sloan Kettering Cancer Center, is associated with 10-year survival of 65%.⁸¹ The majority of ALCL treatment regimens are based on the mature B-cell NHL literature. Seidemann et al⁸² reported results of the NHL-BFM 90 trial,

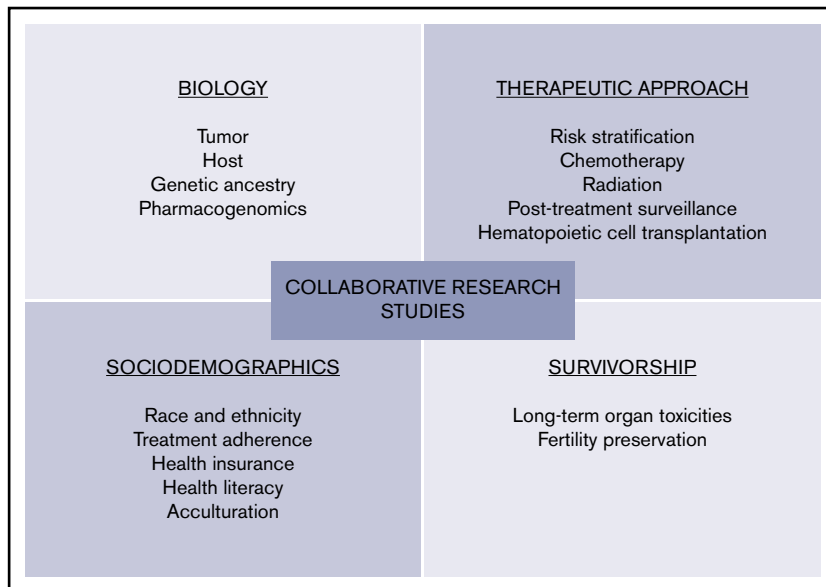
which included a prephase of vincristine, cyclophosphamide, and dexamethasone followed by additional chemotherapy based on lymphoma stage (5-year EFS, 76%) (Table 3). In 2010, Le Deley and colleagues⁸³ reported results of the ALCL99-vinblastine study, which investigated adding vinblastine maintenance therapy to the NHL-BFM 90 backbone in children with high-risk ALCL (Table 3). Per the BFM 90 protocol, patients received a prophase of low-dose cyclophosphamide and corticosteroid followed by 6 courses of moderate-dose or high-dose methotrexate, dexamethasone, ifosfamide, cyclophosphamide, etoposide, cytarabine, doxorubicin, and intrathecal chemotherapy over 4 months. High-risk patients were randomly assigned to receive additional vinblastine during and after therapy. Two-year EFS was 74.1%, and 2-year OS was 92.5% (Table 3).⁸³

Brentuximab vedotin is associated with excellent outcomes in adult ALCL. Crizotinib, an orally available dual ALK/MET inhibitor, has also shown high response rates in phase 1 studies of adults with ALCL.⁸⁴ The ongoing COG-ANHL12P1 study in children and adolescents with ALCL is investigating the efficacy of first-line crizotinib vs brentuximab vedotin, each in combination with multi-agent chemotherapy (NCT01979536). Despite there being no standard therapeutic approach for relapsed pediatric ALCL, survival after recurrence is favorable. The French Society for Pediatric Oncology reported excellent outcomes after single-agent vinblastine in children with relapsed ALCL.⁸⁵

Adult therapeutic approach

First-line therapy for adult ALCL is based largely on the treatment of DLBCL.⁸⁶ The current recommendation for ALK⁺ ALCL in first remission is CHOP-like chemotherapy without transplantation. For relapsed disease, salvage chemotherapy with platinum-based regimens and stem cell transplantation is recommended. Several phase 2 studies have demonstrated efficacy of brentuximab vedotin in adults with ALCL. Pro et al⁸⁷ reported an overall response rate of 86% in adults after receiving brentuximab vedotin for relapsed or

Figure 1. Key areas to advance research and improve outcomes in AYA lymphoma.



refractory ALCL (58% CR), which resulted in approval by the US Food and Drug Administration for this indication. Currently, brentuximab vedotin is used primarily as a bridge to transplantation after relapse; however, its utility as part of up-front therapy in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) is currently under investigation (NCT01777152).

Future directions

Despite excitement about the potential for targeted therapies in ALCL, it is still too soon to omit standard chemotherapy. Standard treatment of AYAs with ALCL generally includes CHOP-like therapy with or without early autologous stem cell transplantation. The benefit of more intensive pediatric-like therapy in AYAs has not been prospectively evaluated. As suggested in the above discussions, expanding our understanding of disease biology will drive the development of novel targeted therapies, which can then be brought to the clinic in the context of consortium-based trials.

Summary, challenges, and strategies for future research

The information gap in AYA lymphoma

This review highlights that even for similar lymphoma subtypes, treatment approaches by pediatric and medical oncologists reliably differ (Table 5).^{37,88} Largely due to low rates of clinical trial enrollment in AYAs, details about cancer biology, care delivery, and therapeutic efficacy in this population have been systematically understudied.^{3,89} As a result, for 15- to 39-year-olds, lymphoma treatment is not necessarily dictated by empiric evidence specific to the age group, but rather by community referral patterns, individual physician preference, and treatment location.⁹⁰

Clinical trials data and consensus recommendations establish standards of care in both pediatric and adult oncology. To develop consensus recommendations for AYAs with lymphoma, critical areas in need of further study include, but are not limited to, biology and molecular prognostic indicators, novel therapeutics, acute and long-term toxicities of therapy, and psychosocial outcomes

(ie, financial burden of treatment, access-to-care, and therapy adherence) (Figure 1).⁹¹

Combining resources and leveraging existing data

In children and older adults, analysis of prospectively collected clinical trial data enables frequent, evidence-based modifications of existing treatment paradigms. In patients treated in the community oncology setting, health outcomes researchers leverage tumor registries and insurance claims data to characterize care delivery and its impact on survival in large population-based cohorts. In AYA lymphoma, a combination of data from these 2 sources is a logical next step as we begin to address outstanding clinical questions. Synthesis of prospectively collected data from AYAs enrolled on pediatric and adult consortium trials will provide details about biology, toxicities, and survival in the cooperative group setting.⁹² Analysis of data from tumor registries and insurance files can provide insight into how community-level predictors (ie, access to care, socioeconomic status, treatment location) influence outcomes of AYAs treated for lymphoma in the community.⁹³

In conclusion, lymphoma in the AYA population is a prime area for collaborative research between pediatric and medical oncologists, as well as between providers in the community and in the consortia. Community providers, often at the front line of diagnosis and management, are uniquely poised to establish a national tumor bank for AYA lymphoma. With broader understanding of prognostic molecular biomarkers in this patient population, we can plan innovative clinical trials whose inclusion criteria are based not only on age, but also on lymphoma subtype and disease biology. Developing well-designed therapeutic trials that span pediatric and adult groups, and that incorporate relevant biologic and health services correlates, is critical to advancing research and improving outcomes in the AYA lymphoma population.

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Authorship

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Correspondence: Justine M. Kahn, Division of Pediatric Hematology/Oncology/Stem Cell Transplantation, Columbia University Medical Center, 161 Fort Washington Ave, IP7, New York, NY 10032; e-mail: jk2034@cumc.columbia.edu.

Appendix

Lymphoma Research Foundation AYA Symposium attendees: Sarah Alexander (The Hospital for Sick Children, University of Toronto); Burt Appel (Hackensack University Medical Center); Saro Armenian (City of Hope); Kristie Blum (The Ohio State University Comprehensive Cancer Center); Catherine Bollard (Children's National Medical Center); Joshua Brody (Icahn School

of Medicine at Mount Sinai); Ryan Cassaday (Fred Hutchinson Cancer Research Center); Jonathan Cohen (Winship Cancer Institute of Emory University); Peter D. Cole (Albert Einstein College of Medicine/The Children's Hospital at Montefiore); Michael Douvas (University of Virginia School of Medicine); Kieron Dunleavy (George Washington University); Andy Evens (Tufts University School of Medicine); Adolfo Ferrando (Columbia University Medical Center); Chris Flowers (Winship Cancer Institute of Emory University); Debra Friedman (Vanderbilt University School of Medicine); Jill Ginsberg (The Children's Hospital of Philadelphia); Leo Gordon (Feinberg School of Medicine at Northwestern University); Tom Gross (National Cancer Institute); Tara O. Henderson (The University of Chicago); David Hodgson (University of Toronto); Justine M. Kahn (Columbia University Medical Center); Frank Keller (Emory University School of Medicine); Kara Kelly (Roswell Park Cancer Institute); Anita Kumar (Memorial Sloan Kettering Cancer Center); Ann LaCasce (Dana-Farber Cancer Institute); Catherine Lai (National Institutes of Health); John Leonard (New York-Presbyterian Hospital Weill Cornell Medical Center); Megan Lim (University of Pennsylvania); Eric Lowe (Children's Hospital of the King's Daughters); Lindsay Morton (National Cancer Institute); Nmazuo Ozuah (Dana-Farber Cancer Institute); Barbara Pro (Northwestern University); Allison Rosenthal (Mayo Clinic, Scottsdale); Christian Steidl (BC Cancer Agency Research Centre); Deborah Stephens (Huntsman Cancer Institute at the University of Utah); Maria-Luisa Sulis (Columbia University Medical Center); and Michael Werner (Executive Vice President, Lymphoma Research Foundation Board of Directors).

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