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Outcomes in Intermediate-Risk Pediatric Lymphocyte-Predominant Hodgkin Lymphoma: A Report from the Children's Oncology Group

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Abstract

Purpose—Optimal management of patients with intermediate-risk lymphocyte-predominant Hodgkin lymphoma (LPHL) is unclear due to their small numbers in most clinical trials. Children's Oncology Group AHOD0031, a randomized Phase III trial of pediatric patients with intermediate-risk Hodgkin lymphoma (HL), included patients with LPHL. We report the outcomes of these patients and present directions for future therapeutic strategies.

Procedure—Patients received two cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC) followed by response evaluation. Slow early responders were randomized to two additional ABVE-PC cycles +/- two dexamethasone, etoposide, cisplatin and cytarabine (DECA) cycles and all received involved field radiotherapy (IFRT). Rapid early responders (RERs) received two additional ABVE-PC cycles. RERs with complete response (CR) were randomized to IFRT or no further therapy. RERs without CR received IFRT.

Results—Ninety-six (5.6%) of 1,711 patients on AHOD0031 had LPHL. Patients with LPHL were more likely to achieve RER (93.6% versus 81.0%; $p=0.002$) and CR (74.2% versus 49.3%; $p=0.000005$) following chemotherapy compared to patients with classical HL (cHL). Five-year event-free survival (EFS) was superior in patients with LPHL (92.2%) versus cHL (83.5%)

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($p=0.04$), without difference in overall survival (OS). Among RERs with CR following chemotherapy ($n=33$), there was no difference in EFS or OS between those randomized to receive or not receive IFRT.

Conclusion—Children and adolescents with intermediate-risk LPHL represent ideal candidates for response-adapted therapy based on their favorable outcomes. The majority of patients treated with the ABVE-PC backbone achieve RER with CR status and can be treated successfully without IFRT.

Keywords

Lymphocyte-predominant Hodgkin Lymphoma; clinical trial; pediatrics

Introduction

Lymphocyte-predominant Hodgkin lymphoma (LPHL) is a variant of Hodgkin lymphoma (HL) with distinct histopathology and clinical presentation. Although LPHL accounts for only 5–8% of all HL in adolescents between 15 and 20 years of age, it is more common in pre-pubertal children, where it represents 10–20% of HL in that age group^{1–4}. Typically, LPHL presents with localized peripheral lymphadenopathy with only rare involvement of the mediastinum or extra-nodal sites^{5,6}. Pediatric patients with early stage disease without bulk or B symptoms often have excellent outcomes with surgical resection alone or minimal chemotherapy^{7,8}. However, for pediatric patients with LPHL with unfavorable features such as higher stage disease, B symptoms, or bulk, management is less clear due to their small number in most intermediate or high-risk HL clinical trials.

Risk-adapted HL therapy using chemotherapy response to guide treatment helps balance efficacy with toxicity^{9–12}. LPHL is the ideal group in which to leverage this paradigm. Children's Oncology Group (COG) AHOD0031 demonstrated that early response assessment in pediatric intermediate-risk HL permits reduction or augmentation in therapy with maintenance of excellent event-free (EFS) and overall survival (OS)¹³. Patients with LPHL who met the same staging and eligibility criteria as patients with classical HL (cHL) were considered intermediate-risk and included in the study. Here we report their outcomes and present directions for future therapeutic strategies.

Patients and Methods

COG study AHOD0031, a randomized, response-based, centrally reviewed protocol approved by the National Cancer Institute and participating institutional review boards, enrolled patients from September 2002 through July 2009¹³.

Patients

Eligible patients included those younger than age 22 years with newly diagnosed, biopsy-proven cHL or LPHL, Ann Arbor¹⁴ stages IB, IAE, IIB, IIAE, IIIA, IVA with or without bulk disease, and IA or IIA with bulk disease. Histology was centrally reviewed for eligibility. Bulk disease included a mediastinal mass greater than one third of the thoracic

diameter on an upright anterior-posterior chest radiograph or extramediastinal nodal aggregate 6 cm in the longest transverse diameter on axial CT.

Treatment

Patients initially received two cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC), followed by a response evaluation of rapid early responder (RER) versus slow early responder (SER) status. Cycles were 21 days in duration. All SER patients were randomized to an additional two cycles of ABVE-PC with or without two cycles of dexamethasone, etoposide, cisplatin and cytarabine (DECA), followed by 21 Gy involved field radiotherapy (IFRT) in 14 fractions of 1.5 Gy per day after completion of chemotherapy. RER patients received two additional cycles of ABVE-PC. Patients who were RERs with complete response (CR) following the total 4 cycles of chemotherapy were randomized to IFRT or no further therapy. RERs with less than CR were non-randomly assigned to IFRT. IFRT was limited to areas of disease defined as involved at presentation.

Response Criteria

Early response status was determined by CT scan, and CR status was determined by CT and gallium or [18F]fluorodeoxyglucose–positron emission tomography (FDG-PET). RER was defined by 60% reduction by CT in the product of perpendicular diameters (PPDs) for all target lesions or return to non-pathologic size after two ABVE-PC cycles. Patients were considered to have a SER if RER was not achieved. CR was defined by 80% reduction by CT in the PPDs for all target lesions or return to non-pathologically enlarged status after all chemotherapy, plus no residual extramediastinal nodal mass >2.0 cm, no residual disease in non-measurable sites, and a negative gallium or FDG-PET scan. Progressive disease (PD) was considered as 50% increase in the PPD of any nodal mass or organ lesions; a new lesion(s); or progression of a nonmeasurable disease site. All response assessments were centrally reviewed by the Quality Assurance Review Center (QARC).

Statistical Analysis

Statistical inference (Chi-square test on categorical variables and ANOVA test on continuous variables) was performed to compare the following demographics and clinical conditions between LPHL and cHL populations: age, gender, race, stage, B symptoms and bulk disease (Table 1). The EFS and OS were calculated with Kaplan-Meier survival analysis and the curves were compared between LPHL and non-LPHL groups with k-sample tests. For the LPHL patients, the EFS and OS curves were also compared across stage, between RER and SER, between IFRT and non-IFRT, between bulk and non-bulk, and between with B symptoms and without B symptoms. The EFS/OS curves were plotted for different levels of each factor (stage, RER/SER, bulk or B symptoms) and k-sample test was performed to obtain the p-value.

Results

Patients and Staging

Ninety-six of the 1711 eligible patients on AHOD0031 had LPHL (5.6%), with the remainder cHL (Table 1). Compared to patients with cHL, patients with LPHL were more likely to be younger (13.3 ± 3.6 vs 14.6 ± 3.3 , $p=0.0001$) or male ($p<0.0001$), and less likely to have B symptoms ($p=0.0012$), bulk ($p<0.0001$), or stage IV disease ($p<0.0001$).

Therapy Response

Of the 94 patients with LPHL with available data on early response (two patients were removed because their RER/SER status was unknown) there were 88 RERs and 6 SERs (Fig. 1). The proportion of patients who were RERs was higher in LPHL compared with cHL (93.6% vs. 81.0%; $p=0.002$). An additional 5 RERs were excluded from further analysis as they were taken off protocol therapy after three cycles and post-therapy response was not known. Of the remaining 83 RERs, 61 had CR and were randomly assigned to receive or not receive IFRT; 22 had less than CR and were non-randomly assigned to IFRT. Patients with LPHL were more likely to achieve a CR following all chemotherapy compared to patients with cHL (74.2% vs. 49.3%; $p=0.000005$). The 6 SERs were randomly assigned to receive or not receive DECA and all received IFRT.

Survival

Among patients with LPHL, 5-year EFS was 92.2% (95% CI, 86.0% to 98.5%) which was superior to EFS of 83.5% (95% CI, 81.3% to 85.7%) for patients with cHL ($p=0.04$) (Fig. 2A). The 5-year OS for the entire AHOD0031 cohort was excellent and did not differ for those with LPHL versus cHL; LPHL 98.9% (95% CI, 95.9% to 100%), cHL 97.3% (95% CI, 96.3% to 98.2%) ($p=0.20$) (Fig. 2B). In LPHL, neither EFS or OS were impacted by stage of disease, bulk status or B symptoms (Table 2).

Although early response was found to be an important prognostic factor for the AHOD0031 study cohort as a whole¹³, it was not found to significantly impact outcomes for patients with LPHL in this study. Five-year EFS and OS was 92.7% (95% CI, 6.5% to 98.9%) and 98.8% (95% CI, 96.2% to 100%) respectively for LPHL RERs compared to 83.3% (95% CI, 36.1% to 100%) and 100% (95% CI, 100%) for LPHL SERs ($p=0.325$ and $p=0.788$) (Fig. 3).

Similar to the findings from the analysis of all patients treated on AHOD0031, IFRT following 4 cycles of ABVE-PC did not improve outcome for the 61 patients with LPHL who were RER with CR and randomized to receive either IFRT ($n=28$) or no IFRT ($n=33$). Five-year EFS was 84.8% (95% CI, 69.5% to 100%) and OS was 96.3% (95% CI, 88.2% to 100%) for patients randomized to receive IFRT versus 93.4% (95% CI, 84.3% to 100%) and 100% (95% CI, 100%) for those randomized to no IFRT ($p=0.287$ and $p=0.284$) (Fig. 4). Outcomes did not apparently differ for the SER patients randomized to receive DECA ($n=5$) or standard therapy ($n=1$).

Events

There were eight relapses and one non-disease related death amongst patients with LPHL. The median time to relapse for patients with LPHL (n=8) was 1082.5 days (range 83-3280 days) compared to 381 days (range 54-4265) for patients with cHL (n=244) ($p<0.0001$). The one death was a trauma-related death which occurred after therapy completion as a first event in a patient who achieved a RER with CR and was randomized to receive IFRT. There were no subsequent malignant neoplasms (SMNs) in the patients with LPHL. Median follow-up for this group is 7.2 years (range 1.1–13.5 years).

Discussion

Patients with LPHL treated on regimens designed for cHL generally experience better outcomes than patients with cHL¹⁵, but may receive more treatment than is needed to achieve cure. Children and young adults with HL who are long-term survivors are at increased risk of late complications associated with chemotherapy and RT including SMNs, infertility, and cardiovascular disease^{16,17}. The ABVE-PC chemotherapy used in AHOD0031 was designed for dose-dense drug delivery to improve treatment efficacy while the response-based treatment design reduces total cumulative chemotherapy doses to reduce risk of long-term sequelae⁹. Although the included patients with LPHL met criteria for categorization as intermediate-risk, in general, as has been reported elsewhere⁵, they had fewer risk factors including lower rates of B symptoms and bulk disease than the patients with cHL, and may benefit from different risk stratification than patients with cHL. Notably, the patients with LPHL had a much higher percentage of RERs compared to patients with cHL, suggesting that although they were treated on a response-based protocol, many of the patients with LPHL may have received more intensive chemotherapy than necessary since it was a protocol designed for cHL. In addition, the intensive treatment explains why EFS and OS were not affected by stage, bulk disease, or presence of B symptoms in patients with LPHL.

All patients with intermediate-risk HL received response-adapted therapy and we identified a subgroup, RERs with CR, whose outcome was not significantly compromised by the exclusion of IFRT¹³. Within the RER with CR subgroup, this analysis demonstrates that those patients with LPHL have exceptional EFS and OS not compromised by the avoidance of IFRT. Patients with LPHL are thus ideal candidates for response-adapted therapy, which may include reduction in therapy, based on their favorable outcomes.

Given the excellent overall outcomes of patients with LPHL, recent pediatric clinical trials have evaluated regimens with the reduction or elimination of chemotherapy or IFRT, especially in low-risk patients^{6,8}. Among early stage patients with LPHL, COG AHOD03P1 demonstrated that 75% of Stage 1A patients can avoid chemotherapy after complete surgical resection alone and >90% can avoid IFRT while maintaining excellent outcomes when treated with three cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide (AV-PC)⁸. The impact of low-dose IFRT on patients with LPHL was evaluated previously on study CCG-5942¹⁸. On this protocol, intermediate-risk (Group 2) patients (including Stage I with adverse disease features, Stage II with adverse disease features and/or with clinical B symptoms, and Stage III) received 6 cycles of cyclophosphamide, vincristine,

prednisone, procarbazine, doxorubicin, bleomycin, and vinblastine (COPP/ABV) and were then randomized to IFRT or no further treatment if they achieved a CR². Five-year EFS for 82 patients with LPHL was 97% and OS 100%, compared to EFS of 84% and OS of 93% for the cohort with cHL. As in our study, patients with LPHL who achieved a CR to chemotherapy had excellent EFS without the addition of IFRT, with 5-year EFS of 100% for patients receiving IFRT and 96% for those treated with chemotherapy alone¹⁸. These findings are comparable to our data, yet were obtained with receipt of considerably more chemotherapy. Similarly, analysis of patients with LPHL treated on the United Kingdom Children's Cancer Study Group HD1 and HD2 studies found that chemotherapy alone resulted in better relapse-free survival than IFRT alone¹⁹. Twenty-two children with stage IA disease received RT alone and 20 (2 with stage IA disease, 11 with stage IIA disease, and 7 with advanced disease) received chlorambucil, vinblastine, prednisolone, and procarbazine (ChIVPP) chemotherapy alone for 5 to 10 courses. The 10-year relapse-free survival rates were 77% in those treated with RT alone and 90% for those treated with chemotherapy alone¹⁹. These data suggest that chemotherapy alone can be a successful strategy in the management of LPHL. However, many of these studies included more intensive chemotherapy regimens that could make additional benefits of IFRT difficult to detect.

Although there is no consensus on the optimal chemotherapy only regimen for children with LPHL, several studies have utilized chemotherapy regimens designed to minimize anthracycline and alkylator exposure²⁰. The Children's Cancer and Leukaemia Group (CCLG) and the Société Française de lutte contre les Cancers et leucémies de l'Enfant et l'adolescent (SCFE) recently reported on the outcomes of a retrospective series of 41 pediatric patients with advanced stage LPHL (clinical stage IIB, III, and IV) treated with diverse regimens²¹. Twenty patients received chemotherapy alone with either cHL or B-cell non-Hodgkin lymphoma (NHL) protocols and all attained a CR. Three patients subsequently relapsed but had a CR to second line therapy. Chemotherapy regimens varied and included doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)/ChIVPP (n=7) and cyclophosphamide, vincristine, and prednisone (CVP) (n=3) as well as rituximab (n=12) in combination with other chemotherapy, most commonly cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) (n=5) or R-ABVD (n=3)²¹. Although numbers were small, the rituximab treatment group was notable for having a lower relapse rate of 8.3% (1/12) compared to the chemotherapy alone group rate of 15% (3/20). Since the lymphocytic and histiocytic cells in LPHL consistently express CD20, rituximab, a chimeric anti-CD20 monoclonal antibody, may be an appropriate approach to consider in order to decrease exposure to cytotoxic chemotherapy. Growing experience using rituximab in young children has not found any obvious acute or long-term toxicity associated with B-cell depletion and has demonstrated efficacy in B-cell NHL^{22–24}.

While LPHL in children and adults is not known to differ biologically, the treatment strategies for the two groups have differed. The National Comprehensive Care Network (NCCN) guidelines (https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf) suggest CVP, ABVD, or CHOP with or without rituximab as the most common regimens for advanced stage LPHL in adults. In adult studies of LPHL, rituximab has been used alone and in combination with other chemotherapy with promising results^{25–28}. Rituximab has been used as a single agent to treat 39 adult patients all of whom achieved a CR or PR after

four weekly doses, with durable responses seen in patients treated with maintenance rituximab every 6 months for 2 years. However, 23 of 39 patients experienced a relapse and 9 had evidence of transformation to aggressive B-cell NHL ²⁵. In a retrospective study of newly diagnosed adult patients with LPHL (n=6), R-ABVD was efficacious with an estimated 6-year EFS and OS of 75% and 100% respectively ²⁶. Similarly, a retrospective analysis of 27 adult patients with advanced stage LPHL demonstrated that R-CHOP was an effective treatment approach with an overall response rate of 100% and a CR rate of 89% ²⁷.

Subsequent malignant neoplasms (SMNs), in particular NHL, following a diagnosis of LPHL have been reported in both adult and pediatric series and could either represent a consequence of therapy or the natural history of LPHL ^{29–31}. Overall, a higher risk of transformation to aggressive B-cell NHL exists for LPHL than for cHL. In a series of patients with LPHL, of 95 patients followed, 14% experienced transformation to an aggressive B-cell NHL up to 20 years from diagnosis at a median of 8.1 years ³². Patients are also at risk for SMNs other than NHL including leukemia, sarcomas, and carcinomas which could be associated with chemotherapy or IFRT, providing further motivation to tailor treatment when feasible ^{5,29,33}. In our cohort of patients with intermediate-risk LPHL, no SMNs or transformations to B-cell NHL have been observed to date. However, the median follow-up time for this group is only 7.2 years, which may not be sufficient time to determine the full SMN risk. Of note, in AHOD0031 patients with LPHL had a longer time to relapse than patients with cHL, consistent with what has been reported in this indolent disease ³⁴. In order to determine the long-term outcomes, AHOD0031 includes late event reporting up to 10 years after therapy to examine the impact of SMN and late organ toxicity on overall survival.

In conclusion, in patients with LPHL treated with ABVE-PC for four cycles, the majority achieved RER with CR status and demonstrated excellent EFS and OS without IFRT. Further follow-up of this group of patients will evaluate for late recurrences and determine if this approach is also associated, as expected, with minimal risk for long-term adverse health outcomes. In the future, based on limited pediatric and more substantial data in adults, incorporating targeted agents such as rituximab into the management of pediatric patients with LPHL may be a testable strategy to further limit exposure to cytotoxic chemotherapy and further improve long-term outcomes. Since LPHL is a rare disease, international collaborative studies using appropriate risk stratification and clear treatment outcomes will play a key role in determining the optimal therapy for these patients.

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Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
ABVE-PC	Doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide

CCLG	Children's Cancer and Leukaemia Group
cHL	Classical Hodgkin Lymphoma
ChIVPP	Chlorambucil, vinblastine, prednisolone, and procarbazine
COG	Children's Oncology Group
COPP/ABV	Cyclophosphamide, vincristine, prednisone, procarbazine, doxorubicin, bleomycin, vinblastine
CVP	Cyclophosphamide, vincristine, and prednisone
CR	Complete response
DECA	Dexamethasone, etoposide, cisplatin, cytarabine
EFS	Event-free survival
FDG-PET	[18F]fluorodeoxyglucose–positron emission tomography
HL	Hodgkin Lymphoma
IFRT	Involved field radiotherapy
LPHL	Lymphocyte-predominant Hodgkin Lymphoma
NCCN	National Comprehensive Care Network
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PD	Progressive disease
PPD	Product of perpendicular diameters
RER	Rapid early responder
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
SCFE	Société Française de lutte contre les Cancers et leucémies de l'Enfant et l'adolescent
SER	Slow early responder
SMN	subsequent malignant neoplasms

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FIGURE 1.

CONSORT Diagram: Numbers represent LP patients only. ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone; CR, complete response; DECA, dexamethasone, etoposide, cisplatin, and cytarabine; IFRT, Involved Field Radiotherapy; RER, rapid early responder; SER, slow early responder.

FIGURE 2.
(A) EFS and (B) OS for other versus LP patients

FIGURE 3.
(A) EFS and (B) OS for RER versus SER LP patients

FIGURE 4.
(A) EFS and (B) OS by IFRT random assignment for LP RER/CR patients

TABLE 1

Study participants

Variable	All patients	Other*	LP**	p-value
	N=1711	N=1615	N=96	
Age at diagnosis in years (mean±SD)	14.5±3.4	14.6±3.3	13.3±3.6	0.0001
Gender				<.0001
Male	907	824 (51.0%)	83 (86.5%)	
Female	804	791 (49.0%)	13 (13.5%)	
Race				0.10
White	1333	1263 (78.2%)	70 (72.9%)	
Black	189	172 (10.7%)	17 (17.7%)	
Other	189	180 (11.1%)	9 (9.4%)	
Stage				<.0001
I	98	84 (5.2%)	14 (14.6%)	
II	1005	970 (60.1%)	35 (36.5%)	
III	354	311 (19.3%)	43 (44.8%)	
IV	254	250 (15.5%)	4 (4.2%)	
B symptoms				0.0012
No	1327	1238 (76.7%)	89 (92.7%)	
Yes	380	373 (23.1%)	7 (7.3%)	
Unknown	4	4 (0.2%)		
Bulk disease				<.0001
No	435	392 (24.3%)	43 (44.8%)	
Yes	1256	1205 (74.6%)	51 (53.1%)	
Unknown	20	18 (1.1%)	2 (2.1%)	

Note:

* Other includes Lymphocyte Depleted, Nodular Sclerosing, Mixed Cellularity, Unknown

** LP indicates Lymphocyte Predominant

TABLE 2

Comparison of 5 year EFS and OS for stage, bulk, and B symptoms

		n	EFS	p-value	OS	p-value
Stage	I	14	100.0%	0.2513	100.0%	0.7483
	II	35	94.0%		100.0%	
	III	43	90.1%		97.6%	
	IV	4	75.0%		100.0%	
Bulk	No	43	94.6%	0.9426	97.6%	0.2793
	Yes	51	89.9%		100.0%	
	Unknown	2				
B symptoms	No	89	91.6%	0.4337	98.8%	0.7728
	Yes	7	100.0%		100.0%	