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Impact of Low-Dose Involved-Field Radiation Therapy on Pediatric Patients with Lymphocyte-Predominant Hodgkin Lymphoma Treated with Chemotherapy: A Report from the Children's Oncology Group

Burton E. Appel, MD,

Tomorrows Children's Institute, Hackensack University Medical Center, Hackensack, NJ

Lu Chen, PhD,

Children's Oncology Group Operations Center, Arcadia, CA

Allen Buxton, MS,

Children's Oncology Group Operations Center, Arcadia, CA

Suzanne L. Wolden, MD,

Memorial Sloan-Kettering Cancer Center, New York, NY

David C. Hodgson, MD, and

Princess Margaret Hospital, Toronto, Canada

James B. Nachman, MD

University of Chicago Children's Hospital, Chicago, IL

Abstract

Background—Treatment of pediatric lymphocyte-predominant Hodgkin lymphoma (LPHL) is controversial but has typically consisted of both chemotherapy and radiation. Radiation therapy is associated with potential late effects in children and adolescents. We examined the impact of radiation therapy on long-term outcome of patients with LPHL treated on CCG-5942, a large pediatric cooperative group study of Hodgkin lymphoma.

Procedure—Eighty-two patients with LPHL were registered on CCG-5942. Fifty-two patients (63%) received chemotherapy alone; 29 patients (35%) received chemotherapy followed by involved-field radiation therapy (IFRT).

Results—The median follow-up of the LPHL patients is 7.7 years; 63 patients (77%) have > 5 years of follow-up. The 5-year event-free survival (EFS) and overall survival (OS) were 97% and 100%. Two relapses occurred, both in patients who did not receive IFRT. There were no significant differences in EFS or OS between patients who received or did not receive IFRT.

Conclusions—This subset analysis demonstrates the chemosensitivity of pediatric LPHL. Patients who had a complete response to chemotherapy had an excellent EFS and OS without the addition of radiotherapy.

Corresponding author: Burton E. Appel, MD, Tomorrows Children's Institute, Hackensack University Medical Center, 30 Prospect Ave., Hackensack, NJ 07601, bappel@HackensackUMC.org, phone: 551-996-5437, fax: 201-487-7340.

Conflict of Interest Statement

None of the authors have any relevant interests to disclose.

This paper is dedicated to the late James Nachman, MD, who was a master clinician, researcher and teacher. His contributions will continue to influence the field of pediatric oncology for decades to come.

Keywords

Lymphocyte-Predominant Hodgkin Lymphoma

Introduction

Lymphocyte-predominant Hodgkin lymphoma (LPHL) is an uncommon subtype of Hodgkin lymphoma (HL), comprising up to 10% of cases in adult and pediatric series. Most cases of LPHL exhibit a nodular pattern, with histopathologic features distinct from classical HL. The neoplastic cells of nodular LPHL, historically known as lymphocytic and histiocytic (L & H) cells, represent a clonal expansion of B cells [1-3]. Unlike the Reed-Sternberg cells of classical HL that express CD15 and CD30 [4], the L & H cells of nodular LPHL express B-cell-associated markers such as CD20, CD79a, J-chain and immunoglobulin transcripts, but lack CD15 and CD30 [5].

LPHL is also clinically distinct from classical HL [6-7]. There is a strong male predominance (approximately 70%) and many children are diagnosed at a younger age than those with classical HL. Most patients present with asymptomatic, non-bulky localized disease involving peripheral lymph nodes. The mediastinum is rarely involved.

Adult patients with low stage LPHL are traditionally treated with radiation therapy (RT) [8] and a recent publication suggested that chemotherapy was ineffective for LPHL in adults [9]. Pediatric patients with LPHL have excellent outcomes on chemotherapy/low dose radiation regimens used for low-stage classical HL [10-12]. However, standard HL treatment exposes pediatric LPHL patients to the potential late effects of anthracyclines and alkylating agents as well as radiation therapy.

Limited data are available to evaluate the role of low-dose, involved field radiation (LD-IFRT) in curing pediatric LPHL. CCG-5942 was a pediatric HL trial in which patients who completely responded to chemotherapy were randomly assigned to receive LD-IFRT or not. Patients achieving a partial response were assigned to LD-IFRT. We report outcomes for patients with LPHL enrolled on CCG-5942 as of March 2007, when follow-up data collection was completed.

Methods

Patients

Children and adolescents under 21 years of age with newly-diagnosed HL were enrolled on CCG-5942 between January 1995 and December 1998. Clinical stage was determined according to the Ann Arbor staging system. Patients were assigned to a Clinical Group (1, 2 or 3) as described previously [13]. Bulk disease was defined as a mediastinal mass greater than or equal to one third of the chest diameter and/or a non-mediastinal node or nodal aggregate greater than 10 cm in largest diameter.

Institutional pathologists made a diagnosis of LPHL based upon the system of Lukes and Butler [14]. Although not an eligibility requirement, institutions were requested to submit tissue for central pathology review.

Treatment Protocol

Details of the risk-stratified chemotherapy treatment protocol have been published previously [13]. Favorable risk (Group 1) patients and intermediate risk (Group 2) patients received 4 and 6 monthly cycles of cyclophosphamide, vincristine, prednisone,

procarbazine, doxorubicin, bleomycin, and vinblastine (COPP/ABV) respectively. High risk (Group 3) patients received 6 cycles of treatment: 2 cycles of COPP/ABV, 2 cycles of high-dose cytarabine with etoposide, and 2 cycles of cyclophosphamide, vincristine, doxorubicin, methylprednisolone and prednisone. Patients were evaluated at completion of chemotherapy; all patients who achieved a complete response were eligible for randomization to receive either LD-IFRT or no further therapy. Patients who did not achieve a complete response to chemotherapy were non-randomly assigned to receive LD-IFRT. A total dose of 21 Gy was given in 12 fractions to all lymph node regions containing radiologically abnormal lymph nodes at the time of diagnosis.

Response Determination

A complete response (CR) in lymph nodes was defined as absence of palpable adenopathy on physical exam in addition to resolution on imaging (CT, chest x-ray, ultrasound or MRI) at the end of chemotherapy. In addition, patients with a CR were required to have resolution of disease in extralymphatic sites. For patients with residual masses after chemotherapy, volumes were estimated by multiplying the length of the lesion in the three principal axes by 0.52. Patients with residual disease in the mediastinum were considered to have a CR if the initial tumor volume was reduced by more than 70% and any mass remaining after chemotherapy that was initially gallium positive had become gallium negative. Patients with residual disease in the abdomen were considered to have a CR if gallium negative and either showed a >70% decrease in volume or each mass was <2 cm³. Patients who had 50% to 70% reduction in tumor volume or >70% reduction but persistent gallium positivity were considered to have a partial response (PR). Disease progression/relapse was defined as pathologically confirmed disease in a previously uninvolved site, clinical or radiological evidence of increased volume in a previously involved site, or biopsy-proven HL after achieving a CR.

The protocol was approved by the National Cancer Institute and the Institutional Review Boards of participating institutions. Written informed consent was obtained from patients, parents and/or guardians in accordance with the precepts of the Helsinki Declaration.

Statistical Analyses

Chi-square test was used to compare demographic and clinical characteristics of LPHL patients and classical HL patients on CCG-5942. Event-free survival (EFS) was defined as the time from study enrollment to the first occurrence of any event (relapse, progression, occurrence of a second malignant neoplasm, or death from any cause). Overall survival (OS) was defined as the time from study enrollment to death from any cause. EFS and OS estimates were based on Kaplan-Meier product-limit estimator. Comparison between survival curves was based on Log rank test. All statistical tests were 2-sided and a p-value of less than 0.05 was considered statistically significant.

Results

Patients

Patients were considered to have LPHL if the institutional diagnosis was LPHL and there was no central review (n=25) or if the central review diagnosis was LPHL (n=57). For 46 of the 57 patients, the central review and institutional diagnosis were in agreement. For 9 of the 57, the institutional diagnosis was not LPHL (7 nodular sclerosis and 2 mixed cellularity); for 2 patients no institutional diagnosis was recorded.

A total of 82 patients with LPHL were enrolled on CCG-5942, representing 9.9% of the entire cohort of 826 eligible patients. The median follow-up of the LPHL cohort is 7.7 years;

63 patients (77%) have > 5 years of follow-up. Demographic and disease characteristics of the 82 patients with LPHL and the 744 patients with classical HL are shown in Table I. 84% of the LPHL patients were male. Virtually all (98%) were asymptomatic and most (87%) had stage I or II disease. None of the 82 patients had bulk disease in the mediastinum and only 6 (7%) had a node or nodal aggregate greater than 10 cm in largest diameter. The differences in gender, age, stage, group, B symptoms, and presence of bulk between patients with LPHL and classical HL were statistically significant.

One of the LPHL patients withdrew after 2 cycles of chemotherapy; it is unknown whether or not IFRT was administered. Characteristics of 81 LPHL patients, grouped by post-chemotherapy treatment, are summarized in Table II.

Outcome

Patients with LPHL on CCG-5942 had superior outcomes compared to those with classical HL. 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 classical HL.

Figure 1 summarizes the treatment given to all 82 patients with LPHL enrolled on CCG-5942. Among the 81 LPHL patients whose RT status is known, 80 completed the chemotherapy as planned. One patient (Group 1) received 6 cycles instead of 4 cycles and no RT. Of the 80 patients who completed the planned chemotherapy, 71 patients achieved a CR by the end of chemotherapy and 5 patients achieved a PR. Response assessment was unknown for 4 patients who received 4 cycles of chemotherapy without RT and remain in remission.

Among the 71 patients who received the planned chemotherapy and achieved a CR, 56 were randomized: 26 to IFRT (5 did not receive RT per patient/parent choice) and 30 to no IFRT (1 received RT per patient/parent choice). Only 3 of the 15 patients who were not randomized received IFRT. Four of the 5 patients who completed the planned chemotherapy and achieved a PR received IFRT (per protocol).

Five -year EFS was 100% for those 29 patients receiving IFRT, and 96% (95% CI = 84%-99%) for those 52 patients treated with chemotherapy alone (Figure 2). For the 50 patients who were randomized and received the assigned treatment, 5-year EFS was 100% for the 21 patients who received IFRT and 96% for the 29 patients who did not receive IFRT; there was one relapse among the 29 patients. No second malignant neoplasms (SMN) were reported.

Two relapses were reported, both in patients who did not receive IFRT. A patient with stage IA LPHL achieved a CR at the end of chemotherapy and was non-randomly assigned to no IFRT. He recurred in previously uninvolved bilateral axillary nodes and left hilar nodes 37 months from diagnosis. This patient is now in second CR more than 3 years after salvage chemotherapy plus rituximab. A patient with Stage IIIA (Clinical Group 2) LPHL in the neck, axilla and left groin who achieved a CR after chemotherapy was randomized to no IFRT. He relapsed locally as well as in the previously uninvolved groin at 55 months from initial diagnosis. Relapse treatment included high dose chemotherapy followed by autologous stem cell rescue. Both patients remain in a continuous second remission for more than 3 and 5 years respectively; neither patient received RT as part of salvage therapy.

Discussion

When children and adults with LPHL are given standard HL treatment, outcomes for LPHL are generally better than for classical HL, particularly for early-stage disease [7, 12].

However, in contrast to classical HL, relapses in LPHL can occur many years after initial diagnosis [6, 11, 15-21]. Retrospective studies of adult and pediatric LPHL that demonstrate excellent overall survival have utilized a variety of regimens, including radiation alone, chemotherapy alone, combined modality therapy, and surgery alone for selected patients.

It is important to avoid over-treating LPHL, since patients are at higher risk of dying from treatment-related toxicity than from recurrent disease [6, 9, 22, 23]. RT can produce deficits in soft tissue and bone growth among younger children [24] and can cause cardiopulmonary disease when the mediastinum is treated [25-27]. RT is also associated with increased risk of second cancers [28-34]. Paradigms of pediatric care currently use low-dose radiation; however, low-dose RT (15 to 25.5 Gy) does not eliminate the risk of developing a SMN based on a recent report [35]. Chemotherapy regimens that include alkylating agents and anthracyclines can cause infertility [36-38], and cardiac failure [39]. Therefore, it is crucial to consider late toxicities when planning treatment for children with early-stage LPHL.

Adults with early-stage LPHL can be cured with 30-40 Gy limited-field radiation therapy [8, 23,40], and several studies have suggested poor outcomes for adults and children with LPHL treated with chemotherapy alone. Chen et al published a retrospective series of 113 adults with early-stage LPHL treated at a single institution between 1970 and 2005 [9]. Ninety-three received RT alone, with 10 year progression-free survival from 72 to 89%. However, the majority of these patients received 36 to 38 Gy to regional or extended fields. Only seven patients were treated with chemotherapy alone, using a variety of chemotherapy regimens. Six of 113 patients died of a second cancer; 5 of the 6 had received RT.

An analysis by Van Grotel et al of 7 pediatric patients with low stage LPHL treated with chemotherapy alone revealed a high rate of early relapse [41]. Four of 7 patients in a CR after 6 cycles of EBVD (epirubicin, bleomycin, vinblastine and dacarbazine) relapsed between 5 and 14 months from diagnosis. Three of the 4 relapses were local; one relapsed with stage III disease. All 4 patients were salvaged with chemotherapy without RT.

The retrospective nature of these studies raises the possibility of selection bias in choosing patients to receive chemotherapy alone. In Chen's study, 4 different chemotherapy regimens were used to treat the 7 patients, making chemosensitivity difficult to evaluate. No data were provided regarding the number of chemotherapy cycles each patient received. It is also possible that the chemotherapy regimens utilized in these series were inadequate. A recent communication suggested that LPHL may best be treated with a regimen designed for NHL, containing an alkylating agent such as cyclophosphamide [42].

A recent analysis of adults with LPHL supports the idea that combined treatment with chemotherapy and RT improves cure rates [43]. Thirty two patients were treated with RT alone before 1993; 56 patients were treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) from 1993 onward. Forty two of the 56 patients received RT along with ABVD. Ten year progression free survival was 91% for those treated with chemotherapy compared to 65% for patients who received RT alone. Although limited by its retrospective nature, this study provides support for the benefit of chemotherapy in LPHL.

Our analysis demonstrates that children with LPHL can have excellent outcomes with chemotherapy alone. However, 4 cycles of COPP/ABV for the lowest-risk patients can be considered fairly toxic by today's standards, including significant exposure to both alkylating agents and anthracycline. In the last decade excellent outcomes for pediatric LPHL using less intensive chemotherapy regimens have been reported. Thirty-three children with stage I/II LPHL treated with 4 cycles of VAMP (vinblastine/doxorubicin/methotrexate/prednisone) had 10-year EFS of 100% [12]. These patients were spared alkylating agents.

However, all patients received IFRT (15 to 25 Gy) and a cumulative anthracycline dose of 200 mg/m².

Recent pediatric clinical trials in North America and Europe have utilized chemotherapy regimens designed to minimize anthracycline and alkylator exposure as well as avoiding RT. The Children's Oncology Group (COG) clinical trial for LPHL, AHOD03P1, used 3 cycles of doxorubicin, vincristine, prednisone and cyclophosphamide. Similar to CCG-5942, the cumulative cyclophosphamide dose was 2.4 gm/m² and total doxorubicin was 150 mg/m². However, procarbazine was eliminated. LD-IFRT was reserved for patients with residual disease after chemotherapy. Follow up of subjects on this trial is ongoing.

In Europe, a regimen consisting of 3 cycles of cyclophosphamide (total dose 1.5 gm/m²), vinblastine and prednisone (CVP) without anthracycline has been piloted. A retrospective series of 55 patients treated with 3 cycles of CVP showed 46 complete responses and 9 partial responses; there were 3 relapses with a median follow up of 41 months [44]. This promising regimen is being used in the current prospective EuroNet Paediatric Hodgkin's Lymphoma Group clinical trial.

In recent years it has also been reported that some pediatric patients with limited-stage LPHL can be cured with surgery alone [17-19,45,46]. These retrospective reports describe patients with a range of clinical stage and extent of surgical resection. COG AHOD03P1 utilized a resection alone strategy for patients with stage IA disease in a single node that was completely resected; chemotherapy was reserved for patients who recurred after observation. A similar approach is being used for stage I, totally-resected LPHL in the current EuroNet trial; results of these studies are not yet available.

CD20 immunopositivity is a hallmark of LPHL. A number of small studies have examined the use of rituximab, an anti-CD20 monoclonal antibody, in patients with newly-diagnosed or recurrent LPHL [47,48]. In most cases, there is an objective response when rituximab is given as a single agent; however, the duration of response appears to be limited. The combination of rituximab with chemotherapy also appears encouraging [21]. Future clinical trials may incorporate rituximab as upfront therapy as a way to decrease exposure to chemoradiotherapy in selected patients.

The development of non-Hodgkin lymphoma (NHL) following a diagnosis of LPHL has been reported in adult series and may represent a consequence of therapy or the natural history of LPHL [20, 22, 49-51]. This phenomenon has been reported in pediatric patients as well. With follow-up ranging from 25 to 87 months, Karayalcin et al reported 2 SMN (both NHL) among 26 LPHL patients enrolled on Pediatric Oncology Group Hodgkin Lymphoma trials from 1984 to 1993 [10]. The French Society of Pediatric Oncology reported 1 NHL in a cohort of 27 patients 10 years after diagnosis [18]. Secondary malignancies other than NHL have been reported in both adult and pediatric series; in some, more deaths resulted from SMN than LPHL [6, 9, 10, 16]. To date, no secondary malignancies have been reported among the LPHL patients treated on CCG-5942; however, they may arise during longer term follow-up.

This analysis has a number of limitations. Of 71 subjects who received the planned chemotherapy and achieved a CR, 15 were not randomized. Only three of these 15 patients received IFRT, thus introducing potential bias in the results. In addition, five of 26 subjects randomized to IFRT did not receive it by choice of the patient or family. In the end, a larger group did not receive IFRT than intended by the study design.

Twenty five of 82 patients (30%) did not have central pathology review. For nine of 55 patients who had a central review diagnosis of LPHL, there were discordant results with the

institutional diagnosis. However, both of the patients who relapsed did have confirmation of LPHL on central pathology review.

The results of this study are limited by the fact that it is a retrospective analysis with relatively small numbers. There were no significant differences in EFS or OS between patients who received or did not receive IFRT; however, this subset analysis may not have sufficient power to detect a small difference between the groups. Finally, the median follow up for this subgroup was 7.7 years; this may not be sufficient time to detect late relapses or secondary malignancies, including NHL.

The excellent outcomes of both randomized and non-randomized patients on CCG-5942 who received chemotherapy alone clearly demonstrate that LPHL in children is chemosensitive and highly curable with chemotherapy alone. The recently-closed COG study AHOD03P1 as well as the ongoing EuroNet study offer treatment with limited chemotherapy without RT for many patients. Both protocols also utilize a surgery-only strategy for selected patients. It is encouraging that in the future, pediatric patients with low-stage LPHL will maintain excellent cure rates while reducing or eliminating late effects of therapy.

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Figure 1.
Treatment given to 82 LPHL patients on CCG-5942

Figure 2.
Event-free survival (EFS) for 81 patients with LPHL on CCG-5942; IFRT vs. No IFRT

Table 1
Patients Enrolled on CCG-5942: Lymphocyte-Predominant versus Classical Hodgkin Pathology

	LPHL (n=82)		Classical HL (n=744)		p-value
	No.	%	No.	%	
Sex					<0.001
Male	69	84.1%	385	51.7%	
Female	13	15.9%	359	48.3%	
Age					0.002
1<5	4	4.9%	22	3.0%	1
5 to 9	18	22.0%	83	11.2%	
10 to 15	49	59.8%	423	56.9%	
16-21	11	13.4%	216	29.0%	
Clinical Stage					<0.001
I	49	59.8%	86	11.6%	
II	22	26.8%	409	55.0%	
III	9	11.0%	111	14.9%	
	2	2.4%	138	18.5%	
Clinical Group					<0.001
I	66	1 80.5%	220	29.6%	
II	14	17.1%	383	51.5%	
III	2	1 2.4%	141	19.0%	
B Symptoms					<0.001
Absent	80	97.6%	536	72.0%	
Present	2	2.4%	208	28.0%	
Bulk Disease (>10 cm)					0.018
Absent	76	92.7%	614	82.5%	
Present	6	7.3%	130	17.5%	

Table II
Characteristics of 81 LPHL Patients, Grouped by Post-Chemotherapy Treatment

	No IFRT (n=52)	IFRT (n=29)
Randomly assigned	29	21
Non-randomly assigned	23	8
Clinical group		
Group 1	44	21
Group 2	8	6
Group 3	10	2
Sex		
Male	45	23
Female	7	6
B symptoms		
Absent	51	28
Present	1	1
Bulk Disease (>10 cm)		
Absent	50	25
Present	2	4