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Excellent Outcomes Following Response-Based Omission of Radiotherapy in Children and Adolescents with Intermediate or High-Risk Hodgkin Lymphoma

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Abstract

Several pediatric Hodgkin lymphoma (HL) consortia have demonstrated safe omission of radiotherapy (RT) in early stage HL, whereas feasibility of omitting RT in advanced HL is still under investigation. This is a single institution retrospective analysis of twenty-seven patients with intermediate or high-risk HL (age 2–22 years), treated with a modification of the dose-intensive OEPA-COPDAC (vincristine, etoposide, prednisone, doxorubicin - cyclophosphamide, vincristine, prednisone, dacarbazine) regimen, with radiation restricted to only sites of inadequate early response (Deauville 3 and/or 75% tumor shrinkage). Their outcome was compared to a historical cohort (n=42) treated with Stanford V or ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), who received consolidative involved-field RT. RT was omitted in 15/27(56%) of patients treated with OEPA-COPDAC, majority of whom (67%) had high-risk disease. At a median follow up of 3.1 years, the 3-year PFS was 100% in patients who received OEPA-COPDAC, versus 83.3% (95% CI: 68.2 – 91.7%) in the historical cohort, $p=0.03$. Our analysis demonstrates excellent survival with omission of RT in more than 50% of patients with pediatric advanced HL, treated with a dose-intensive chemotherapy regimen. When administered, RT was restricted to only sites of inadequate early response. Results of large prospective studies are needed to validate these findings.

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Keywords

Hodgkin lymphoma; radiotherapy; positron emission tomography; advanced disease; pediatric

Introduction

Hodgkin lymphoma (HL) in children and adolescents is highly curable and long-term survival exceeds 95% with combination of chemotherapy and radiation therapy (RT).¹ However treatment-related sequelae significantly contribute to morbidity amongst survivors.² Consequently, efforts have focused on optimizing therapy while maintaining excellent cure rates, through risk-based and response-based strategies.³ Such efforts include decreasing RT dose and field, and when possible, eliminating RT in patients who have a favorable early response.

Several pediatric consortia have demonstrated response-based omission of radiation in patients who have low-risk disease, without any significant impact on event-free survival (EFS). The Pediatric Hodgkin Lymphoma Consortium (PHLC) which includes St. Jude Children's Research Hospital, Dana-Farber Cancer Institute, Lucile Packard's Children Hospital at Stanford, Mass General Hospital and Maine Medical Center, showed successful omission of RT in patients with early stage disease (Stage IA, IIA, < 3 nodal sites, non-bulky) who achieved a complete response (CR) (defined as > 75% tumor reduction and negative gallium or positron emission tomography scan) after two cycles of VAMP (vincristine, doxorubicin, methotrexate and prednisone) chemotherapy.⁴

Likewise, the German Society of Pediatric Oncology and Hematology -Hodgkin Lymphoma (GPOH-HD) 95 trial showed RT could be safely omitted in their lowest risk patients who were in CR after two cycles of OEPA (vincristine, etoposide, prednisone, and doxorubicin) or OPPA (vincristine, procarbazine, prednisone and doxorubicin) chemotherapy.⁵ In the same trial, patients with advanced disease received two to four cycles of COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine) or COPP (cyclophosphamide, vincristine, prednisone, procarbazine) chemotherapy, followed by radiation to all involved sites of disease. The successor GPOH-HD 2002 study further demonstrated that the procarbazine-free OEPA-COPDAC, and OPPA-COPP were equivalent regimens.

The Children's Oncology Group (COG) in a large randomized phase III study in HL (AHOD0031), evaluated if RT could be omitted in patients with intermediate-risk disease who were rapid early responders (RER) and in CR after four cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide-prednisone, and cyclophosphamide). Their results showed no difference in 4-year EFS irrespective of administration of RT (87.9% in RT arm versus 84.3% without RT).⁶ However, the feasibility of eliminating RT in children and adolescents with high-risk HL is still under investigation and previous studies showed lower EFS in patients who did not receive radiation, although there was no impact in the overall survival (OS).^{5,7}

Building on the experience of successive GPOH-HD trials, the European Pediatric and Adolescent Hodgkin Lymphoma Network (EuroNet-HD) undertook its first international

cooperative trial (EuroNet-HD-PHL- C1) (NCT00433459), which evaluated the omission of RT in all patients (irrespective of disease stage) who had an adequate response to two cycles of OEPA. Unlike in prior GPOH-HD studies, response was defined by both an adequate 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) scan, and volumetric reduction on computed tomography (CT). Patients who did not have an adequate early response received RT to all involved disease sites. Interim results of this study show elimination of RT in 48% of all patients enrolled with no decrement in EFS between irradiated and non-irradiated patients.⁸

In 2011, the Dana-Farber/Boston Children's Cancer and Blood Disorders Center adopted the GPOH-HD derived OEPA-COPDAC chemotherapy backbone^{5,9} with slight modifications, as standard of care for patients not enrolled on a research study. Deviating from the EuroNet-HD C1 treatment plan, and modelled after concurrent PHLC research studies of the time, we also instituted a response-based paradigm of administering radiation to only the sites of inadequate early response. We report our single institution experience of this modified OEPA-COPDAC and response-based radiation elimination strategy, in children with intermediate or high-risk disease. We also compare the outcomes of patients treated with our current standard of care, to a historical cohort treated with standard regimens and who all received involved-field RT (IFRT).

Patients and Methods

Patient Identification

Following approval from the Institutional Review Board (IRB), we queried the department of pathology database at Boston Children's hospital for all patients less than 22 years of age diagnosed with HL at our institution from January 1, 2005 through December 31, 2015. One hundred and thirty-five (135) patients were identified. Cases were selected for inclusion in our analysis if they were newly diagnosed with classical HL, received treatment in our institution and had Ann Arbor Stage IA_E, IB_E, IIA bulky (peripheral lymph node aggregate >6cm or mediastinal mass greater than one-third of the intra-thoracic diameter), IIA_E IIB, IIB_E, IIIA, IIIB or Stage IV at diagnosis. Seventy patients met the inclusion criteria.

We identified 27 consecutive patients who were treated with our current standard of care (OEPA-COPDAC) with response-based omission of RT, and a historical cohort consisting of 43 subjects treated with either Stanford V regimen¹⁰ or ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and consolidative IFRT. One of the patients in the historical cohort who was treated in the recent years did not receive IFRT, and was excluded from the analysis. The remaining 69 subjects were included in this analysis (Figure. 1). For this analysis, we risk stratified these 69 subjects into intermediate-risk (IA_E, IB_E, IIA bulky, IIA_E, IIB and IIIA) and high-risk (IIB_E, IIIB, IVA and IVB) disease.

Treatment

Twenty-seven subjects were treated with OEPA-COPDAC regimen from 2011 – 2015. Table 1 compares our institutional adoption of the OEPA-COPDAC regimen with the EuroNet-HD treatment schema highlighting the minor differences in our risk group stratification and

number of COPDAC cycles administered by risk group. The dosing and timing of chemotherapy was same as previously published.⁹ All subjects first received two cycles of OEPA followed by two to four cycles of COPDAC (cyclophosphamide, vincristine prednisone, dacarbazine). Patients with intermediate-risk disease received two to four cycles of COPDAC, while those with high-risk disease received four cycles of COPDAC. All the subjects underwent interval response assessment with FDG-PET and CT after the two cycles of OEPA. An adequate early response was defined as a negative FDG-PET (Deauville 3) and 75% tumor reduction based on the product of the perpendicular diameter on CT. Patients who had an adequate response after two OEPA cycles were offered omission of RT after risk/benefit discussions involving patients and their families, and both the pediatric and radiation oncologists. All patients with an inadequate response at the early response assessment received 25.5 Gy RT in 1.5 Gy daily fractions. The treatment volume was limited to the sites of inadequate response, and not to all sites of initial involvement. No attempt was made to include entire nodal chain; however, the supraclavicular nodes were included with mediastinal nodal irradiation. Radiation was started within two to four weeks of completion of chemotherapy.

The 42 patients in the historical cohort were treated between 2005–2011. Thirty-one were treated with Stanford V regimen for twelve weeks, and the remainder eleven subjects received six cycles of ABVD. Of the patients treated with Stanford V, twenty-five were enrolled on existing PHLC research studies. All patients in this cohort received 15 – 25.5 Gy of IFRT in 1.5 Gy daily fractions.

Statistical Analysis

The primary end points were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from diagnosis to progression or death from any cause and OS was defined as time from initial diagnosis to death from any cause. Survival distributions were examined using Kaplan-Meier curves and the differences between groups analyzed using the log-rank test, while differences in the distribution of categorical variables were analyzed using Fisher's exact test or the chi-square test and the *t*-test for continuous variables, using a significant two-sided *p* value < 0.05. All statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, TX, USA)

Results

Patient characteristics are summarized in Table 2. The median age of all 69 patients was 15.6 years (range 4.7–21.2 years) – 16 years in those treated with our current standard of care, versus 15.3 years in the historical cohort. Females constituted 51% of all the patients and nodular sclerosis was the predominant histologic subtype (80%). Eighteen of the 27 patients treated with OEPA-COPDAC (67%) had high-risk disease, versus 13 out of the 42 patients (31%) in the historical cohort. (*p*=0.004). Only one patient, who was from the historical cohort, had an E lesion (IIA_E). The distribution of bulky disease was similar between both cohorts – 30% in OEPA-COPDAC and 31% in the historical cohort. There was no difference in the proportion of patients with B symptoms (44% versus 43% in the historical cohort).

Fifteen out of the 27 patients (56%) treated with our current standard of care did not receive RT. This was equal for both intermediate and high-risk disease. None of the patients who had an adequate early response received RT. In all cases, the patients and their families agreed with their treatment provider's recommendation to omit radiotherapy. Similarly, all patients with an inadequate early response after 2 cycles of OEPA received RT to the sites of inadequate response. Two early patients with intermediate-risk disease received two cycles of COPDAC; all others received four cycles of COPDAC. The median duration of follow up for patients treated with OEPA-COPDAC was 3.1 years, compared to 6.3 years in the historical cohort. None of the patients treated with OEPA-COPDAC and our response-based approach has experienced disease progression or relapse to date. One patient progressed on treatment and six others relapsed in the historical cohort. Five of the 7 subjects who relapsed received Stanford V chemotherapy with cyclophosphamide instead of mechlorethamine when the latter agent was unavailable. The 3-year PFS for subjects treated using our response-based approach was 100% versus 83.3% (95% confidence interval (CI): 68.2 – 91.7%), $p = 0.03$ (Figure 2) and 3-year OS of 97.6% (95% CI: 84.2 – 99.6%) in the historical cohort (Figure 3).

Discussion

Utilizing early response assessment of FDG-PET and CT, we avoided RT in 56% of patients with intermediate or high-risk HL treated with OEPA-COPDAC. We have not observed any treatment failures in this cohort at a median follow up of three years. Given that we only recently adopted this treatment paradigm, the follow-up duration was shorter compared to our historical cohort who received RT and other standard chemotherapy regimens. Nevertheless, most of the treatment failure in the historical cohort occurred within two to three years of completion of therapy consistent with earlier pediatric HL studies^{5–7}.

In children with advanced disease, administering RT to all sites of disease involvement may lead to significant risk of late effects including cardiovascular disease and second malignancies, but more limited radiotherapy fields may partially mitigate this risk.^{11,12} To further limit exposure to normal tissues, we only irradiated sites of disease that had an inadequate response to two cycles of OEPA. Radiotherapy to involved node or involved site delivers considerably less radiation to normal tissues with the goal of decreasing toxicity,¹³ as do techniques using deep inspiration breath hold, intensity modulated radiation therapy and proton beam.¹⁴ Overall, the decision to withhold consolidative radiotherapy must be balanced by the recognition that some children may relapse, requiring more intensive chemotherapy and radiotherapy for salvage. Our institutional practice includes a multidisciplinary discussion with the patient and family, pediatric oncologist and radiation oncologist to review the recommendations, including the risks and benefits of giving or omitting radiation. In adults, the application of adjuvant RT in advanced HL is even more controversial, and several randomized trials have questioned its role.^{12,15–18} The results of these trials appear to suggest a benefit in adult patients with advanced HL who have not achieved complete remission or who have residual disease after chemotherapy.

We adapted the EuroNet-HD backbone with some modifications. Our intermediate-risk stratum, unlike Treatment Group 2 (TG2) in the predecessor GPOH-HD studies, included

patients with stage IIA bulky disease. Also, the EuroNet-HD did not exclude these patients from their most favorable group until a retrospective analysis of the C1 trial showed that patients in their lowest risk group (Treatment Group 1) who had bulky disease (volume 200ml) or ESR 30mm/hour had poorer EFS.⁸ These patients will now be assigned to the intermediate risk group in the current EuroNet-PHL-C2 trial (NCT02684708). Furthermore, most of our patients with intermediate-risk disease, received four cycles of COPDAC instead of two cycles administered in the EuroNet-C1 trial and GPOH-HD studies. The TG2 patients in the GPOH-HD 95 study who did not receive IFRT had the lowest EFS (10-year EFS 68.5% versus 91.4% if RT was administered, $p < 0.001$).⁵ We speculated that two cycles of OEPA plus two cycles of COPDAC was not sufficient treatment in the absence of consolidative RT. Since our goal was to minimize the use of radiotherapy, we administered six cycles of chemotherapy to most patients with intermediate-risk disease. Hence, it is possible we may have ‘over-treated’ some of these patients. However, OEPA-COPDAC is a well-tolerated regimen with both low cumulative dose of anthracyclines and alkylators as well as a minimal toxicity profile.⁹ The two additional cycles of COPDAC administered to patients with intermediate-risk disease resulted in only a modest increase in the cumulative dose of cyclophosphamide from 2 to 4 g/m² without additional anthracycline exposure. This appeared to be an acceptable trade-off, to avoid the potential late effects of radiation.

Early interim FDG-PET has emerged as an important predictive and prognostic tool in HL therapy, particularly in adults.^{19–21} However, FDG-PET is not well validated as a predictive tool in childhood HL and its optimal use with pediatric dose-intensive regimens is still under investigation.³ Moreover, there is no consensus on what constitutes an adequate PET response, or the best time (in relation to cycles of therapy) to obtain interval disease assessments and there are questions around how best to incorporate it with CT measurements of tumor reduction. We used a Deauville score of 3 to delineate PET negative disease. In contrast, the EuroNet-C1 study used the International Harmonization Project Criteria (IHP), with a negative PET being the equivalent of Deauville 2.^{22,23} Although widely accepted, the Deauville scoring method is subject to inter-reader variability,²⁴ and a quantitative PET methodology that extends the Deauville score to a continuous scale has been suggested.²⁵

In conclusion, although limited by the retrospective design and small number of patients, utilizing a response-based paradigm, we omitted radiation in more than 50% of patients with intermediate or high-risk HL treated with the dose-intensive OEPA-COPDAC regimen whilst maintaining an excellent survival. The standard practice in most pediatric centers is to administer IFRT in advanced HL, however we restricted RT to only the sites of inadequate early disease response. In our patients, we demonstrate that this strategy is feasible, but results of prospective studies are needed to validate our findings.

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Abbreviations

ABVDA	driamycin {doxorubicin}, bleomycin, vinblastine, dacarbazine
CT	Computed tomography
EuroNet-HD	European Pediatric and Adolescent Hodgkin Lymphoma Network
FDG-PET	18-fluoro-positron emission tomography
GPOH-HD	German Society of Pediatric Oncology and Hematology Hodgkin Lymphoma
HL	Hodgkin lymphoma
IFRT	Involved-field radiation therapy
OEPA-COPDAC	Vincristine, etoposide, prednisone, doxorubicin – cyclophosphamide, vincristine, prednisone, dacarbazine
OS	Overall survival
PFS	Progression-free survival
PHLC	Pediatric Hodgkin lymphoma Consortium
RT	Radiation therapy

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FIGURE 1.

Flow diagram showing patients who were included in the analysis. *ABVD*; *adriamycin* {*doxorubicin*}, *bleomycin*, *vinblastine*, *dacarbazine*, *HL*; *Hodgkin lymphoma*, *LP*; *lymphocyte predominant*; *OEPA-COPDAC*; *vincristine*, *etoposide*, *prednisone*, *doxorubicin*, *cyclophosphamide*, *vincristine*, *prednisone*, *dacarbazine*, *RT*; *Radiation therapy*

FIGURE 2.

Progression-free survival (PFS) of patients treated with OEPA-COPDAC versus historical control. *OEPA-COPDAC*; vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, vincristine, prednisone, dacarbazine *CI*; confidence interval

FIGURE 3. Overall survival (OS) of patients treated with OEPA-COPDAC versus historical control. *OEPA-COPDAC; vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, vincristine, prednisone, dacarbazine CI; confidence interval*

TABLE 1

Comparison between EuroNet-HD C1 trial treatment schema and DF/BCCBDC institutional standard of care

	EuroNet-HD C1	DF/BCCBDC
Intermediate-Risk		
Stages	IA _E , IB _E , IIA _E IIB, IIIA	IA _E , IB _E , IIA _E IIB, IIIA + <i>IIA bulky disease^a</i>
Treatment	OEPA × 2 + COPDAC × 2 +/- RT	OEPA × 2 + <i>COPDAC × 2-4</i> +/- RT
High-Risk		
Stages	IIB _E , IIIA _E , IIIB, IVA, IVB	IIB _E , IIIB, IVA, IVB
Treatment	OEPA × 2 + COPDAC × 4 +/- RT	OEPA × 2 + COPDAC × 4 +/- RT
Early Response Assessment	After 2 cycles of OEPA	After 2 cycles of OEPA

^a defined as peripheral lymph node aggregate >6cm or mediastinal mass ratio>33%

DF/BCCBDC (Dana-Farber/Boston Children's Cancer and Blood Disorders Center), COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine), EuroNet-HD-C1 (European Pediatric and Adolescent Hodgkin Lymphoma Network C1 trial), OEPA (vincristine, etoposide, prednisone, doxorubicin)

TABLE 2

Patient Characteristics

	OEPA-COPDAC	Historical Cohort	Total	P-value
Number of patients	27	42	69	
Median age in years (range)	16.0 (4.7–21.2)	15.3 (7.5–20.9)	15.6 (4.7–21.2)	NS
Sex (%)				
Male	15(56)	19(45)	34(49)	NS
Female	12(44)	23(55)	35(51)	
Histology (%)				
Nodular sclerosis	24(89)	31(74)	55(80)	NS
B symptoms (%)				
Present	12(44)	18(43)	30(43)	NS
Bulky disease (%)				
Present	8(30)	13(31)	21(30)	NS
Disease distribution (%)				
Intermediate-risk^a	9(33)	29(69)	38(55)	0.004
<i>Stage IIA bulky</i>	4(15)	9 (21)	13(19)	
High-risk^b	18(67)	13(31)	31(45)	
Chemotherapy (%)				
ABVD × 6 cycles	-	12(28)	12(19)	
Stanford V × 12 weeks	-	31(72)	31(48)	
OEPA-COPDAC × 4–6 cycles	27(100)	-	27(33)	
Adequate Early Response^c (%)				
Adequate	15(56)	-	-	NA
Inadequate	12(44)	-	-	
Radiotherapy Omitted (%)				
Yes	15(56)	-	15(22)	<0.001
No	12(44)	42(100)	54(78)	

^a Ann Arbor Stage IAE, IBE IIA with bulk disease (defined as peripheral lymph node aggregate >6cm or mediastinal mass ratio>33%), IIAE IIB or IIIA.

^b Ann Arbor Stage IIB, IIIB, IVA and IVB.

^c Adequate response (FDG-PET Deauville 3 + 75% shrinkage in product of perpendicular diameter on computed tomography)

ABVD (Adriamycin {Doxorubicin}, Bleomycin, Vinblastine, Dacarbazine), NS (Not statistically significant), OEPA-COPDAC (Vincristine, Etoposide, Prednisone, Adriamycin-Cyclophosphamide, Vincristine, Prednisone, Dacarbazine)