Published in final edited form as:

Pediatr Blood Cancer. 2017 December ; 64(12): . doi:10.1002/pbc.26681.

Outcome of Adolescents and Young Adults Compared to Children with Hodgkin Lymphoma Treated with Response-Based Chemotherapy on Pediatric Protocols: A Children's Oncology Group Report

Karen S. Fernández, MD^{1,*}, Cindy L. Schwartz, MD, MPH², Lu Chen, PhD³, Louis S. Constine, MD⁴, Allen Chauvenet, MD⁵, and Pedro A. de Alarcón, MD⁶

¹Valley Children's Healthcare. Cancer and Blood Diseases Center. 9300 Valley Children's Place, Madera, CA

²MD Anderson Cancer Center 1515 Holcombe Blvd Box 87. Houston, TX 77030

³City of Hope and Beckman Research Institute. 1500 East Duarte Road, Duarte, CA 91010

⁴University of Rochester Medical Center. 601 Elmwood Avenue, Box 647, Rochester, NY 14642

⁵Department of Pediatrics. West Virginia University. 830 Pennsylvania Ave, Charleston, WV 25302

⁶University of Illinois College of Medicine at Peoria. 530 NE Glen Oak Ave, Peoria IL 61637

Abstract

PURPOSE—We evaluated the outcome of children (< 15 years) vs. that of adolescents and young adults (AYA; 15–21 years) treated for Hodgkin lymphoma (HL) in two Pediatric Oncology Group (POG)/Children's Oncology Group (COG) clinical trials, P9425 and P9426 that used dose-dense, response-based chemotherapy and reduced dose radiotherapy.

PATIENTS AND METHODS—Subjects 21 years or younger with HL were eligible for these studies. Subjects with low-risk (stage IA, IIA and IIIA₁ without large mediastinal adenopathy biopsy-proven HL, eligible for P9426, were treated with 2 to 4 28-day cycles of doxorubicin, bleomycin, vincristine and etoposide (ABVE) chemotherapy and 25.5 Gy of involved field radiotherapy. Subjects with intermediate-risk (stages IB, IIA, IIIA₁ with large mediastinal adenopathy, and IIIA₂) and high-risk (stages IIB, IIIB and IV) biopsy-proven HL, eligible for P9425, were treated with 3 to 5 21-day cycles of ABVE plus prednisone and cyclophosphamide (ABVE-PC) chemotherapy and 21 Gy of involved region radiotherapy. We compared the 5-year event-free survival (EFS), based on Kaplan-Meier product-limit method, of children vs. that of AYA.

*Correspondence to: Karen S. Fernandez, MD. Valley Children's Healthcare. Cancer and Blood Diseases Center. 9300 Valley Children's Place, Madera, CA 93636. Phone: 559-353-5478 Fax: 559-353-5490. kfernandez@valleychildrens.org.

Previous Presentations:

Part of this manuscript was presented as an oral presentation at the American Society of Hematology in 2012.

The authors have no conflict of interest pertinent to this publication.

RESULTS—Four hundred seventy-one subjects were enrolled on P9425 and P9426 combined. Of these subjects 203 were AYA, 104 with intermediate and high-risk HL and 99 with low-risk HL. The 5-year EFS of children did not significantly differ from that of AYA (85.9% vs. 87.1% respectively) with a median follow up of 7.7 years ($p=0.51$).

CONCLUSION— Given the equivalent and excellent results of therapy, HL represents an opportunity for adult and pediatric cancer treatment collaborative groups to jointly design clinical trials targeted to AYA. These trials should focus on both treatment efficacy, as well as the quality of life of AYA while receiving chemotherapy and in reduction of long-term side effects in the survivorship years.

Keywords

AYA; Hodgkin lymphoma; Pediatric protocols

INTRODUCTION

Hodgkin Lymphoma (HL) is a curable malignancy affecting all age groups; in high-income countries it is the most common malignant disease in adolescents. It is highly sensitive to chemotherapy and radiotherapy with cure rates greater than 80%. Modern treatment strategies for adults and children use somewhat different approaches to achieve these outcomes. Children are now treated with response-based, dose-dense therapies such as ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide), OEPA/COPDac (vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, dacarbazine), or OEPA/COPP (vincristine, etoposide, prednisone, doxorubicin, cyclophosphamide, procarbazine), regimens designed to optimize the balance between enhanced efficacy and reduced toxicity. Adults in the US receive 4–8 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) based on stage and response while the dose-intensive escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine) has been the primary approach for European adults with high-risk disease^{1,2,3,4}.

The treatment for adolescent/young adult patients (AYA) ages 15–22 years has been determined by whether these young patients are referred to pediatric or medical oncologists. Eichenauer and Foltz showed progression-free survivals (PFS) of 76–80% for patients ages 15–18 vs. 22–45 using a variety of adult regimens. These data were used to justify the treatment of adolescents with adult regimens without consideration of potential benefits of pediatric specific HL therapies in terms of efficacy, reduction of late effects, or quality of life. Muller et. al. reported, however, that adolescents age 14–21 treated with a pediatric regimen had better event free survival (EFS) at 5 and 10 years than those treated with an adult regimen (ABVD)^{5,6,7}.

In this report, we compared the outcomes of children vs. AYA enrolled on two concurrent Pediatric Oncology Group (POG) trials for low-risk (P9426) and intermediate/high-risk (P9425) HL^{1,5,6,8}.

ABVE (doxorubicin, bleomycin, vincristine and etoposide) was used in P9426, while ABVE-PC (ABVE, prednisone, cyclophosphamide) was used in P9425. The dose of each chemotherapeutic drug in ABVE and ABVE-PC was specifically selected to limit the cumulative dose below recognized thresholds for known long-term toxicities^{1,8}. Radiation dose was also reduced relative to contemporaneous adult regimens. In these trials, dose density was introduced to enhance early response rates. Using response-based therapy, the total amount of chemotherapy was reduced for those patients achieving a rapid response. A secondary effect was the short duration of therapy (8–9 weeks of chemotherapy) for early responders, enabling AYA to return to peers, school and work more rapidly.

If the results for children and adolescents are similar on the pediatric regimens, then it is reasonable to directly compare pediatric vs. adult regimens based on overall efficacy, long-term toxicity, and quality of life in the specific context of AYA. The excellent outcomes for HL should encourage maximal cooperation between adult and pediatric investigators to ensure that we are delivering the optimal therapies to all AYA. We report herein our analysis of the outcome of pediatric vs. AYA patients treated on P9425 and P9426 trials with the intent of assessing the value of treating AYA according to these pediatric regimens.

METHODS

Subjects

Subjects 21 years or younger with histologically proven HL were eligible for these studies. Informed consent was obtained according to institutional review board standards. Eligibility criteria for P9426 included low-risk stages IA, IIA, and IIIA₁ (involvement of splenic, celiac or portal nodes) without bulk lymph nodes (peripheral nodal tissue < 6 cm in diameter or large mediastinal adenopathy with a ratio of mass/thoracic diameter [M/T ratio] < 0.33). Lymphocyte-predominant HL was excluded from P9426 during the early years of the study. Eligibility for P9425 included stages IB, IIA with bulk lymph nodes (peripheral nodal tissue > 6 cm or M/T ratio > 0.33), IIIA₁ with bulky lymph nodes in the intermediate-risk group and; IIB, IIIB, IVA and IVB in the high-risk group. From Nov 1999 through completion in March 2001, P9425 enrollment was restricted to disease stages IIB, IIIB, or IV.

Therapy

The ABVE chemotherapy regimen in P9426, a modification of ABVD, replaced vinblastine and dacarbazine with vincristine and etoposide to maintain dose-intensity while avoiding delays and reductions of therapy attributable to myelosuppression. For P9425 ABVE-PC chemotherapy regimen eliminated procarbazine and limited doses of doxorubicin and etoposide to decrease long-term adverse events. Patients received two ABVE cycles (P9426) or three ABVE-PC cycles (P9425) before early response evaluation (Figure 1). Rapid early responders (RER) (< 50% two-dimensional reduction in tumor size, M/T ratio < 0.33, and negative gallium scan) proceeded to radiotherapy 25.5 Gy to the involved nodal chains defined prior to chemotherapy (involved field radiotherapy [IFRT]) for those subjects on P9426 or 21 Gy to involved and adjacent nodal chains (involved region radiotherapy) for those on P9425. Two additional chemotherapy cycles were given to slow early responders (SER) before the same radiotherapy. Subjects received granulocyte colony-stimulating factor

(5 µg/kg/day) to maintain dose intensity with chemotherapy cycles of 21 days in P9425. Patients were randomly assigned to receive or not receive dexrazoxane (300 mg/m² intravenously) with every dose of doxorubicin (Figure 1).

Statistical methods

We retrospectively analyzed the two POG studies: P9425 and P9426 and compared the survival rate of children to the survival rate of AYA. For the purpose of our analysis, children were defined as subjects <15 years of age at diagnosis and AYA as those 15 to 21 years of age at diagnosis. Demographic variables were compared between the two age groups by Chi-square test. Event-free survival (EFS) was defined as the minimum time from study enrollment to disease relapse/progression, second malignancy, or death due to any cause. Overall survival (OS) was defined as time from study entry to death from any cause or until last contact if subject did not die. Subjects without these events were censored at the time of last contact. EFS estimates were based on Kaplan-Meier product-limit method with confidence interval based on the “exponential” Greenwood formula⁹. The log rank test was used to investigate differences in EFS outcomes between groups.

Cox proportional Hazards model was used to examine the association between multiple risk factors and EFS¹⁰. Patient follow-up was collected through June 2008. All p-values were 2-sided and p value <0.05 was considered statistically significant. All analyses were performed in Stata version 12 (StataCorp. College Station, TX).

RESULTS

From October 1996 through September 2000, P9426 enrolled 294 subjects, with 255 eligible subjects. From March 1997 through March 2001, P9425 enrolled 219 subjects, with 216 eligible subjects, 53 with intermediate-risk and 163 with high-risk disease.

Of 471 eligible subjects treated on P9425 and P9426 combined, 203 were AYA, including 104 with intermediate and high-risk HL and 99 with low-risk HL. Table 1 shows subject characteristics by the two age groups. On P9425, 48% (104/216) were AYA, compared to 38% (99/255) AYA on P9426 (p=0.042).

Overall there were more males than females enrolled in these studies. This was primarily attributable to the male dominance in the younger cohort (67.2 % vs. 54.2%, p=0.004). The most common histology in both groups was nodular sclerosis (NS). The distribution of histology differed between the 2 groups (p<0.001), with AYA having a higher proportion of NS subjects (89.5% vs. 68.3%) and a lower proportion of Lymphocyte Predominant (LP) and Mixed Cellularity (MC) histology combined (10.5% vs. 31.7%).

The 5-year EFS of AYA compared to children treated on P9425 and P9426 combined was 85.9% (95% CI 80.2%–90.0%) vs. 87.1% (95% CI 82.4%–90.6%) respectively. With a median follow-up of 7.7 years (range 1.4–10.9 years), there was no difference in EFS of AYA vs. younger children (p =0.51) overall or within each risk group.

The 5-year EFS for AYA vs. children on P9426 was 87.2% (95% CI: 78.5–92.6%) vs. 88.9% (95% CI: 82.7%–92.9%), and the OS was 97.9% (95% CI: 92.0–99.5%) vs. 97.4% (95% CI:

93.2–99.0%); for P9425 the 5-year EFS of AYA vs. children was 84.5% (95% CI: 75.9%–90.2%) vs. 84.7% (95% CI: 76.5%–90.2%); and the OS was 92.9% (95% CI: 85.7–96.6%) vs. 95.4% (95% CI: 89.3–98.1%). Figure 2 shows the EFS curves by study and age. Comparison of the EFS curves between AYA and children with low-risk vs. the combined curves of intermediate and high-risk showed a P value of 0.68, and 0.70, respectively.

The evaluation of response to therapy according to study/risk group did not differ between AYA vs. children for P9425. For P9426 the RER rate was 50.3% for children vs. 37.8% for AYA ($p=0.052$). While this univariate analysis is of borderline significance, the data was not corrected for histology which may account for the difference in response. In the low-risk group the histological subtype for children was NS in 49.4% (77/156), MC in 27.6% (43/156) and LP in 14.1% (22/156), compared to AYA with NS in 79.8% (79/99), MC in 11% (11/99) and LP in 4.0% (4/99) ($p<0.001$). For P9426, univariate analysis showed an RER rate for NS patients of 48.6% (36/74) for children vs. 32.1% (25/78) for AYA ($p=0.037$); for MC/LP patients the RER rate was 53.1% (34/64) for children vs. 60.0% (9/15) for AYA ($p=0.63$). However, in multivariate Cox regression analysis where gender, histology, risk group, early response, and age-group are all included in the analysis, age-group (AYA vs. children) did not predict EFS (Hazard Ratio (HR)=1.02, $p=0.93$), nor did gender (male vs. female, HR=1.05, $p=0.86$), risk group (intermediate vs. low, HR=1.39, $p=0.38$; high vs. low, HR=1.00, $p=0.99$), or SER vs. RER (HR=1.29, $p=0.31$). Histologic subtype (NS vs. Other, HR=2.01, $p=0.069$) was of borderline significance in this analysis.

DISCUSSION

With overall survival for AYA with HL exceeding 90% in most trials, the future goals of clinical trials must not focus only on treatment efficacy, but also on the benefits of each approach. The quality of life for AYA, while receiving chemotherapy and the reduction of long term long-term side effects in the survivorship years is critically important. These important parameters will need to be addressed when treating AYA if the expectation is that disease outcomes are similar on all treatment regimens.

In this report we present our combined analysis of the EFS and OS of AYA vs. younger children in the clinical trials P9426 and P9425 for the treatment of HL. We did not find a statistically significant difference between the EFS and OS of AYA vs. younger children either in the combined analysis or in analysis of each protocol separately.

The studies of Eichenouar and Foltz show that adolescents and adults have similar outcomes when treated on the same regimens. However, a trial from Hungary found that the EFS of AYA was inferior when treated with an adult based treatment regimens compared to a more dose intensive pediatric regimen. Yung et. al. reported that outcome for British adolescents age 15–17 years treated according to older adult protocols was inferior to that reported in the literature for children^{5,6,7,11}. These findings may reflect benefit of dose intensive therapies for AYA, but a direct comparison of pediatric and adult regimens could be impacted if there is truly a different response to therapy based on age. Such analyses also will need to take into account the impact of histology differences between children and AYA. Our study did not show evidence of an effect of histologic subtype in this pediatric/adolescent cohort.

AYA have equivalent results to adults when they are treated with a treatment regimen commonly used to treat adult subjects with HL^{5,6}. They also have similar EFS and OS to children when treated with a pediatric treatment regimen. The results obtained with either approach are excellent with OS greater than 80%. If this similarity of disease outcomes were confirmed, then the effect of different regimens in terms of quality of life and long term survival becomes the major differentiator.

Excellent results come at a price. Both chemotherapy and radiotherapy have serious long-term adverse events including cardiac, endocrine, pulmonary complications and risk for second malignancies. Given the excellent results of therapy, future clinical trials must take into consideration decreasing long-term adverse effects of therapy while preserving the excellent OS. P9426 and P9425 were designed with these principles in mind^{1,9}. P9426 for low-risk HL decreased the amount of medication based on response and substituted etoposide for dacarbazine from the ABVD regimen. P9425 eliminated procarbazine to protect fertility, but also intensified and compressed therapy per cycle with the intent of increasing the number of subjects achieving RER and thus decreasing the overall exposure to therapy (Table 2). Radiation doses and fields were also decreased when compared to the contemporaneous adult-based clinical trials. Both protocols were successful in decreasing total dose of therapy for over 50% of the subjects treated (RER) while preserving an excellent EFS and OS. The rapid delivery of therapy to AYA on these trials (with RER requiring only 8–9 weeks of chemotherapy prior to radiation), also may minimize the acute impact of cancer on quality of life, facilitating earlier re-entry to school, work, and other social activities. This will impact the long-term social, occupational and economic outcomes of HL therapy. More recent pediatric trials maintain this approach of dose-dense therapies, but have also identified cohorts who do not need any radiation¹².

It has been recognized that AYA often are not enrolled in clinical trials, limiting the possibility of developing therapies that are optimized to address their medical and psychosocial needs^{13,14}. Our analysis as well as those by Eichenauer and Foltz point to the need of collaboration between adult and pediatric clinical trial groups^{5,6}. HL represents an opportunity for these groups to jointly design clinical trials targeted to AYA. The focus of upcoming trials should be placed not only in treatment efficacy but also in the quality of life of AYA during therapy but equally important in the reduction of long-term side effects in the survivorship years.

Acknowledgments

Research Support:

Research support from COG grants U10CA180886, U10CA18899, U10CA098413

The primary author is supported by the Jim and Katie Owens Professorship Endowment

Abbreviations

ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
ABVE	Doxorubicin, Bleomycin, Vincristine and Etoposide

ABVE-PC	Doxorubicin, Bleomycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide
AYA	Adolescents Young Adults
BEACOPP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone and Procarbazine
COG	Children's Oncology Group
EFS	Event Free survival
HL	Hodgkin Lymphoma
IFRT	Involved Field Radiation Therapy
LP	Lymphocyte Predominant
MC	Mixed Cellularity
M/T	Mass/Toracic Ratio
NS	Nodular Sclerosis
OEPA/COPP	Vincristine, Etoposide, Prednisone, Doxorubicin, Cyclophosphamide, Procarbazine
OEPA/COPDac	Vincristine, Etoposide, Prednisone, Doxorubicin, Cyclophosphamide, Dacarbazine
OS	Overall Survival
PFS	Progression Free Survival
POG	Pediatric Oncology Group
RER	Rapid Early Response
SER	Slow Early Response

References

1. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood*. Sep 3; 2009 114(10):2051–2059. [PubMed: 19584400]
2. Mauz-Korholz C, Hasenclever D, Dorffel W, et al. Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: the GPOH-HD-2002 study. *J Clin Oncol*. Aug 10; 2010 28(23):3680–3686. [PubMed: 20625128]
3. Bonadonna G, Santoro A. ABVD chemotherapy in the treatment of Hodgkin's disease. *Cancer Treat Rev*. 1982; 9:21–35.
4. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med*. Jun 12; 2003 348(24):2386–2395. [PubMed: 12802024]

5. Eichenauer DA, Bredenfeld H, Haverkamp H, et al. Hodgkin's lymphoma in adolescents treated with adult protocols: a report from the German Hodgkin study group. *J Clin Oncol.* Dec 20; 2009 27(36): 6079–6085. [PubMed: 19901121]
6. Foltz LM, Song KW, Connors JM. Hodgkin's lymphoma in adolescents. *J Clin Oncol.* Jun 1; 2006 24(16):2520–2526. [PubMed: 16735704]
7. Muller J, Molnar Z, Illes A, et al. Hodgkin's lymphoma in adolescents: where to treat it—in an adult or pediatric institution? *Orv Hetil.* 2008; 149(47):2221–7. doi: 10.1556. [PubMed: 19004744]
8. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2012; 59(7):1259–1265. [PubMed: 22911615]
9. Kalbfleisch, JD., R, L. Prentice The statistical analysis of failure time data. New York: John Wiley & Sons; 1980.
10. Cox D. Regression Models and Life-Tables. *J R Stat Soc series.* 1972; B34(2):187–220.
11. Yung L, Smith P, Hancock BW, et al. Long term outcome in adolescents with Hodgkin's lymphoma: poor results using regimens designed for adults. *Leuk Lymphoma.* Aug; 2004 45(8): 1579–1585. [PubMed: 15370209]
12. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol.* 2014 Nov 10; 32(32):3651–8. [PubMed: 25311218]
13. Tai E, Beaupin L, Bleyer A. Clinical trial enrollment among adolescents with cancer: supplement overview. *Pediatrics.* 2014; 133(Suppl 3):S85–90. [PubMed: 24918212]
14. Herbertson R, Hancock BW. Hodgkin Lymphoma in adolescents. *Cancer Treat Rev.* Aug. 2005; 31(5):339–360.

P9425 Intermediate Risk: IB, IIA-LMA High Risk: IIB, IIIB, IVA, IVB

P9426 Low Risk: IA, IIA and IIIA

Figure 1. Treatment Schemas

ABVE-PC= Adriamycin, Bleomycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide

RER = Rapid early response

SER = Slow Early Response

RT= radiotherapy

ABVE= doxorubicin, bleomycin, vincristine, etoposide

ABVE-PC= ABVE, prednisone, cyclophosphamide

RER= rapid early response

SER= slow early response

Figure 2. Outcome of AYA vs Children treated with P9425 and P9426 Protocols. **A)** EFS of AYA vs children in P9425 and P9426 combined **B)** EFS and OS of AYA vs children in P9425 **C)** EFS and OS of AYA vs children in P9426

Table 1

Patient Characteristics

	< 15 years N %	15 years N %	Total N %	P*
STUDY				0.042
P9425	112 41.8%	104 51.2%	216 45.8%	
P9426	156 8.2%	99 48.8%	255 54.2%	
GENDER				0.004
Male	180 67.2%	110 54.2%	290 61.6%	
Female	88 32.8%	93 45.8%	181 38.4%	
HISTOLOGY**				<0.001
Nodular Sclerosis	170 67.7%	171 87.7%	341 76.4%	
Mixed Cellularity	57 22.7%	16 8.2%	73 16.4%	
Lymphocyte Predominant	22 8.8%	4 2.1%	26 5.8%	
Lymphocyte Depleted	2 0.8%	4 2.1%	6 1.4%	
RISK				0.091
Low Risk (POG9426) (IA, IIA, IIIA1 without LMA)	156 58.2%	99 48.8%	255 54.1%	
Intermediate Risk (POG9425) (IB, IIA-LMA, IIIA1-LMA, IIIA2)	30 11.2%	23 11.3%	53 11.3%	
High Risk (POG9425) (IIB, IIIB, IV)	82 30.6%	81 39.9%	163 34.6%	

* Based on Chi-square test

** Among patients with available central pathology review or early response data

Comparison of cumulative doses of chemotherapy used in pediatric (P) vs adult (A) regimens

Table 2

	Low-Stage HL Regimens		Advanced- Stage HL Regimens			
	P (P9426)	A	P (P9425)	A	A	
	ABVE ⁵ 2/4 cycles	ABVD ¹⁶ 2 cycles	ABVE-PC ⁷ 3/5 cycles	ABVD ¹⁶ 4 - 6 cycles	Esc BEACOPP × 2 ¹⁶ ABVD × 2	
Adriamycin	100/200	100	180/300	200/300	170	
Bleomycin	40/80	20	45/75	40/60	40	
Vincristine	6/12	0	8.4/13	0	2.8	
Vinblastine	0/0	24	0	48/72	24	
Dacarbazine	0/0	1400	0	2800/4200	1400	
Etoposide	1000/2000	0	1125/1875	0	1200	
Prednisone	0/0	0	1200/2000	0	560	
Cyclophosphamide	0/0	0	2400/4000	0	2500	
Procarbazine	0/0	0	0	0	1400	
Radiation dose	25.5 Gy	20 - 30 Gy	y	30 - 36 Gy	30 - 36 Gy	