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

Debra L. Friedman, Lu Chen, Suzanne Wolden, Allen Buxton, Kathleen McCarten, Thomas J. FitzGerald, Sandra Kessel, Pedro A. De Alarcon, Allen R. Chen, Nathan Koberinsky, Peter Ehrlich, Robert E. Hutchison, Louis S. Constine, and Cindy L. Schwartz

Listen to the podcast by Dr Mauz-Koerholz at www.jco.org/podcasts

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on October 13, 2014.

Presented as an abstract at the 52nd American Society of Hematology Annual Meeting, Orlando, FL, December 4-7, 2010.

Supported by National Cancer Institute Grant No. U10 CA98543 to the Children's Oncology Group Chair.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00025259

Corresponding author: Debra L. Friedman, MD, MS, Division of Pediatric Hematology/Oncology, Vanderbilt-Ingram Cancer Center, 397 Preston Research Building, 2220 Pierce Ave, Nashville, TN 37232; e-mail: debra.l.friedman@vanderbilt.edu.

© 2014 by American Society of Clinical Oncology

0732-183X/14/3232w-3651w/\$20.00

DOI: 10.1200/JCO.2013.52.5410

ABSTRACT

Purpose

The Children's Oncology Group study AHOD0031, a randomized phase III study, was designed to evaluate the role of early chemotherapy response in tailoring subsequent therapy in pediatric intermediate-risk Hodgkin lymphoma. To avoid treatment-associated risks that compromise long-term health and to maintain high cure rates, dose-intensive chemotherapy with limited cumulative doses was used.

Patients and Methods

Patients received two cycles of doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone (ABVE-PC) followed by response evaluation. Rapid early responders (RERs) received two additional ABVE-PC cycles, followed by complete response (CR) evaluation. RERs with CR were randomly assigned to involved-field radiotherapy (IFRT) or no additional therapy; RERs with less than CR were nonrandomly assigned to IFRT. Slow early responders (SERs) were randomly assigned to receive two additional ABVE-PC cycles with or without two cycles of dexamethasone, etoposide, cisplatin, and cytarabine (DECA). All SERs were assigned to receive IFRT.

Results

Among 1,712 eligible patients, 4-year event-free survival (EFS) was 85.0%: 86.9% for RERs and 77.4% for SERs ($P < .001$). Four-year overall survival was 97.8%: 98.5% for RERs and 95.3% for SERs ($P < .001$). Four-year EFS was 87.9% versus 84.3% ($P = .11$) for RERs with CR who were randomly assigned to IFRT versus no IFRT, and 86.7% versus 87.3% ($P = .87$) for RERs with positron emission tomography (PET)–negative results at response assessment. Four-year EFS was 79.3% versus 75.2% ($P = .11$) for SERs who were randomly assigned to DECA versus no DECA, and 70.7% versus 54.6% ($P = .05$) for SERs with PET-positive results at response assessment.

Conclusion

This trial demonstrated that early response assessment supported therapeutic titration (omitting radiotherapy in RERs with CR; augmenting chemotherapy in SERs with PET-positive disease). Strategies directed toward improved response assessment and risk stratification may enhance tailoring of treatment to patient characteristics and response.

J Clin Oncol 32:3651-3658. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Pediatric Hodgkin lymphoma (HL) is highly curable, but for a meaningful minority, recurrent disease¹ and therapy-associated adverse health outcomes²⁻¹¹ remain a challenge.

To balance efficacy with toxicity, risk-adapted HL therapy has successfully used presenting characteristics and chemotherapy response.¹²⁻²⁷ Early response (ER) to chemotherapy is predictive of long-term outcome²⁵⁻²⁷ and can help physicians to tailor subsequent therapy.^{12,16} Postchemotherapy

Fig 1. Study schema. ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone; CR, complete response; DECA, dexamethasone, etoposide, cisplatin, and cytarabine; IFRT, involved-field radiation therapy; PD, progressive disease; RER, rapid early responder; SER, slow early responder.

response has informed radiotherapy planning,^{13,14,18,20} but ER, a measure of chemosensitivity, may be more informative.

We designed the first pediatric Hodgkin lymphoma study with randomized therapy stratification on the basis of ER to dose-intensive chemotherapy, with therapy reduction for rapid early responders (RERs) to decrease risk of adverse health sequelae and therapy augmentation for slow early responders (SERs) to improve cure.

PATIENTS AND METHODS

Children's Oncology Group (COG) study AHOD0031, approved by the National Cancer Institute and participating institutional review boards, enrolled patients from September 2002 through July 2009.

Patients

Eligible patients included those younger than age 22 years with newly diagnosed, biopsy-proven HL, Ann Arbor²⁸ stages IB, IAE, IIB, IIAE, IIIA, IVA with or without bulk disease, and IA or IIA with bulk disease. Staging was determined with contrast-enhanced computed tomography (CT) scanning and bilateral bone marrow biopsies. B symptoms included weight loss > 10%, unexplained recurrent fever > 38°, or drenching night sweats. Bulk disease included a mediastinal mass with diameter greater than one third of the thoracic diameter on an upright anterior-posterior (AP) chest radiograph or extramediastinal nodal aggregate > 6 cm in the longest transverse diameter on axial CT.

Treatment

Patients received two cycles of doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone (ABVE-PC) followed by ER evaluation (Fig 1). RERs received two additional ABVE-PC cycles followed by complete response (CR) evaluation. RERs with CR were randomly assigned to undergo involved-field radiotherapy (IFRT) or observation; RERs with less than CR were nonrandomly assigned to receive IFRT. SERs

were randomly assigned to receive or not receive two cycles of dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by two ABVE-PC cycles. All SERs were assigned to receive IFRT. ABVE-PC and DECA cycles were delivered at 21-day intervals with granulocyte colony-stimulating factor support.

IFRT consisted of 21 Gy in 14 fractions of 1.5 Gy per day using AP/PA techniques and was scheduled to begin within 4 weeks after chemotherapy completion. Compliance with protocol-specified fields was ensured by mandated central review by the Quality Assurance Review Center (QARC). Treatment was limited to involved areas of disease at presentation. Gross tumor volume included any lymph nodes measuring > 1.5 cm in a single axis on CT. Clinical target volume included the anatomic compartment containing involved nodes. The planning target volume was determined by the addition of a 1.0-cm margin around the clinical target volume to account for patient motion and set-up variability, with allowable modification at the discretion of the treating radiation oncologist with concern for extended treatment of normal tissue. If assigned to IFRT, patients with pulmonary metastases received 10.5 Gy of whole-lung radiation, regardless of resolution of pulmonary lesions, and those with liver metastases received 15 Gy to the entire liver; partial transmission blocks were used for both sites.

Treatment Change During Study Period

At study onset, initial chemotherapy treatment included three cycles of ABVE-PC; SERs were randomly assigned to receive or not receive two DECA cycles, and all patients received one additional ABVE-PC cycle. Among the first 108 patients, there were 100 RERs and eight SERs, which differed from the predicted 80% to 20% RER-SER distribution, suggesting three-cycle response was insufficiently discriminatory for therapy stratification. In July 2003, AHOD0031 was amended so that ER was determined after two ABVE-PC cycles. The 100 RERs with three-cycle ER were not included in IFRT comparison analyses, given that two-cycle ER was unknown. The eight SERs with three-cycle ER were included in the DECA comparison, given that two-cycle ER would not have differed (Fig 2).

Fig 2. CONSORT diagram. ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone; CR, complete response; DECA, dexamethasone, etoposide, cisplatin, and cytarabine; ER, early response; IFRT, involved-field radiation therapy; RER, rapid early responder; SER, slow early responder.

Central Review

ER status was determined by CT scan, and CR status was determined by CT and gallium or [^{18}F]fluorodeoxyglucose–positron emission tomography (FDG-PET) scanning. Functional imaging was requested but not required after two ABVE-PC cycles. With rising PET availability in institutions, PET was often assessed at this time point as well; these assessments were referred to as PET-2. ER determination was initially conducted at the institutional level. The study was amended in March 2006 to mandate QARC central review of ER. QARC reviewed all RERs for CR status at the completion of four ABVE-PC cycles, with review of the institutional gallium or PET scan for RERs with CR. FDG-PET examinations were analyzed at QARC using MIMvista (MIMvista, Cleveland, OH), which allowed consistent manipulation of data sent from many different scanners from various vendors. FDG-PET avidity was judged in comparison with background blood pool activity. Only patients with QARC-confirmed CR were eligible for IFRT random assignment.

Response Criteria

RER. Patients were determined to have a rapid early response if, on CT scan, regardless of PET response, a 60% or greater reduction was found in the product of perpendicular diameters (PPD) for all target lesions or there was a return to normal size after two ABVE-PC cycles.

SER. Patients were considered to have a slow early response if rapid early response was not achieved.

CR. Patients were determined to have CR if there was an 80% or greater reduction in the PPD or a return to normal size for all target lesions, plus no residual extramediastinal nodal mass > 2.0 cm, no residual disease in nonmeasurable sites, and a negative gallium or FDG-PET scan.

Progressive Disease. Progressive disease (PD) was considered as a 50% or greater increase in the PPD of any nodal mass or organ lesions; a new lesion(s); or progression of a nonmeasurable disease site.

Statistical Analyses

The primary study questions were randomized comparisons of IFRT or no IFRT in RERs with CR and DECA or no DECA in SERs. The primary end point was **event-free survival** (EFS). Events included relapse/progression, second malignant neoplasm (SMN), and death. The accrual target was 1,700 patients with an estimated 640 randomly assigned RERs with CR and 320 randomly assigned SERs. Power estimation was based on one-sided log-rank test, assuming 7.5 years of accrual and 1 year of follow-up after the last accrual, providing approximately 88% power to detect a 5% decrease in EFS for no IFRT (93% v 88%) and a 10% increase in EFS for DECA (82% v 92%) with the assumption of seven of eight failures occurring before 3 years. The overall α

levels were .20 and .05 for the IFRT and DECA comparisons, respectively. Interim efficacy monitoring was planned and performed annually on the basis of the Lan-Demets method with spending function α^2 .²⁹ The prespecified monitoring boundary nominal *P* values at years 1 through 7 were .003, .010, .019, .034, .053, .077, and .104, respectively, for IFRT comparisons, and .001, .002, .004, .008, .012, .017, and .022, respectively, for DECA comparisons. With interim monitoring, the nominal *P* values needed to establish significant differences at the final analysis were .167 and .035 for IFRT and DECA comparisons, respectively. Analyses were based on intention to treat. EFS and overall survival (OS) were computed using the Kaplan-Meier product limit estimator³⁰ from the time of study enrollment or time of random assignment, as appropriate. Log-rank tests were used to compare EFS or OS between groups.³¹ *P* values were two-sided, except for the two primary comparisons that were based on one-sided tests per the original study design.

We also conducted exploratory analyses, including only patients for whom data indicated compliance with random assignment and excluding patients with either incomplete data or data indicating noncompliance.

RESULTS

Patients and Staging

Among 1,734 enrolled patients, 1,712 were eligible, given that 18 did not meet diagnosis criteria, one received a pretreatment corticosteroid, and three did not have all required pretreatment evaluations (Fig 2; Table 1).

Mean and median ages at diagnosis were 14.6 and 15.2 years (range, 1.9 to 21.9 years), respectively. Pathologies included 80.8% nodular sclerosis, 9.1% mixed cellularity, 5.7% lymphocyte predominant, 0.2% lymphocyte depleted, and 4.2% not specified by institution. Stages included 4.8% stage IA bulk, 35.9% IIA bulk, 1.6% IAE/IIAE, 0.9% IB, 21.3% IIB, 20.6% IIIA, and 14.8% IVA.

Therapy Response and Study Withdrawal

There were 1,369 RERs (100 with post-cycle-3 response) and 305 SERs (eight with post-cycle-3 response; Fig 2). Of the 1,369 RERs, 762 had CR and were randomly assigned to receive or not receive IFRT; 571 had less than CR and were nonrandomly assigned to IFRT. An additional 36 RERs withdrew before radiotherapy random assignment because of PD (*n* = 3), physician decision (*n* = 4), patient decision (*n* = 14), loss to follow-up (*n* = 1), receipt of nonprotocol therapy (*n* = 3), and for reasons unknown (*n* = 11). Of 305 SERs, 304 were randomly assigned to receive or not receive DECA.

Thirty-eight patients withdrew after ER determination because of PD (*n* = 1), death (*n* = 1), other toxicity (*n* = 2), physician decision (*n* = 12), patient decision (*n* = 10), loss to follow-up (*n* = 2), receipt of nonprotocol therapy (*n* = 2), and for reasons unknown (*n* = 8).

Survival

EFS and OS are at 4 years on the basis of March 2012 data, at which time, among all patients who were alive at last follow-up, 65% had contact within 1 year and 77% had contact within 2 years. Among patients who were enrolled onto the study within 5 years of March 2012 and were alive at last contact, 82% had contact within 1 year and 91% had contact within 2 years. Median follow-up for patients censored for EFS or OS is 4.2 years.

There were 260 first events, which included relapse/progressive disease (*n* = 242), SMN (*n* = 11), or death (*n* = 7). This resulted in EFS of 85.0% (95% CI, 83.2% to 86.7%). There were an additional 35 patients who died after another event (relapse only³⁰; SMN only³;

Table 1. Study Participants

Characteristic	No.	%
Age, years		
0-4	29	1.7
5-9	147	8.6
10-14	641	37.4
15-21	895	52.3
Sex		
Male	908	53.0
Female	804	47.0
Race		
White	1,334	77.9
Black	189	11.0
American Indian/Alaskan Native	4	0.2
Asian	49	2.9
Native Hawaiian/Pacific Islander	6	0.4
Other/not reported	130	7.6
Ethnicity		
Non-Hispanic	1,405	82.1
Hispanic	257	15.0
Not reported	50	2.9
Stage		
I	98	5.7
II	1,006	58.8
III	354	20.7
IV	254	14.8
Histology		
Nodular sclerosis	1,383	80.8
Mixed cellularity	156	9.1
Lymphocyte predominant	97	5.7
Lymphocyte depleted	4	0.2
Unknown/unreported	72	4.2
B symptoms		
Yes	381	22.2
No	1,327	77.5
Not reported	4	0.2
Bulk disease		
Yes	1,257	73.4
No	435	25.4
Not reported	20	1.2

relapse and SMN²), resulting in OS of 97.8% (95% CI, 97.0% to 98.5%; Fig 3A).

Early response was an important prognostic factor; EFS and OS were significantly higher in RERs versus SERs (Fig 3B). In RERs, EFS and OS were 86.9% (95% CI, 84.8% to 88.7%) and 98.5% (95% CI, 97.6% to 99.1%), respectively. In SERs, EFS and OS were 77.4% (95% CI, 72.0% to 81.9%) and 95.3% (95% CI, 92.0% to 97.2%), respectively.

With respect to the IFRT random assignment, EFS was 87.9% (95% CI, 83.7% to 91.1%) in those receiving radiotherapy versus 84.3% (95% CI, 79.8% to 87.9%) in those with chemotherapy alone (*P* = .11). OS for those receiving IFRT versus chemotherapy alone was 98.8% (95% CI, 96.8% to 99.5%) versus 98.8% (95% CI, 96.9% to 99.6%), respectively (*P* = .51; Fig 3C). EFS and OS did not significantly change with inclusion of patients with ER at three cycles or patients who were noncompliant with the IFRT random assignment.

For the DECA random assignment among SERs, EFS for those receiving DECA was 79.3% (95% CI, 71.6% to 85.1%) compared with 75.2% (95% CI, 67.3% to 81.4%) in those who did not receive DECA

Fig 3. Event-free survival (EFS) and overall survival (OS). (A) EFS and OS for the entire study cohort. (B) EFS and OS for two-cycle rapid early responders (RERs) and slow early responders (SERs; EFS, $P < .001$; OS, $P < .001$). (C) EFS and OS by involved-field radiation therapy (IFRT) random assignment for RERs with complete remission (EFS, $P = .11$; OS, $P = .51$). (D) EFS and OS by dexamethasone, etoposide, cisplatin, and cytarabine (DECA) random assignment for SERs (EFS, $P = .11$; OS, $P = .16$). (E) EFS by IFRT random assignment for RERs with complete remission and negative (neg) cycle-2 positron emission tomography (PET) results ($P = .87$) and for RERs with complete remission and positive/equivocal (pos/equ) cycle-2 PET results ($P = .80$). (F) EFS by DECA random assignment for SERs with neg cycle-2 PET ($P = .54$) and for SERs with pos/equ cycle-2 PET results ($P = .05$).

($P = .11$). OS did not differ between those receiving or not receiving DECA: 96.5% (95% CI, 91.7% to 98.5%) versus 94.3% (95% CI, 88.9% to 97.1%), respectively ($P = .16$; Fig 3D). EFS and OS did not significantly change when the analysis was limited to patients who were compliant with random assignment.

Because of the era of the study, FDG-PET was not required for ER determination. However, 1,135 patients had a PET-2 evaluation (PET assessment after two ABVE-PC cycles), of whom 746 were eligible for the two random assignments in the study.

In 550 RERs with CR, PET-2 results did not affect EFS for the IFRT random assignment. Among patients with PET-2–negative results, EFS with and without IFRT was 86.7% (95% CI, 80.7% to 90.9%) versus 87.3% (95% CI, 81.7% to 91.3%), respectively ($P = .87$). Among patients with PET-2–positive results, EFS with and without IFRT was 83.1% (95% CI, 69.9% to 90.8%) versus 78.1% (95% CI, 62.3% to 87.9%), respectively ($P = .80$; Fig 3E).

PET-2 results were available for 196 SERs who were randomly assigned to receive or not receive DECA. Among SERs with PET-2–negative results, EFS with DECA was 90.1% (95% CI, 77.9% to 95.8%) and without DECA, 85.6% (95% CI, 73.2% to 92.5%; $P = .54$). Among SERs with PET-2–positive results, EFS with DECA was 70.7% (95% CI, 52.7% to 82.9%); this was marginally superior to EFS without DECA, which was 54.6% (95% CI, 37.3% to 69.0%; $P = .05$; Fig 3F).

Toxicity

During therapy, 83.8%, 24.9%, and 16.9% of participants reported grade 3 or higher hematologic toxicity, febrile neutropenia, and infection, respectively. Seven deaths occurred as first events as a result of infection ($n = 2$), car accident ($n = 2$), seizure (known seizure disorder; $n = 1$), and cause unknown ($n = 2$). Infectious deaths were each a result of Gram-negative sepsis and candidemia in the setting of nonprolonged neutropenia. Eleven SMNs occurred as first events: basal cell carcinoma ($n = 1$), mycosis fungoides ($n = 1$), thyroid cancer ($n = 1$), testicular cancer ($n = 1$), leukemia/myelodysplastic syndrome (MDS; $n = 3$), lymphoma ($n = 3$), and osteosarcoma ($n = 1$). Two additional SMNs (synovial sarcoma and MDS) occurred after relapse treatment in patients treated with radiotherapy. All but one patient received radiotherapy. The thyroid cancer and sarcoma were within radiotherapy fields.

DISCUSSION

This is the largest pediatric HL phase III trial to be conducted, and the only study using a dose-intensive chemotherapy regimen with randomized ER-directed titration of therapy, to our knowledge. We demonstrated that ER to chemotherapy is prognostic of EFS and OS and can be used to tailor therapy. We identified a population of intermediate-risk patients with HL (RERs with CR) for whom IFRT could be avoided without compromising outcome. We also identified a population (SERs with PET-2–positive results) for whom EFS was higher with chemotherapy augmentation, albeit with borderline statistical significance. These data support previous COG studies that have demonstrated the prognostic significance of ER,^{17,25} titration of therapy on the basis of ER,^{12,16,24} and avoidance of IFRT on the basis of CR to chemotherapy.^{18,20}

AHOD0031 chemotherapy was similar to that used in COG P9425, wherein 217 patients nonrandomly received three or five ABVE-PC cycles on the basis of three-cycle response, followed by IFRT.¹² Our EFS was similar to that of COG P9425 for the entire cohort (83.4% v 84%) and RERs (85.1% v 86%), but lower for SERs (75.2% v 83%); the SER difference is driven by the SERs with PET-2–positive results. However, COG P9425 included patients with stage IIIB and IVB disease, IFRT for all patients, and had different response criteria. AHOD0031 included 28% RERs who were randomly assigned to receive no IFRT, and SERs were randomly assigned to receive four ABVE-PC cycles with or without two DECA cycles plus IFRT. In COG P9425, all RERs received IFRT, and SERs received five ABVE-PC cycles plus IFRT. Albeit with differing inclusion and response criteria, AHOD0031 can be compared with GPOH-HD 2002, wherein the TG-2 and 3 groups had a combined EFS of 87.7%, which was comparable with 85% in AHOD0031. In GPOH-HD 2002, patients in the TG2-3 group received four to six cycles of chemotherapy and IFRT of 19.8 Gy, and 6% received 30-Gy boosts.²³ Patients in AHOD0031 received four to six cycles of chemotherapy, 22% received no IFRT, and the remainder received 21 Gy without an additional boost.

Several COG trials have examined regimens that exclude radiotherapy. These include COG C521 and P8725, which used 12 and 8

Table 2. Four-Year EFS by Clinical Presentation and Two-Cycle/Four-Cycle Response

	SERs			RERs			RERs With CR			RERs With < CR			All Patients		
	No.	EFS (%)	SE (%)	No.	EFS (%)	SE (%)	No.	EFS (%)	SE (%)	No.	EFS (%)	SE (%)	No.	EFS (%)	SE (%)
Stage															
I	5	75.0	21.7	84	93.1	3.0	59	94.2	3.3	23	90.4	6.5	90	91.2	3.2
II	181	75.8	3.3	726	86.6	1.3	405	86.8	1.7	300	88.0	2.0	930	84.7	1.2
III	65	83.7	4.8	271	88.6	2.0	167	87.8	2.7	95	91.2	3.0	342	87.8	1.9
IV	46	74.9	6.6	188	82.6	2.9	85	83.7	4.2	101	82.4	3.9	239	80.8	2.6
B symptoms*															
Yes	75	74.7	5.2	259	81.5	2.5	142	84.0	3.1	106	80.5	3.9	347	80.4	2.2
No	221	78.2	2.9	1,010	88.2	1.1	574	88.0	1.4	413	89.3	1.6	1,251	86.4	1.0
Bulk disease*															
Yes	238	73.6	3.0	914	85.6	1.2	494	85.3	1.6	398	87.3	1.8	1,173	83.2	1.1
No	53	94.2	3.3	345	90.2	1.7	214	91.9	2.0	120	88.1	3.0	409	90.9	1.5

Abbreviations: CR, complete response; EFS, event-free survival; RERs, rapid early responders; SERs, slow early responders.

*Patients with missing data on clinical presentation were excluded.

cycles of mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, dacarbazine, vinblastine backbone therapy, respectively. There with no EFS differences noted between the combined-modality and chemotherapy-only arms,^{15,32} but considerable treatment burden. In COG C5942, patients with CR at chemotherapy completion were randomly assigned to receive or not receive IFRT. EFS, but not OS, was lower among those treated with chemotherapy alone.^{18,20} The use of ER assessment and dose-intensive chemotherapy in AHOD0031 allowed for EFS similar to that of C5942^{18,20} while identifying patients (RERs with CR, 44% [762 of 1,712] of the intermediate-risk group) for whom radiotherapy can be eliminated without sacrificing EFS.

Early PET scanning can inform further therapy.³³⁻³⁶ In AHOD0031, PET did identify those SERs who might benefit from early therapy augmentation. SERs with PET-2–negative results had 4-year EFS that was consistent with EFS of RERs, but SERs with PET-2–positive results had inferior EFS that was improved by treatment augmentation (70.7% with v 54.6% without DECA; Table 2).

Excellent cure rates remain the primary goal of clinical trials, but in HL, risk for SMNs and chronic health problems²⁻¹¹ negatively affects long-term EFS, which is the true metric of therapeutic success. This trade-off between early EFS and later occurring toxicity is demonstrated by a state-transition model of HL to simulate the lifetime clinical course, comparing chemotherapy to combined-modality therapy. Accounting for mortality from HL and late effects of treatment, Yeh and Diller³⁷ found a longer conditional life expectancy with initial treatment with chemotherapy alone.

Our regimen was designed to administer cumulative doses of alkylating agents and anthracyclines associated with low risk of long-term toxicities and to identify a group of patients for whom radiotherapy could safely be eliminated, given that even lower doses of radiotherapy may increase SMN risk.⁸ Etoposide is associated with a small risk for subsequent leukemia³⁸; however, the cumulative dose in AHOD0031 was minimized. Although it is premature to assess the impact of this therapy, most AHOD0031 patients are beyond the high-risk period for etoposide-associated leukemia. There are only 13 SMNs that have been reported (0.7% of patients), with only four leukemia/MDSs (0.2%), one of which was diagnosed after recurrent disease.

Follow-up time is important to establish differences in study arms. In the German Hodgkin's Lymphoma Study Group HD6 trial, the superiority of the chemotherapy-only arm became evident only after 12 years of follow-up.³⁹ In contrast, the 10-year follow-up for COG 5942 was similar to 3-year results.^{18,20} To determine the long-term outcomes of the patients in this trial, we have included late reporting up to 10 years after therapy to examine the contribution of later events to EFS.

Although AHOD0031 established a response-based paradigm for treating and titrating HL therapy that was successful overall, some limita-

tions should be acknowledged. This study was conducted over a period of time during which there were important advances in FDG-PET. However, the study was well underway as such advances came to clinical practice, and we were therefore unable to use newer methodologies for interpretation or include PET in ER determination. Moving forward, use of such methodologies will establish a more sensitive interpretation of PET in ER to better inform reduction or augmentation of therapy. The patients with stage IVA disease had an EFS of 80.8% in the entire group and 74.9% in the 19% with slow early response; thus, further examination is required to design more effective therapy for these patients. It is also essential to understand factors that led to the inferior outcome for the SERs with PET-2–positive results. Although outcomes were marginally significantly improved by augmentation, additional modifications are required to improve outcomes for this group. Multivariable analyses of patterns of failure and risk factors are ongoing to inform future strategies, including improved risk stratification and response criteria.

Treatment with dose-intensive ABVE-PC, despite these limitations, successfully induced ER and allowed titration of therapy, permitting avoidance of radiotherapy for RERs with CR and setting the paradigm for augmentation of therapy for SERs with PET-2–positive results. In 44% of our cohort (RERs with CR), we demonstrated that IFRT could be spared, reducing the potential for the associated long-term toxicities. In the context of a chemotherapy regimen that is of short duration (12 weeks in RERs), with low cumulative chemotherapy doses that are generally below thresholds for late toxicity, this represents a highly significant reduction of therapy and associated long-term toxicities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Debra L. Friedman, Suzanne Wolden, Pedro A. De Alarcon, Allen R. Chen, Nathan Koblinsky, Peter Ehrlich, Louis S. Constine, Cindy L. Schwartz

Provision of study materials or patients: Debra L. Friedman, Suzanne Wolden, Cindy L. Schwartz

Collection and assembly of data: Debra L. Friedman, Suzanne Wolden, Thomas J. FitzGerald, Sandra Kessel, Robert E. Hutchison, Cindy L. Schwartz

Data analysis and interpretation: Debra L. Friedman, Lu Chen, Suzanne Wolden, Allen Buxton, Kathleen McCarten, Thomas J. FitzGerald, Peter Ehrlich, Cindy L. Schwartz

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

- Howlader N, Noone AM, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), Bethesda, MD, National Cancer Institute, 2012. http://seer.cancer.gov/csr/1975_2009_pops09/
- Armstrong GT, Liu Q, Yasui Y, et al: Late mortality among 5-year survivors of childhood cancer: A summary from the Childhood Cancer Survivor Study. *J Clin Oncol* 27:2328-2338, 2009
- Bhatia S, Yasui Y, Robison LL, et al: High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: Report from the Late Effects Study Group. *J Clin Oncol* 21:4386-4394, 2003
- Castellino SM, Geiger AM, Mertens AC, et al: Morbidity and mortality in long-term survivors of Hodgkin lymphoma: A report from the Childhood Cancer Survivor Study. *Blood* 117:1806-1816, 2011
- Constine LS, Tarbell N, Hudson MM, et al: Subsequent malignancies in children treated for Hodgkin's disease: Associations with gender and radiation dose. *Int J Radiat Oncol Biol Physics* 72:24-33, 2008
- Friedman DL, Constine LS: Late effects of treatment for Hodgkin lymphoma. *J Natl Compr Cancer Netw* 4:249-257, 2006
- Mertens AC, Yasui Y, Liu Y, et al: Pulmonary complications in survivors of childhood and adolescent cancer: A report from the Childhood Cancer Survivor Study. *Cancer* 95:2431-2441, 2002
- O'Brien MM, Donaldson SS, Balise RR, Whittemore AS, and Link MP: Second malignant neoplasms in survivors of pediatric Hodgkin's

lymphoma treated with low-dose radiation and chemotherapy. *J Clin Oncol* 28:1232-1239, 2010

9. Schellong G, Riepenhausen M, Bruch C, et al: Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: Report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. *Pediatr Blood Cancer* 55:1145-1152, 2010

10. Sklar C, Whitton J, Mertens A, et al: Abnormalities of the thyroid in survivors of Hodgkin's disease: Data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 85:3227-3232, 2000

11. Sklar CA, Mertens AC, Mitby P, et al: Premature menopause in survivors of childhood cancer: A report from the childhood cancer survivor study. *J Natl Canc Inst* 98:890-896, 2006

12. 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*, 114:2051-2059, 2009

13. Donaldson SS, Link MP, Weinstein HJ, et al: Final results of a prospective clinical trial with VAMP and low-dose involved-field radiation for children with low-risk Hodgkin's disease. *J Clin Oncol* 25:332-337, 2007

14. Dörffel W, Lüders H, Rühl U, et al: Preliminary results of the multicenter trial GPOH-HD 95 for the treatment of Hodgkin's disease in children and adolescents: Analysis and outlook. *Klin Padiatr* 215:139-145, 2003

15. Hutchinson RJ, Fryer CJ, Davis PC, et al: MOPP or radiation in addition to ABVD in the treatment of pathologically staged advanced Hodgkin's disease in children: Results of the Children's Cancer Group Phase III Trial. *J Clin Oncol* 16:897-906, 1998

16. Kelly KM, Sposto R, Hutchinson R, et al: BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: A report from the Children's Oncology Group. *Blood*, 117:2596-2603, 2011

17. Kung FH, Schwartz CL, Ferree CR, et al: POG 8625: A randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with stages I, IIA, IIIA1 Hodgkin Disease: A report from the Children's Oncology Group. *J Pediatr Hematol Oncol* 28:362-368, 2006

18. Nachman JB, Sposto R, Herzog P, et al: Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease

who achieve a complete response to chemotherapy. *J Clin Oncol* 20:3765-3771, 2002

19. Friedmann AM, Hudson MM, Weinstein HJ, et al: Treatment of unfavorable childhood Hodgkin's disease with VEPA and low-dose, involved-field radiation. *J Clin Oncol* 20:3088-3094, 2002

20. Wolden SL, Chen L, Kelly KM, et al: Long-term results of CCG 5942: A randomized comparison of chemotherapy with and without radiotherapy for children with Hodgkin's Lymphoma—A report from the Children's Oncology Group. *J Clin Oncol* 30:3174-3180, 2012

21. Dieckmann K, Pötter R, Hofmann J, et al: Does bulky disease at diagnosis influence outcome in childhood Hodgkin's disease and require higher radiation doses? Results from the German-Austrian Pediatric Multicenter Trial DAL-HD-90. *Int J Radiat Oncol Biol Phys* 56:644-652, 2003

22. Fryer CJ, Hutchinson RJ, Krailo M, et al: Efficacy and toxicity of 12 courses of ABVD chemotherapy followed by low-dose regional radiation in advanced Hodgkin's disease in children: A report from the Children's Cancer Study Group. *J Clin Oncol* 8:1971-1980, 1990

23. Mauz-Körholz C, Hasenclever D, Dörffel W, et al: Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPE-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: The GPOH-HD-2002 study. *J Clin Oncol* 28:3680-3686, 2010

24. 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* 59:1259-1265, 2012

25. Weiner MA, Leventhal B, Brecher ML, et al: Randomized study of intensive MOPP-ABVD with or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV Hodgkin's disease in pediatric patients: A Pediatric Oncology Group study. *J Clin Oncol* 15:2769-2779, 1997

26. Carde P, Koscielny S, Franklin J, et al: Early response to chemotherapy: A surrogate for final outcome of Hodgkin's disease patients that should influence initial treatment length and intensity? *Ann Oncol* 13:86-91, 2002 (suppl 1)

27. Metzger ML, Weinstein HJ, Hudson MM, et al: Association between radiotherapy vs no radiotherapy based on early response to VAMP chemotherapy and survival among children with favorable-risk Hodgkin lymphoma. *JAMA* 307:2609-2616, 2012

28. Lister TA, Crowther D, Sutcliffe SB, et al: Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 7:1630-1636, 1989

29. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. *Biometrika* 70:659-663, 1983

30. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958

31. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data*. New York, NY, John Wiley & Sons, 1980

32. Weiner MA, Leventhal BG, Marcus R, et al: Intensive chemotherapy and low-dose radiotherapy for the treatment of advanced-stage Hodgkin's disease in pediatric patients: A Pediatric Oncology Group study. *J Clin Oncol* 9:1591-1598, 1991

33. Advani R, Maeda L, Lavori P, et al: Impact of positive positron emission tomography on prediction of freedom from progression after Stanford V chemotherapy in Hodgkin's disease. *J Clin Oncol* 25:3902-3907, 2007

34. Gallamini A, Hutchings M, Rigacci L, et al: Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: A report from a joint Italian-Danish study. *J Clin Oncol* 25:3746-3752, 2007

35. Gallamini A, O'Doherty M, Report of satellite workshop on interim-PET in Hodgkin lymphoma: 8th International Symposium on Hodgkin Lymphoma, Cologne, 23 October 2010. *Leuk Lymphoma* 52:583-586, 2011

36. Kobe C, Dietlein M, Franklin J, et al: Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. *Blood* 112:3989-3994, 2008

37. Yeh JM, Diller L: Pediatric Hodgkin lymphoma: Trade-offs between short- and long-term mortality risks. *Blood* 120:2195-2202, 2012

38. Smith MA, Rubinstein L, Anderson JR, et al: Secondary leukemia or myelodysplastic syndrome after treatment with epipodophyllotoxins. *J Clin Oncol* 17:569-577, 1999

39. Sieber M, Tesch H, Pfistner B, et al: Treatment of advanced Hodgkin's disease with COPP/ABV/IMEP versus COPP/ABVD and consolidating radiotherapy: Final results of the German Hodgkin's Lymphoma Study Group HD6 trial. *Ann Oncol* 15:276-282, 2004

Affiliations

Debra L. Friedman, Vanderbilt University School of Medicine and Vanderbilt-Ingram Cancer Center, Nashville, TN; Lu Chen and Allen Buxton, Children's Oncology Group, Monrovia, CA; Suzanne Wolden, Memorial Sloan Kettering Cancer Center, New York; Robert E. Hutchison, State University of New York Upstate Medical University, Syracuse; Louis S. Constine, University of Rochester, Rochester, NY; Kathleen McCarten, Thomas J. FitzGerald, and Sandra Kessel, Quality Assurance Review Center, Providence, RI; Pedro A. De Alarcon, University of Illinois College of Medicine, Peoria, IL; Allen R. Chen, Johns Hopkins University, Baltimore, MD; Nathan Koberinsky, Sanford Medical Center and Roger Maris Cancer Center, Fargo, ND; Peter Ehrlich, C.S. Mott Children's Hospital and University of Michigan, Ann Arbor, MI; and Cindy L. Schwartz, MD Anderson Cancer Center, Houston, TX.

GLOSSARY TERMS

event-free survival: calculated from the date of diagnosis to the date of the first event, which is resistance, relapse, death, or second malignant neoplasm.

overall survival: the duration between random assignment and death.