ABVD Without Radiation for Newly Diagnosed Pediatric and Young Adult Patients With Hodgkin Lymphoma: A Single Center Retrospective Analysis of 28 Consecutive Patients

Elliot Stieglitz, MD,† Tu Dinh, BSc,* Andrew S. Phelps, MD,‡ Miguel H. Pampaloni, MD, PhD,‡ Adam B. Olshen, PhD,†§ and Elizabeth Robbins, MD**

Summary: Hodgkin lymphoma (HL) is the most common malignancy affecting adolescents and young adults. Treatment with a combination of chemotherapy and radiation results in cure rates of >90%. However, radiation therapy causes significant late effects and avoiding radiation entirely for patients who respond to chemotherapy is an accepted strategy. Since 2011, 28 consecutive patients diagnosed with classic HL have been treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for 4 to 6 cycles. Patients who achieved a complete metabolic response (CMR) as assessed by [^{18}F] fluorodeoxyglucose positron emission tomography by the end of chemotherapy did not receive radiation. Among the 27 evaluable patients, 26/27 (96.2%) achieved a CMR with ABVD alone with 24/27 (88.9%) having achieved a CMR after 2 cycles. Event-free survival at 5 years is 90.5% and overall survival is 100% with a median follow-up time of 22.4 and 22.1 months, respectively. Treating pediatric and young adult HL patients with ABVD alone results in CMRs in >95% of patients. Patients who were refractory to ABVD or relapsed after treatment eventually achieved remission with a combination of standard and novel salvage therapies. This regimen demonstrates the feasibility of avoiding upfront radiation in newly diagnosed pediatric HL patients.

Key Words: Hodgkin lymphoma, chemotherapy, radiation, ABVD

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Hodgkin lymphoma (HL) is a common and highly curable malignancy in children and young adults, accounting for 5% to 6% of childhood cancers.[1,2] Conventional treatment protocols combining chemotherapy and radiation therapy have led to 5-year survival rates of >90%.[3–5] Given these excellent survival rates, an important treatment goal is to minimize therapy-related late effects. Radiation therapy in particular is associated with significant late effects, most prominently cardiac toxicity and the development of secondary malignant neoplasms.[6] Even with low-dose radiation, the estimated cumulative incidence of secondary malignant neoplasm is 29% at 30 years.[7]

Treatment of HL with chemotherapy alone has been shown to be effective in early stage disease.[8–10] Multiple studies have demonstrated that response-based therapy using [^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) evaluation can help identify patients in whom radiation might be safely omitted.[11–15] Although omitting radiation from HL treatment results in a modest increase in disease recurrence, overall survival (OS) does not appear to be decreased because of the efficacy of salvage regimens for patients with relapsed disease and because of the increased mortality from late effects in patients who received radiation.[16–18]

In adults with HL, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) remains the standard chemotherapy regimen.[19–21] In children with HL, treatment with doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC), followed by risk-adapted radiation therapy has been widely used by the Children's Oncology Group. ABVD has known efficacy, with a favorable fertility preservation profile and avoidance of the secondary leukemia risk associated with etoposide. Since 2011, newly diagnosed pediatric HL patients at the University of California, San Francisco (UCSF) have been treated with ABVD without the addition of radiation if they achieved a complete metabolic response (CMR) as assessed by PET.

MATERIALS AND METHODS

Patients

This is a retrospective analysis of all patients diagnosed with classic HL treated at UCSF Benioff Children's Hospital in San Francisco between January 2011 and July 2017. The cutoff for follow-up was August 1, 2017. A total of 28 consecutive pediatric and young adult patients with classic HL were treated with ABVD. The study was approved by the institutional review board at the UCSF.

Staging and Disease Monitoring

Patients were staged according to the Ann Arbor staging system.[22] Bulky disease was defined as a mediastinal mass measuring >1/3 the maximum intrathoracic diameter or a nodal mass >6 cm as assessed on computed tomographic scan. Risk categorization was determined by stage, the presence of B symptoms, and the presence of bulky disease: low risk was defined as nonbulky stage IA or IIA

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From the *Department of Pediatrics, Benioff Children's Hospital; †Helen Diller Family Comprehensive Cancer Center; ‡Department of Radiology and Biomedical Imaging; and §Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA.
E.S. and T.D. contributed equally.
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Reprints: Elizabeth Robbins, MD, 550 16th Street San Francisco CA 94158 (e-mail: Elizabeth.Robbins@ucsf.edu).
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disease; intermediate risk disease was defined as stage IB, IIB, bulky stage IA, bulky stage IIA disease, stage IIIAE, bulky stage IIIA, or stage IVA disease; and high risk was defined as stage IIIB or stage IVB disease. Response to therapy was assessed by FDG-PET starting after 2 cycles of ABVD and periodically thereafter in patients with positive scans. PET scans were reviewed by a single radiologist and scored based on the 5-point Deauville scale.[23] Patients were considered to have achieved a CMR if the Deauville score was ≤ 2. Duration of follow-up was extracted from patients' electronic medical records.

Treatment

All pediatric HL patients were treated with ABVD upon diagnosis. FDG-PET was performed after 2 cycles to determine response to therapy. Low-risk patients with a negative PET scan after 2 cycles received either 2 or 4 more cycles of ABVD, for a total of 4 or 6 cycles, at the discretion of the provider. Intermediate and high-risk patients received a total of 6 cycles of ABVD therapy. Patients who were PET positive, defined as a Deauville score of ≥ 3, after 2 cycles were evaluated by PET every 2 cycles until negative. Patients who achieved a CMR by PET were not treated with radiation. Patients with disease responsive to ABVD but whose end of therapy PET scans were still greater than Deauville 2 would receive involved field radiation therapy (IFRT). Toxicity grading was determined using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical Analyses

Patient demographics and clinical characteristics extracted from the electronic medical record included: age at diagnosis, sex, race, ethnicity, classic HL subtype by histology, stage, "B" symptoms, mediastinal mass, and bulky disease (Table 1) (Supplemental Table SI, Supplemental Digital Content 1, http://links.lww.com/JPHO/A237). Study data were collected and managed using the research electronic data capture (REDCap) tools hosted at UCSF.[24] Survival curves were estimated using the Kaplan-Meier method and utilizing R statistical software.

TABLE 1. Baseline Characteristics of Hodgkin Lymphoma Patients

Characteristics	Patients No. (%)
Age at diagnosis (y)	
Median	16.1
Range	6.8-21.1
Sex	
Male	16 (57.1)
Female	12 (42.9)
Race	
Asian	6 (21.4)
Black or African American	2 (7.1)
White	16 (57.1)
Unknown	4 (14.3)
Ethnicity	
Hispanic/Latino	5 (17.9)
Not Hispanic/Latino	23 (82.1)
Histology, classic subtype	
Nodular sclerosis	18 (64.3)
Mixed cellularity	2 (7.1)
Lymphocyte rich	1 (3.6)
Not otherwise specified	7 (25.0)
Stage	
I	1 (3.6)
II	16 (57.1)
III	3 (10.7)
IV	8 (28.6)
"B" symptoms	
Present	8 (28.6)
Absent	20 (71.4)
Mediastinal mass ($>1/3$ intrathoracic diameter)	
Present	17 (60.7)
Absent	11 (39.3)
Bulky disease (>6 cm)	
Present	22 (78.6)
Absent	6 (21.4)

RESULTS

ABVD Treatment and Outcomes

All 28 patients received at least 1 cycle of ABVD (Table 2). One patient was lost to follow-up after moving out of state following 1 cycle of chemotherapy. The remaining 27 patients received 3 to 6 cycles of ABVD (Fig. 1). The first patient in the series, who was PET negative after 2 cycles of ABVD, received IFRT following 4 cycles of ABVD as per preference of the treating physician. This patient was included in the chemotherapy response analysis but not in the survival analysis. No other patients received therapeutic radiation.

Response to treatment was assessed by FDG-PET. A CMR was defined as a Deauville score of ≤ 2. Among the 27 patients who received at least 2 of cycles chemotherapy, 26/27 (96.2%) achieved a CMR with ABVD alone: 24/27 (88.9%) achieved a CMR after 2 cycles of ABVD, 1/27 (3.7%) achieved a CMR after 4 cycles, and 1/27 (3.7%) achieved a CMR after 6 cycles (Table 3). Among the 23/27 patients with bulky disease and/or a mediastinal mass, 22/23 (95.7%) achieved a CMR: 20/23 (87%) achieved a CMR after 2 cycles of ABVD, 1/23 (4.3%) after 4 cycles, and 1/23 (4.3%) after 6 cycles.

Survival

The median follow-up time was 22.4 months (range, 0.1 to 62.5) for event-free survival (EFS) and 22.1 months (range, 0.1 to 62.5) for OS. A total of 26/28 patients (92.9%) were in continuous complete remission at the time of last follow-up. The EFS at 5 years was 90.5% and OS at 5 years was 100% (Fig. 2).

A total of 2 events were recorded: 1 patient was refractory to chemotherapy after 2.4 months and 1 patient relapsed 6 months after completing chemotherapy. The patient with refractory disease was a 17-year-old boy who presented with stage IIA bulky disease and a mediastinal mass. A biopsy of progressive left cervical adenopathy after 3 courses of ABVD demonstrated refractory HL. The patient then received 2 courses of ifosfamide, carboplatin, and etoposide with a partial response; followed by 2 doses of brentuximab vedotin, with progressive disease; followed by 4 doses of nivolumab monotherapy. He then received an autologous stem cell transplant followed by 30 Gy IFRT to sites of disease at diagnosis and relapse. He has remained disease free for 8 months.

The patient with relapsed disease was a 16-year-old boy with stage IIA bulky (12 cm) disease and a mediastinal mass. The PET scan after 2 cycles of ABVD was Deauville 3 due to FDG activity in the cervical region. The patient achieved a CMR (Deauville 2) after 4 cycles of ABVD and was treated with a total of 6 cycles of ABVD. Six months after

TABLE 2. ABVD Chemotherapy and Cumulative Doses

Drug	Route	Dose (mg/m^2)	Days Administered	Cumulative Doses (4 Cycles) (mg/m^2)	Cumulative Doses (6 Cycles)
Doxorubicin	IV	25	1, 15	200	300
Bleomycin	IV	10 units/m^2	1, 15	80 units/m^2	120 units/m^2
Vinblastine	IV	6	1, 15	48	72
Dacarbazine	IV	275	1, 15	2200	3300

IV indicates intravenous.

completing chemotherapy the patient developed recurrent HL at the site of the initial cervical disease. The patient received brentuximab vedotin in combination with bendamustine but developed anaphylaxis while receiving his second dose of brentuximab. The patient was then treated with ifosfamide in combination with vinorelbine after which he achieved a CMR. He then received an autologous stem cell transplant and radiation to sites of disease at diagnosis.

Side Effects

In terms of acute toxicity, 1 patient had grade 3 appendicitis, 1 patient had grade 3 hyponatremia, and 3 patients had grade 3 vomiting. Three patients had fever and neutropenia and 1 patient had a grade 3 fever without neutropenia. No grade 4 nonhematologic toxicities were observed. In terms of long-term toxicity, no patients have developed secondary malignancies or grade 2 or higher cardiac disease.

DISCUSSION

Numerous randomized studies of treatment of HL with chemotherapy alone have shown efficacy with this approach while sparing the toxicity of radiation.[9–11,25–27] Chemotherapy regimens that spare radiation for HL patients who demonstrate early responses are therefore commonplace in both pediatric and adult practices. The choice of a chemotherapeutic backbone is important: a more effective regimen will likely result in more patients treated without radiation. Although ABVE-PC is standard for many pediatric trials in the United States, ABVD is the cornerstone of most upfront adult trials. In 2011 at UCSF we adopted ABVD as the standard of care for pediatric HL patients. Measures of efficacy of this approach include the number of patients who achieve a CMR with chemotherapy and the number who remain in continuous complete remission after achieving a CMR without consolidation with radiation. Of note, a Deauville score of 3 is often used as a measure of CMR but we chose to define CMR using the more stringent cutoff of Deauville 2.[28–30]

Our results show that ABVD is an effective regimen to achieve CMRs in children and young adults with all stages of HL. Overall, 24/27 (88.8%) patients obtained a CMR after 2 cycles of ABVD, and 26/27 (96.3%) reached a CMR by the end of chemotherapy with ABVD. Even among patients with high-risk features including bulky disease or a mediastinal mass, 20/23 (87.0%) achieved a CMR after 2 cycles of ABVD and 22/23 (95.7%) reached this endpoint by the end of chemotherapy. One patient (5.6%) did not

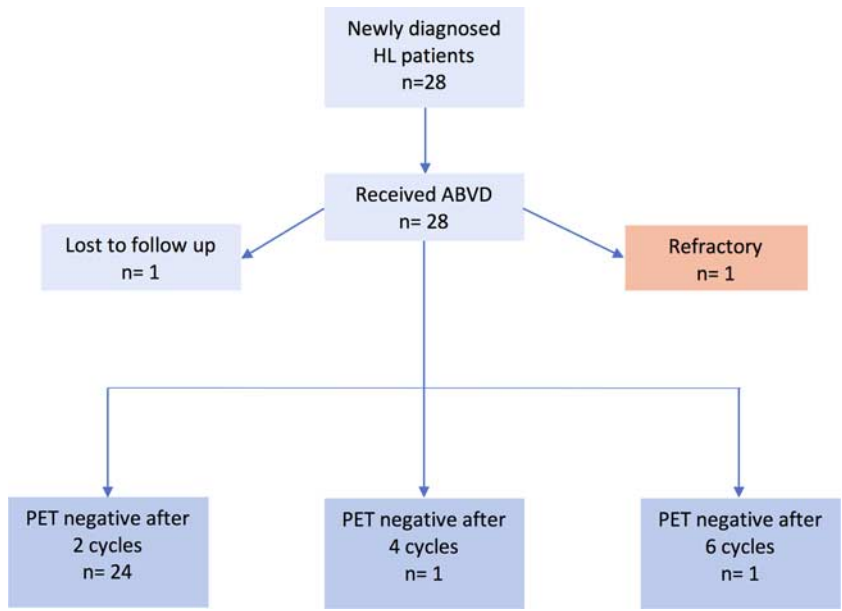

FIGURE 1. Treatment delivered and PET response. Twenty-eight patients were diagnosed with HL. Twenty-seven patients received at least 4 cycles of ABVD and 1 patient was lost to follow-up after a single cycle. Twenty-four of 27 patients achieved a negative PET (Deauville score ≤ 2) at the end of 2 cycles, 1 patient achieved a negative PET at the end of 4 cycles, 1 patient achieved a negative PET at the end of 6 cycles and 1 patient was refractory to ABVD. ABVD indicates doxorubicin, bleomycin, vinblastine, and dacarbazine; HL, Hodgkin lymphoma; PET, positron emission tomography. full color online

TABLE 3. Time in Months to Complete Metabolic Response

	No. Patients Achieving a Complete Metabolic Response				
Risk Category	**PET2**	**PET4**	**PET6**	**Refractory**	**Total**
Low	2	0	0	0	2
Intermediate	20	1	1	1	23
High	2	0	0	0	2
Total	24	1	1	1	27

Complete metabolic response is defined as a Deauville score of ≤ 2 after 2, 4, or 6 cycles of ABVD.
PET indicates positron emission tomography.

achieve a CMR; he presented with stage IIA bulky disease refractory to ABVD, ifosfamide, carboplatin, and etoposide, and brentuximab vedotin.

Our results also show that ABVD alone, without radiation, may be adequate therapy for children and young adults who achieve a CMR by PET. EFS at 5 years was 90.5% and OS was 100%. This compares favorably to results of clinical trials that utilized chemotherapy and risk-adapted radiation. Intermediate risk pediatric HL patients treated on Children's Oncology Group protocol AHOD0031 with ABVE-PC who had a rapid early response and were randomized to no involved field radiation had an EFS of 87.6% at 2 years and 84.3% at 4 years.[5]

Chemotherapy with 4 to 6 cycles of ABVD was well-tolerated with minimal grade 3 nonhematologic side effects and no grade 4 nonhematologic side effects.

This retrospective analysis suggests that ABVD is an effective regimen for pediatric patients and young adults, and that eliminating radiation in patients with negative PET scans may prove to be an attractive approach for this patient population. However, there are several limitations to this study, as it represents the experience of a single center with a modest sample size and a relatively short follow-up time. It is possible that rates of recurrent disease might be greater than expected, or that late adverse effects of ABVD chemotherapy could develop. Although relapses due to the omission of radiation typically occur within 2 years,[5] it is encouraging that only 1 relapse has been observed in this series to date. Another limitation of the study is the small number of patients with high-risk disease (stages IIIB, IVB); caution should be used in extrapolating these results to a high-risk population.

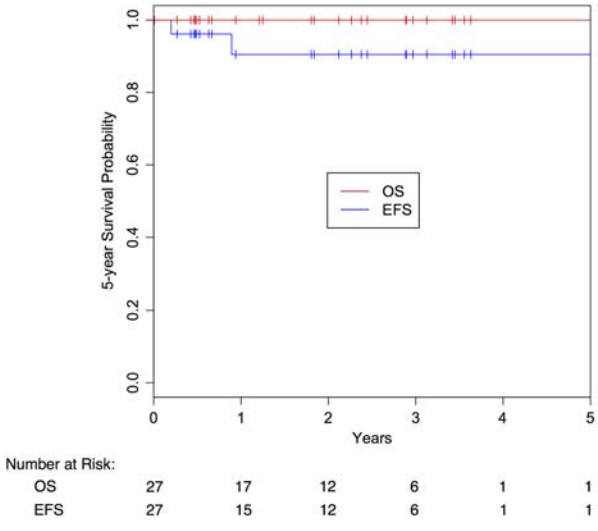

FIGURE 2. EFS and OS curves. All twenty-eight patients were included in the survival estimate. EFS was 90.5% and overall survival was 100% at 5 years. The number of patients at risk for EFS and OS are shown in a table at the bottom of the figure. EFS indicates event-free survival; OS, overall survival. full color online

These promising results with ABVD without radiation warrant a prospective multicenter trial through a collaborative clinical network to test the elimination of radiation for newly diagnosed pediatric HL patients with CMRs to chemotherapy. A trial comparing ABVD with the more common pediatric regimen ABVE-PC would also provide valuable information. New immunotherapies such nivolumab and brentuximab vedotin may make a treatment approach without radiation even more feasible. These therapies have proven to be effective in relapsed HL, and, if incorporated into upfront treatment regimens, may further improve the efficacy of chemotherapy without radiation in HL.

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