original reports

Brentuximab Vedotin Combined With Chemotherapy in Patients With Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

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abstract

PURPOSE To improve curability and limit long-term adverse effects for newly diagnosed early-stage (ES), unfavorable-risk Hodgkin lymphoma.

METHODS In this multicenter study with four sequential cohorts, patients received four cycles of brentuximab vedotin (BV) and doxorubicin, vinblastine, and dacarbazine (AVD). If positron emission tomography (PET)-4–negative, patients received 30-Gy involved-site radiotherapy in cohort 1, 20-Gy involved-site radiotherapy in cohort 2, 30-Gy consolidation-volume radiotherapy in cohort 3, and no radiotherapy in cohort 4. Eligible patients had ES, unfavorable-risk disease. Bulk disease defined by Memorial Sloan Kettering criteria (> 7 cm in maximal transverse or coronal diameter on computed tomography) was not required for cohorts 1 and 2 but was for cohorts 3 and 4. The primary end point was to evaluate safety for cohort 1 and to evaluate complete response rate by PET for cohorts 2-4.

RESULTS Of the 117 patients enrolled, 116 completed chemotherapy, with the median age of 32 years: 50% men, 98% stage II, 86% Memorial Sloan Kettering–defined disease bulk, 27% traditional bulk (> 10 cm), 52% elevated erythrocyte sedimentation rate, 21% extranodal involvement, and 56% > 2 involved lymph node sites. The complete response rate in cohorts 1-4 was 93%, 100%, 93%, and 97%, respectively. With median follow-up of 3.8 years (5.9, 4.5, 2.5, and 2.2 years for cohorts 1-4), the overall 2-year progression-free and overall survival were 94% and 99%, respectively. In cohorts 1-4, the 2-year progression-free survival was 93%, 97%, 90%, and 97%, respectively. Adverse events included neutropenia (44%), febrile neutropenia (8%), and peripheral neuropathy (54%), which was largely reversible.

CONCLUSION BV + AVD × four cycles is a highly active and well-tolerated treatment program for ES, unfavorable-risk Hodgkin lymphoma, including bulky disease. The efficacy of BV + AVD supports the safe reduction or elimination of consolidative radiation among PET-4–negative patients.

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ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The standard of care for the treatment of early-stage (ES), unfavorable-risk Hodgkin lymphoma (HL) with disease bulk has long been considered combined modality therapy.[1] However, there are potential long-term toxicities associated with consolidative radiation therapy, particularly to the mediastinum, such as cardiopulmonary disease and secondary malignancies.[2,3] To minimize these toxicities, modern radiotherapy (RT) for HL treats a significantly reduced radiation field and the current standard of care is involved-site radiotherapy (ISRT), which encompasses the prechemotherapy disease volume with minimal margins.[4] Radiation of only residual computed tomography (CT) abnormalities following a positron emission tomography (PET)–negative response after chemotherapy was explored in the German Hodgkin Study Group (GHSG) HD15 study.[5,6] In addition, RT dose has been successfully reduced from 30 to 20 Gy for select patients with ESHL.[7,8]

In addition to the reduction of volume and dose of RT, there have been multiple efforts to eliminate RT in

CONTEXT

Key Objective

Can consolidative radiotherapy (RT) be reduced or eliminated in patients with ES, unfavorable-risk Hodgkin lymphoma who achieve a complete metabolic response after four cycles of brentuximab vedotin (BV) in combination with doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy?

Knowledge Generated

Treatment with BV + AVD × four cycles with and without RT was found to be well-tolerated and highly active, associated with high positron emission tomography-2 and positron emission tomography-4 negativity rates and an overall 2-year progression-free survival of 94%.

Treatment with BV + AVD × four cycles alone was associated with a 2-year progression-free survival of 97%.

Relevance

Reduction or elimination of consolidative RT in patients with early-stage Hodgkin lymphoma, often presenting with bulky mediastinal disease, will translate into reduced long-term toxicity. Larger, randomized studies of short-course BV + AVD without RT in patients who achieve a complete metabolic response after chemotherapy are needed to confirm the data.

appropriately selected patients with ESHL.[9] PET-adapted treatment programs have been successful for patients with nonbulky ES disease; multiple studies report minimally inferior disease control yet similar survival for interim and end-of-therapy PET-negative patients receiving short-course doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy alone without consolidative radiation.[10-13] However, patients with relative disease bulk with baseline tumor size ≥ 5 cm have inferior outcomes with short-course ABVD alone.[14,15] In addition, patients presenting with bulky disease who achieve negative interim and end-of-treatment PET results after six cycles of ABVD chemotherapy alone can achieve similar outcomes when compared with combined modality programs.[16-18]

Although risk-adapted approaches on the basis of interim and end-of-treatment (EOT) PET scans have refined treatment strategies, approximately 15% of patients with bulky HL will relapse. To improve the efficacy of frontline therapy, brentuximab-vedotin (BV), an antibody-drug conjugate comprising an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting monomethyl auristatin E, has been safely combined with doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy.[19,20] In the phase III ECHELON-1 study, BV + AVD × six cycles was compared with standard ABVD for untreated advanced-stage HL and the BV arm was associated with a 6% improvement in 3-year progression-free survival (PFS) although increased toxicity was also noted, including neutropenia, neutropenic fever, and peripheral neuropathy.[21,22] We hypothesized that treatment with short-course BV + AVD may facilitate the safe reduction or elimination of consolidative radiation in patients with ES, bulky HL.

We designed a multicenter pilot study with the chemotherapy backbone of four cycles of BV + AVD. If a patient achieved a negative EOT PET-4 scan, then four sequential consolidation approaches were studied with de-escalating radiation dose and field: 30-Gy ISRT in cohort 1, 20-Gy ISRT in cohort 2, 30-Gy consolidation-volume radiotherapy (CVRT) in cohort 3, and no radiation in cohort 4. Previously, we reported the results of the first cohort (BV + AVD × four cycles followed by 30-Gy ISRT), which was found to be safe and well-tolerated without significant pulmonary toxicity.[23] Here, we report the final analysis of all patients in this study.

METHODS

Patients

In this multicenter pilot study, there were four treatment cohorts. Patients between the ages 18 and 60 years with untreated, stage I/II, biopsy-proven, CD30+ classical HL were enrolled. In cohort 1, eligible patients had any of the following unfavorable-risk factors including bulky mediastinal mass (> 1/3 mediastinal mass ratio on posterior-anterior chest X-ray or ≥ 10 cm by CT imaging in transaxial plane), erythrocyte sedimentation rate ≥ 50 mm/h or erythrocyte sedimentation rate ≥ 30 mm/h in patients with B symptoms, extranodal involvement, > 2 lymph node sites (as defined by GHSG), or infradiaphragmatic disease. In cohort 2, the same unfavorable-risk criteria were applied for eligibility; however, the definition of disease bulk was updated to reflect the Memorial Sloan Kettering (MSK) definition: maximal transverse or coronal diameter of the largest lymph node mass at any site > 7 cm on CT imaging.[15] In cohorts 3 and 4, eligible patients with ESHL were required to have presence of disease bulk by MSK criteria. Across cohorts, stage IIB disease with disease bulk (X) and/or extranodal involvement (E) were included. Additional eligibility criteria are provided in the Data Supplement (online only).

This study was conducted at MSK Cancer Center; Wilmot Cancer Institute, University of Rochester; Stanford Cancer Institute, Stanford University; and City of Hope Medical Center (ClinicalTrials.gov identifier: NCT01868451). The

institutional review board of each institution approved the study, and written informed consent was obtained for all patients before enrollment.

Study Design

BV (1.2 mg/kg), doxorubicin (25 mg/m^2), vinblastine (6 mg/m^2), and dacarbazine (375 mg/m^2) were administered on days 1 and 15 of each 28-day cycle for a total of four cycles. Prophylactic growth factor support was mandatory. Patients with a PET-negative response after four cycles of BV and AVD chemotherapy and those with a PET-positive response but subsequent biopsy negative for HL received 30-Gy ISRT in cohort 1, 20-Gy ISRT in cohort 2, 30-Gy consolidation-volume RT in cohort 3, and no RT in cohort 4. In the experimental cohorts 2 and 3, one parameter, either dose or field, was reduced. In cohort 2, the dose was reduced to 20 Gy maintaining the standard field (ISRT), and in cohort 3, the field was reduced with CVRT while maintaining the standard dose (30 Gy). The treatment schema is summarized in Figure 1.

In cohorts 1 and 2, ISRT was administered per standard guidelines and under the direction of lymphoma radiation oncologists (J.Y., J.Y., L.S.C., R.T.H., and S.V.D.).[4,24] Typical ISRT fields were designed with consideration of the prechemotherapy and postchemotherapy gross tumor volume. This volume was then expanded in a nonisotropic way to account for microscopic disease spread to create a clinical target volume (CTV). The resulting CTV was then tailored to account for a decrease in mediastinal involvement after chemotherapy to allow for maximal sparing of cardiopulmonary tissues. The CTV was then expanded by 0.5-1.0 cm for the planning target volume to account for setup error. In cohort 3, an experimental radiation field CVRT was administered with the intention to deliver radiation only to PET-negative, remaining CT abnormalities of previously involved lymph nodes or organs measuring 1.5 cm or greater in any dimension after BV + AVD.

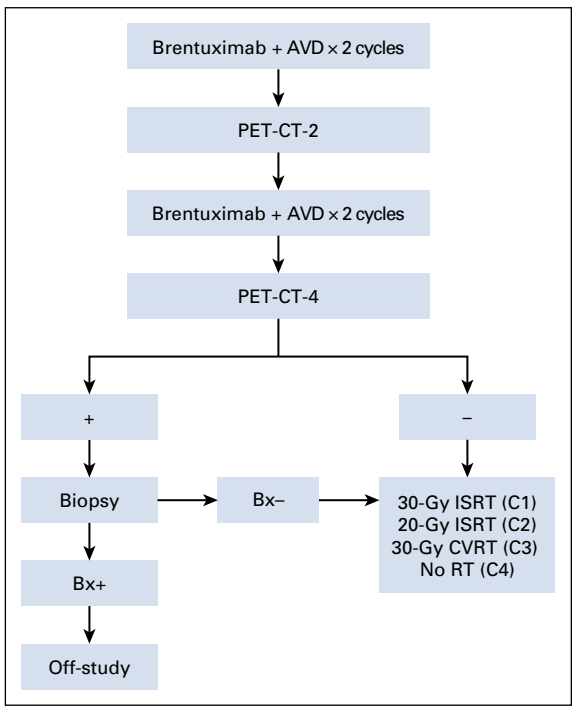

FIG 1. Treatment schema. AVD, doxorubicin, vinblastine, and dacarbazine; Bx, biopsy; CT, computed tomography; CVRT, consolidation-volume radiotherapy; ISRT, involved-site radiotherapy; PET, positron emission tomography; RT, radiotherapy.

Study Assessments

PET scan was performed at baseline, after two and four cycles of BV + AVD, and at EOT. All PET scans were interpreted using the 5-point scale (5-PS); a score of 1, 2, or 3 was considered negative.[25] PET scans were reviewed by radiologists at each site. At MSK, PET scans were centrally reviewed by the study radiologist (H.S.). The interim PET after two cycles was exploratory; treatment was not altered on the basis of the result. If PET-4 scan was positive (5-PS score 4 or 5), patients underwent subsequent biopsy unless it was deemed clinically unfeasible or unsafe by treating oncologist and site principal investigator (PI). Overall response (complete response [CR], partial response, stable disease, and progressive disease) was determined by site PI.

Adverse events were assessed per the Common Terminology Criteria of Adverse Events (v4.03).

To assess the impact of the treatment on fertility, we assessed anti-Mullerian hormone (AMH) levels before and after therapy.

Statistical Analysis

In cohort 1, the primary study objective was to evaluate safety of the combination BV + AVD followed by RT, with special attention to potential increased risk for pulmonary toxicity. In cohorts 2-4, the primary aim was to evaluate the rate of PET-negative CRs at the EOT. A Simon 2-stage design was applied where a 75% CR rate was considered not promising and a 91% response rate was considered promising. Secondary objectives included evaluation of PFS and assessment of correlation between interim PET-2 and PET-4 and outcome. PFS was estimated using the Kaplan-Meier method. The study database was frozen on December 10, 2020.

RESULTS

Patients and Treatment

From June 3, 2013 to June 14, 2019, a total of 117 patients were enrolled onto this pilot study, 30 patients in cohort 1 and 29 patients each in cohorts 2-4, respectively. Patient flowcharts for each cohort are detailed in the Data Supplement. The baseline characteristics of the patients in the four cohorts are provided in Table 1. Notably, 86% of patients had MSK-defined disease bulk (> 7 cm in transverse or coronal dimension), 27% traditionally defined

TABLE 1. Baseline Characteristics

Characteristic	Cohort 1, No. (%)	Cohort 2, No. (%)	Cohort 3, No. (%)	Cohort 4, No. (%)	Total, No. (%)
No. of patients	30	29	29	29	117
Enrollment by site					
MSKCC	27 (90)	18 (62)	17 (59)	23 (79)	85 (73)
University of Rochester	3 (10)	8 (28)	5 (17)	5 (17)	21 (18)
Stanford	0 (0)	2 (7)	4 (14)	1 (3)	7 (6)
City of Hope	0 (0)	1 (3)	3 (10)	0 (0)	4 (3)
Age, years, median (range)	31 (18-59)	33 (19-55)	31 (20-58)	30 (20-58)	32 (18-59)
Male	16 (53)	17 (59)	15 (52)	11 (38)	59 (50)
CD30+ HL	30 (100)	29 (100)	29 (100)	29 (100)	117 (100)
CD20+ HL	4 (13)	3 (10)	8 (28)	1 (3)	16 (14)
Stage II	30 (100)	29 (100)	28 (97)	28 (97)	115 (98)
Unfavorable risk features					
Disease bulk by MSK definition[a]	23 (77)	20 (69)	29 (100)	29 (100)	101 (86)
Disease bulk by traditional CT definition[b]	12 (40)	9 (31)	6 (21)	7 (24)	32 (27)
Elevated ESR[c]	20 (67)	12 (41)	12 (41)	17 (59)	61 (52)
B symptoms	15 (50)	11 (38)	8 (28)	12 (41)	46 (39)
Extranodal involvement	9 (30)	6 (21)	4 (14)	5 (17)	24 (21)
Nodal sites > 2	13 (43)	21 (72)	10 (34)	22 (76)	66 (56)
Infradiaphragmatic site	1 (3)	1 (3)	1 (3)	1 (3)	4 (3.4)
Anterior mediastinal mass bulk (> 7 cm), cm, median transverse size (range), n = 116	12.9 (7.7-16.9)	10.0 (7.2-17.3)	8.7 (7.2-17.5)	9.0 (7.2-16.5)	9.95 (7.2-17.5)
Advanced stage by GHSG criteria	12 (40)	9 (31)	1 (3)	5 (17)	27 (23)
IIBX	6 (20)	7 (24)	0 (0)	3 (10)	16 (14)
IIBE	4 (13)	0 (0)	0 (0)	1 (3)	5 (4)
IIBXE	2 (7)	2 (7)	1 (3)	1 (3)	6 (5)

Abbreviations: CT, computed tomography; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; MSKCC, Memorial Sloan Kettering Cancer Center.

[a]> 7 cm in maximal transverse or coronal dimension.

[b]> 10 cm in maximal transverse dimension.

[c]> 50 or > 30 with B symptoms.

bulk (> 10 cm in transverse dimension), and 23% advanced-stage disease by GHSG criteria: IIBX (n = 16), IIBE (n = 5), and IIBXE (n = 6). Because of the change in eligibility criteria, there was a greater proportion of patients with disease bulk per MSK criteria in cohorts 3 and 4 but a greater proportion of patients with traditional disease bulk in cohort 1 compared with cohorts 2-4.

Across all cohorts, 99% of patients (116 out of 117) received the planned four cycles of chemotherapy and in cohorts 1-3, 94% (82 out of 87) received the planned consolidative radiation therapy (see patient flowcharts in the Data Supplement). One patient in cohort 1 came off study because of toxicity (grade 3 hypertension and peripheral neuropathy) after one treatment of BV + AVD. In cohort 1, four patients did not receive 30-Gy ISRT: one refused RT, one received proton-beam RT off-study, and two patients had biopsy-confirmed primary refractory disease. In cohort 2, one patient refused 20-Gy ISRT.

Safety and Toxicity

There was a low rate of dose modification such as delays, holds, or reductions during administration of the four cycles of BV + AVD. The primary reason for dose modification was development of peripheral neuropathy, which led to dose reduction of BV, typically from 1.2 to 0.9 mg/kg. Further details regarding dose modifications are shown in Table 2.

The safety profile for BV + AVD is summarized in Table 3. Although any grade neutropenia was common (44%), the rate of febrile neutropenia was low (8%). Per protocol, all patients received mandatory growth factor support. There was a high rate of peripheral sensory neuropathy (n = 63 patients, 54%) associated with BV + AVD, but most was

TABLE 2. Dose Delays and Reductions (n = 116)[a]

Delay or Reduction	No.	%
Total No. of treatments planned	928	100
Total No. of treatments administered	923	99
Total No. of treatments delayed	24	2.6
Reason for delay		
Upper respiratory infection	2	
Pneumonia	2	
Fever	4	
Abdominal pain	5	
Neutropenia	3	
Transaminitis	3	
Chest pain	2	
Clostridium difficile infection	1	
Colonic obstruction	1	
Patient scheduling	1	
Total No. of treatment reductions[b]	12	1.3
Reason for dose reduction		
Fever and abdominal pain	4	
Rash	1	
Febrile neutropenia	2	
Peripheral neuropathy	4	
Colonic obstruction	1	
Total No. of treatments held	5	0.5
Reason for treatment hold		
Abdominal pain and neuromuscular pain	1	
Peripheral neuropathy	3	
Patient declined further treatment	1	

[a]Did not include the patient from cohort 1 who received only one treatment and developed grade 3 hypertension and peripheral neuropathy. Patient was taken off study.

[b]Dose reduction of brentuximab vedotin alone in 10 cases, of brentuximab vedotin and vincristine in one case, and of all drugs in one case.

TABLE 3. Summary of Adverse Events

Toxicity	No.	%
Adverse events		
Any adverse event	117	100
Grade 3 or higher adverse event	84	72
Adverse event resulting in discontinuation	4	3
Death during treatment	0	0
Death because of drug-related adverse events	0	0
Hospitalizations	24[a]	21
Common adverse events (≥ 10% of patients)[b]		
Neutropenia		
Any grade	52	44
Grade ≥ 3	45	39
Febrile neutropenia		
Any grade	9	8
Grade ≥ 3	9	8
Constipation		
Any grade	81	69
Grade ≥ 3	2	2
Vomiting		
Any grade	30	26
Grade ≥ 3	2	2
Fatigue		
Any grade	93	80
Grade ≥ 3	1	1
Peripheral sensory neuropathy		
Any grade	63	54
Grade ≥ 3	3	3
Peripheral motor neuropathy		
Any grade	5	4
Grade ≥ 3	2	2
Diarrhea		
Any grade	22	19
Grade ≥ 3	4	3
Abdominal pain		
Any grade	39	33
Grade ≥ 3	7	6

[a]Among these 24 patients, there were 41 unique hospitalizations.

[b]The events listed include the most clinically important common adverse events. Excluded adverse events are nausea, alopecia, and anemia.

low-grade (n = 60, 95%) and resolved (n = 48, 76%) or improved to grade 1 (n = 15, 24%) at the time of the last follow-up visit. Clinically significant, treatment-associated pulmonary toxicity was not reported.[25] During treatment, there were 41 serious adverse events requiring hospitalization in 24 patients; the most common reasons were fever and neutropenia, abdominal pain, and infection. Further details on hospitalizations are included in the Data Supplement. There were no treatment-related deaths.

In 27 patients with AMH levels obtained before and after therapy (median of 57 days), concentrations of AMH decreased from a median of 1.8 ng/mL (interquartile range 1.0-3.0) pretreatment to a median of 0.8 ng/mL (interquartile range 0.5-2.0) posttherapy. Five patients successfully conceived after therapy.

Response to Therapy

Overall rates of PET negativity (5-PS score 1-3) were 87% at PET-2, 88% at PET-4, and 85% at EOT (see Table 4 and the Data Supplement). In cohorts 1-4, the CR rate at EOT was 93%, 100%, 93%, and 97%, respectively; thus, the primary efficacy end points per protocol were met for

TABLE 4. PET Results

PET-2					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	All
5-Point Score	n = 29 (%)	n = 29 (%)	n = 29 (%)	n = 29 (%)	N = 116 (%)
Negative (1-3)	26 (90)	26 (90)	22 (76)	27 (93)	101 (87)
4	3 (10)	3 (10)	7 (24)	1 (3)	14 (12)
5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
X	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)

PET-4					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4[a]	All
5-Point Score	n = 29 (%)	n = 29 (%)	n = 29 (%)	n = 29 (%)	N = 116 (%)
Negative (1-3)	27 (93)	27 (93)	24 (83)	24 (83)	102 (88)
4	2 (7)	2 (7)	4 (14)	1 (3)	9 (8)
5	0 (0)	0 (0)	1 (3)	1 (3)	2 (2)
X	0 (0)	0 (0)	0 (0)	3 (10)	3 (3)

EOT PET					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4[a]	All
5-Point Score	n = 27 (%)	n = 29 (%)	n = 29 (%)	n = 29 (%)	N = 114 (%)
Negative (1-3)	25 (93)	26 (90)	23 (79)	24 (83)	99 (85)
4	2 (7)	2 (7)	1 (3)	1 (3)	6 (5)
5	0 (0)	0 (0)	3 (10)	0 (0)	4 (3)
X	0 (0)	1 (3)	1 (3)	4 (14)	5 (4)

EOT CR Rate					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CR rate	27 (93)	29 (100)	27 (93)	28 (97)	111 (96)

NOTE. Further details regarding workup and outcome of patients who did not achieve negative PET-4 or EOT PET are described in the Data Supplement.

Abbreviations: CR, complete response; EOT, end of treatment; PET, positron emission tomography.

[a]Cohort 4 did not include involved-site radiotherapy. Cohort 4 PET-4 results are listed under both PET-4 and EOT PET (same time point).

cohorts 2-4. The EOT PET negativity rate is lower than the CR rate because many patients who had a positive EOT PET were found to not have residual lymphoma after repeat imaging and/or biopsy (Data Supplement).

Survival Outcomes

With median follow-up of 3.8 years (5.9, 4.5, 2.5, and 2.2 years for cohorts 1-4, respectively), the overall 2-year PFS was 94% (95% CI, 89.7 to 98.3) and 2-year overall survival was 99.1% (97.3 to 1.0) (see Fig 2A). In cohorts 1-4, the 2-year PFS was 93.1% (83.9 to 1.0), 96.6% (89.9 to 1.0), 89.7% (78.5 to 1.0), and 96.6% (89.9 to 1.0), respectively. For both cohorts 1 and 2, the 4-year PFS was 93.1%. Among the 116 patients who completed BV + AVD chemotherapy, there were seven disease-related events (Data Supplement). In cohort 1, there were two patients who had a positive PET-4 after BV + AVD × four cycles and biopsy-proven primary refractory disease. In cohort 2, one patient relapsed 34 months after initiation of chemotherapy. In cohort 3, two patients had a positive EOT PET after completion of 30-Gy CVRT and biopsy-proven primary refractory disease and one patient relapsed 9 months after treatment initiation. In cohort 3, three patients experienced early treatment failures post-CVRT with two relapses occurring outside of the CVRT field but within the theoretical ISRT field. In cohort 4, one patient had a positive PET-4 and/or EOT PET and biopsy-proven primary refractory disease.

Patients with relapsed, refractory HL received various salvage therapies followed by high-dose therapy and autologous stem-cell transplant (HDT/ASCT), and six of seven patients are in ongoing remission at this time (Data Supplement). There were two deaths on study. One patient with dermatomyositis and relapsed HL received gemcitabine, dexamethasone, and cisplatin chemotherapy, HDT/ASCT, radiation, and allogeneic stem-cell transplant and died of respiratory failure after allogeneic stem-cell transplant because of polymyositis-associated interstitial lung disease, likely complicated by pulmonary involvement with HL (cohort 3). There was one additional death because of motor vehicle accident unrelated to lymphoma in a patient in ongoing remission (cohort 2).

Prognostic Factors

There were no clear baseline risk factors associated with disease-related events, and interim PET-2 was not correlated with risk of relapse. Among the seven patients with primary refractory or relapsed disease, two met criteria for advanced-stage disease by GHSG (IIBXE and IIBX) and four (57%) had mediastinal masses measuring ≥ 13 cm maximal transverse diameter. The overall CR rate was 96% (111 out of 166); however, the CR rate for patients with traditional disease bulk (> 10 cm) was 88% (29 out of 32) versus 98% (82 out of 84) for nonbulky patients; all three primary refractory patients has mediastinal masses ≥ 13 cm.

DISCUSSION

The results of this pilot study of BV + AVD with and without consolidative RT for ES, unfavorable-risk HL, including patients with disease bulk, demonstrate excellent efficacy across all four cohorts with an overall 2-year PFS of 94%. Clinical outcomes were similar in cohorts 1-3, regardless of the consolidative RT strategy. In cohort 4 with chemotherapy alone, the 2-year PFS was 96.6%, highlighting the

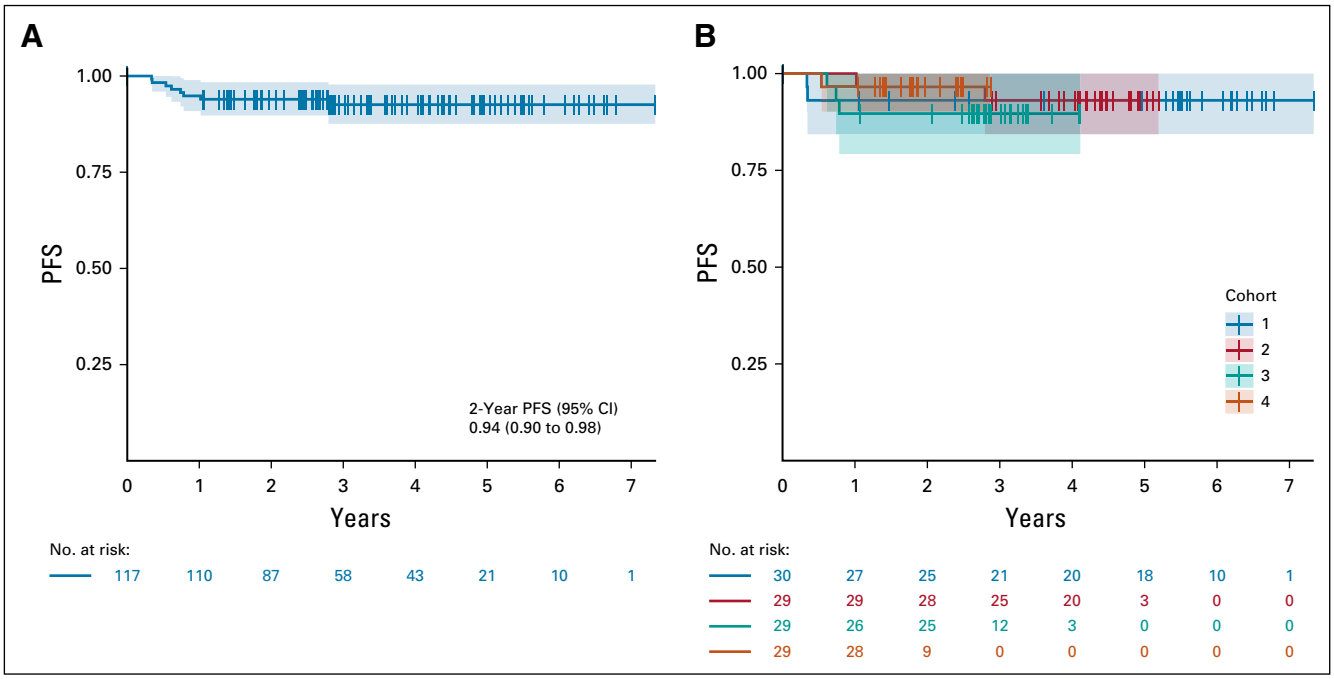

FIG 2. (A) Overall PFS. (B) PFS by cohort. PFS, progression-free survival.

efficacy of the BV + AVD regimen in ES, bulky HL. To our knowledge, this is the largest published study reporting outcomes associated with frontline BV + AVD in patients with bulky stage I or II classical HL.[21,26,27]

The ultimate goal of treatment for patients with bulky ESHL is to achieve high rates of cure with frontline therapy while minimizing long-term toxicity from therapy. In this study, we assessed if the use of a highly active, minimally toxic, induction chemotherapy program, BV + AVD, would result in a high rate of PET negativity and allow for the reduction or elimination of consolidative radiation therapy. The study was designed to decrease the radiation dose and field in a stepwise fashion to assess PET outcomes sequentially prior to eliminating RT in the final cohort. Cohorts 1-3 demonstrated high rates of PET-2 and PET-4 negativity and justified the assessment of whether consolidative RT could be safely omitted following four cycles of BV + AVD.

The well-established treatment approach for patients with bulky ESHL is combined modality therapy, typically with 4-6 cycles of ABVD followed by radiation therapy on the basis of data from the HD11 study.[8] Importantly, the outcome for cohort 2 in our study (BV + AVD followed by 20-Gy ISRT) was superior to that reported for ABVD × four cycles followed by 20-Gy involved-field radiation therapy (IFRT) in HD11 (the arm associated with an inferior outcome), but similar to outcomes reported for bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) × four cycles followed by 20-Gy IFRT, thereby suggesting that BV + AVD is a more active chemotherapy program and allows the reduction in RT dose to 20 Gy. The novel radiation field of CVRT was applied in cohort 3 and was associated with similar outcomes compared with cohorts 1 and 2; however, two of the three treatment failures in cohort 3 occurred within the theoretical ISRT field and outside the CVRT field, suggesting that RT focused on the prechemotherapy volume may be more efficacious. Detailed analysis comparing the ISRT and CVRT approaches including field sizes, relapses, dosimetry, and off-target organ exposure is forthcoming in an alternate publication. Overall, after receipt of BV + AVD × four cycles, our study suggests that an ISRT dose of 30 Gy may not be required.

A primary aim with ESHL treatment, however, is to completely eliminate RT since the HD11 long-term follow-up results show a significant number of events related to treatment-related secondary neoplasms and organ toxicity, which were equivalent between the 20- and 30-Gy IFRT arms.[28] In early-stage, nonbulky HL, PET-adapted treatment approaches, such as RAPID or CALGB 50604, have been shown to be less effective for patients who have larger baseline lymph node masses, ≥ 5 or 7 cm.[14,15] In our study, we included patients with relative disease bulk (> 7 cm in either transverse or coronal dimension on CT) and our results suggest that short-course BV + AVD is likely more efficacious compared with short-course ABVD for this patient population.

To avoid consolidative RT, increasingly, patients with bulky, ESHL are being treated with ABVD × six cycles if they achieve interim and EOT PET negativity on the basis of data from the RATHL study and GITIL/FIL HD0607 Trial.[16,17] Herein, we demonstrate that BV + AVD × four cycles alone

in cohort 4 was associated with a 2-year PFS of 96.6%, which appears at least as efficacious as ABVD × six cycles but is associated with a shorter duration of therapy (four *v* six cycles), involves less anthracycline exposure, and does not include bleomycin. Although the median follow-up for cohort 4 is relatively short in our study (2.2 years), most events occurred early in cohorts 1-3, the shape of the Kaplan-Meier curves is similar across all four cohorts with few late relapses, and with chemotherapy alone in ESHL, most relapses occur within the first 2 years post-treatment. Thus, it is likely that BV + AVD × four cycles alone will be associated with a high cure rate in this patient population.

BV + AVD, similar to BEACOPP, has enhanced efficacy and facilitates reduction or elimination of RT; however, unlike BEACOPP, BV + AVD does not carry the risks of infertility, prolonged fatigue, and myelodysplasia or acute leukemia.[29-31] In addition, the BV + AVD regimen does not include bleomycin and reduces the risk of serious pulmonary toxic effects.[23] Previously published studies of BV + AVD have reported high rates of neutropenia (58%-76%) and febrile neutropenia (19%-35%); however, in our study, the incidence of neutropenia of any grade was 44% and febrile neutropenia was 8%, which is similar to that reported for six cycles of ABVD, likely because of the fact that growth factor support was mandatory per protocol. In contrast to ABVD, there were higher rates of peripheral sensory neuropathy, but this was predominantly low-grade and largely reversible. In addition, rates of abdominal pain, likely neuropathic in origin, were higher with BV + AVD compared with ABVD. BV + AVD was associated with a similar post-treatment decline in AMH levels, as is observed with ABVD.[26] Encouragingly, five patients were able to successfully conceive after treatment; however, further data will be required to characterize the impact of this regimen on fertility.[18]

In conclusion, this study represents among the best-reported outcomes to date for patients with bulky ESHL. Given the limited number of patients per cohort and the nonrandomized design, the current pilot study was not designed to definitively compare the four treatment arms; however, the outcomes establish BV + AVD × four cycles as a highly active and well-tolerated regimen. The encouraging outcomes associated with short-course BV + AVD chemotherapy alone in this study provided support for the UK RADAR study, an ongoing randomized clinical trial comparing ABVD and BV + AVD for ESHL. In future, other novel agents, including checkpoint inhibitors, will be studied to enable omission of RT and reduce long-term toxicity in bulky ESHL.

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Brentuximab Vedotin Combined With Chemotherapy in Patients With Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

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