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blood advances

Impact of cumulative dose of brentuximab vedotin on outcomes of frontline therapy for advanced-stage Hodgkin lymphoma

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Key Points

- The majority of patients with Hodgkin lymphoma treated in the real world did not receive the planned CDB.
- There is no significant association between the CDB frontline therapy and PFS.

In the pivotal study ECHELON-1, brentuximab vedotin (BV), doxorubicin, vinblastine, and dacarbazine (A + AVD) demonstrated superior efficacy compared with bleomycin + AVD for the treatment of advanced-stage classic Hodgkin lymphoma (cHL). However, there are minimal available data regarding the frequency of dose reductions or omission of BV during curative therapy and the potential impact on patient outcomes. In a real-world analysis, we retrospectively reviewed the characteristics and outcomes of 179 patients with stage III or IV cHL treated with frontline A + AVD from January 2010 to April 2022. Treatment consisted of up to 1.2 mg/kg of BV and standard dose AVD IV on days 1 and 15 of each 28-day cycle for up to 6 cycles. At the time of treatment, the median patient age was 37 years, and a high-risk International Prognostic Score was observed in 46% of patients. Overall, 91% of patients received 6 cycles of AVD; 55% of patients did not receive the intended cumulative dose of BV (CDB); 28% of patients received two-thirds or less than the planned CDB. At a median follow-up time of 27.4 months (95% confidence interval [CI], 24.8-29), the median progression-free survival (PFS) was not reached, and the 12-month PFS was 90.3% (95% CI, 85.9-95.0). The impact of CDB on PFS was not significant (P = .15), nor was high CDB significantly associated with increased adverse events. In real-world experience, A + AVD is a highly effective treatment for patients with advanced-stage cHL, including for patients with prominent dose reductions of BV.

Introduction

In the pivotal phase 3 study, ECHELON-1, brentuximab vedotin (BV), doxorubicin, vinblastine, and dacarbazine (A + AVD) demonstrated a survival advantage among patients aged ≥18 years with stage III or IV classic Hodgkin lymphoma (cHL), compared with those who received doxorubicin, bleomycin,

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The full-text version of this article contains a data supplement.

vinblastine, and dacarbazine (ABVD).[1-3] Consequently, A + AVD is one of the standards of care for all patients with advanced-stage cHL. BV is a monoclonal antibody drug conjugated with a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E, which targets CD30 on the Hodgkin lymphoma Reed-Steenberg cell.[4]

The ECHELON-1 trial showed that adding BV and eliminating bleomycin from frontline therapy in the A + AVD regimen lowered the incidence of pulmonary toxicity compared with the ABVD regimen. However, A + AVD showed higher rates of neutropenia and febrile neutropenia, which led to the recommendation of primary prophylaxis with granulocyte colony-stimulating factor (G-CSF).[5] Moreover, peripheral neuropathy (PN) occurred more frequently in patients receiving A + AVD than in those receiving ABVD, which led to BV discontinuation in 10% of the A + AVD group in the ECHELON-1 trial.

In a single-center retrospective study of patients with advanced-stage cHL treated in a real-world setting with A + AVD, 22% of patients required at least 1 dose reduction of BV, and 46% had at least 1 dose omission of BV because of various toxicities.[6] It is unknown whether the cumulative dose reduction of BV because of toxicities affects the efficacy and safety of frontline therapy. We evaluated the safety and outcomes of patients with stage III-IV cHL treated with standard-of-care A + AVD in a large real-world analysis across 9 academic US institutions.

Methods

Patient selection

The study cohort consisted of 179 adult patients (aged ≥18 years) with Ann Arbor stage III or IV cHL treated with frontline A + AVD unrelated to any trial, as described in the ECHELON-1 trial.[1,2] The A + AVD regimen consisted of 1.2 mg of BV per kilogram of body weight (mg/kg; maximum dose, 120 mg), 25 mg of doxorubicin per square meter of body surface area, 6 mg of vinblastine per square meter of body surface area, and 375 mg of dacarbazine per square meter of body surface area IV on days 1 and 15 of each 28-day cycle for up to 6 cycles. Primary prophylaxis with G-CSF was provided at physician's discretion. Patients were treated between January 2010 and April 2022 at 9 US institutions described in supplemental Table 1 in the supplemental Appendix. Patients were stratified into 3 cohorts according to the cumulative dose of BV (CDB): 1 cohort without dose reduction/omission (12 administrations of BV at 1.2 mg/kg, ie, 14.4 mg/kg) and 2 cohorts of near equal size with dose reduction/omission of BV: moderately reduced CDB ranging from 10.5 to 14.1 mg/kg (ie, 73%-98% of the intended CDB) and severely reduced CDB ranging from 2.4 to 9.6 mg/kg (ie, 17%-67% of the intended CDB).

The study excluded patients treated with BV in 21-day cycles (rather than the standard 28 days) or an intended dose of BV above or below 1.2 mg/kg because of potential differences in safety and efficacy. The study did not include patients who received BV monotherapy before AVD because of the different pharmacokinetics and patient populations. The Eastern Cooperative Oncology Group performance status was used to describe performance status at baseline, and the International Prognostic Score (IPS) was used to divide patients into prognostic groups.[7-9] B symptoms are defined as the presence of weight loss (>10% of body weight over the past 6 months), drenching night sweats, and/or fever. Common Terminology Criteria for Adverse Events version 5.0 was used to grade adverse events.[10] Events were documented according to electronic health records. Follow-up data were collected through August 2022. The study was approved by the institutional review board at each participating institution and conducted in accordance with institutional guidelines and the principles of the Declaration of Helsinki. The institutional review board approved the request of waiver of informed consent and a waiver of authorizations because the study does not involve diagnostic or therapeutic intervention or any type of direct patient contact.

Statistical methods

Descriptive statistics are provided, including mean, standard deviation, median, and range for continuous variables, and frequency counts and percentages for categorical variables. The association between categorical variables was evaluated using the χ^2 or Fisher exact test, and the difference in a continuous variable between patient groups was evaluated using the Mann-Whitney test. The primary end point was progression-free survival (PFS), and the secondary end points were adverse events and overall survival (OS).

PFS time was calculated from the date of initiation of frontline therapy to relapse or progression of the disease, death, or last follow-up. OS time was defined as the time from the start of frontline therapy to death or last follow-up. Data of patients who were alive during follow-up were censored at the last follow-up date. The Kaplan-Meier method was used to estimate PFS and OS, and the difference in PFS/OS was evaluated using the log-rank test. The median follow-up time was calculated using the reverse Kaplan-Meier method.[11] Univariable Cox proportional hazards model was fitted for PFS on continuous covariates. Statistical software SAS 9.4 (SAS, Cary, NC), S-Plus 8.2 (TIBCO Software Inc, Palo Alto, CA), and SPSS 21 (IBM Corp, Armonk, NY) were used for all the analyses.

Results

Baseline characteristics

From January 2010 to April 2022, 179 patients at 9 academic sites in the United States were treated with A + AVD. Overall, 56% of the patients were men, 73% had stage IV disease, 66% had B symptoms, 44% had an IPS of 4 to 7, and the median age was 37 years (21% of patients were aged ≥60 years). Baseline characteristics are shown in Table 1.

Therapy

Overall, 91% of patients received 6 cycles of chemotherapy AVD (range, 2-6 cycles), 41% had at least 1 dose omission of BV, and 30% had at least 1 dose reduction of BV. Considering the number of events with dose reduction and omission of BV, 28% of patients received a severely reduced CDB between 2.4 and 9.6 mg/kg, 27% received a moderately reduced CDB between 10.5 and 14.1 mg/kg, and 45% received the intended CDB of 14.4 mg/kg, with a median CDB of 13.2 mg/kg for all the patients. There were statistically significant ($P = .0029$) differences in the median age across CDB groups (median age of 52 years [range, 18-79 years] in the group with CDB between 2.4 and 9.6 mg/kg, 43 years

Table 1. Patient characteristics

Characteristics		All patients N = 179	%
Race	White non-Hispanic	124	69
	Black or Afro-American	24	13
	Asian	6	3
	Not available	3	2
Ethnicity	Not Hispanic or Latino	157	88
	Hispanic or Latino	22	12
Sex	Female	79	44
	Male	100	56
Subtype of cHL	Nodular sclerosis	110	61
	Lymphocyte rich	2	1
	Mixed cellularity	12	7
	Lymphocyte depleted	1	1
	NOS	47	26
	Nodular sclerosis syncytial variant	3	2
	HIV associated	3	2
	Iatrogenic immunodeficiency, EBV$^+$	1	1
Stage	III	49	27
	IV	130	73
ECOG	Not available	3	2
	0	95	53
	1	73	41
	2	7	4
	3	1	1
B symptoms	Absent	61	34
	Present	118	66
IPS	0 or 1	18	10
	2 or 3	83	46
	4 to 7	78	44
Age, y	Median (range)	37 (18-79)	
	<60	142	79
	≥60	37	21

EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

[range, 21-74 years] in the group with CDB between 10.5 and 14.1 mg/kg, and 29 years [range, 18-76 years] in the group with CDB of 14.4 mg/kg). Overall, only 4 patients received consolidative radiotherapy in the first remission.

In addition, 96% of patients received prophylactic G-CSF, with a median number of cumulative administrations of pegfilgrastim of 12 (range, 1-12).

Further patient characteristics and details regarding CDB are described in supplemental Table 1 in the supplemental Appendix.

Safety

The safety profiles are summarized in Table 2 and supplemental Table 2. Overall, any-grade neutropenia was reported in 60%, and febrile neutropenia was reported in 18% of patients. For the patients who presented with at least 1 episode of febrile neutropenia, the median age was 48 years (range, 18-73 years), and 88% had received G-CSF in the 15 days before the event.

All-grade PN occurred in 75% of patients, including grade ≥3 PN (ie, at least severe symptoms, limiting self-care activities of daily living) in 12% of patients. The median age of the patients who experienced grade 3 neuropathy was higher than those without grade 3 neuropathy (50 vs 36 years; *P* value = .026).

Higher CDB did not show statistically significant association with grade ≥3 neuropathy. The proportion of patients with grade ≥3 neuropathy was 4% in the CDB 14.4 mg/kg group, 17% in the CDB 10.5 to 14.1 mg/kg group, and 22% in the group of CDB 2.4 to 9.6 mg/kg group (*P* = .007). At the last follow-up, 35% of patients had complete resolution of their PN, and 34% had partial improvement.

Neuropathy and hematotoxicity/febrile neutropenia were the reasons for dose reduction of BV in 72% and 11% of cases, respectively, and for dose omission of BV in 60% and 10% of cases, respectively.

During therapy, 49% had at least 1 emergency department visit (median, 1 visit [range, 1-9]), and 41% were hospitalized at least once (median duration of hospital stay of 7.5 days [range, 1-79 days]). Furthermore, 4 patients presented with grade ≥3 elevation of lipase, 6 with grade ≥3 elevation of alanine aminotransferase, 7% with deep vein thrombosis, and 4% with pulmonary embolism.

Efficacy

After 2 to 3 cycles of A + AVD, interim positron emission tomography/computed tomography (PET/CT) demonstrated that 73% of patients had a Deauville score[12] ranging from 1 to 3, 17% had a score of 4, 6% had a score of 5, and 4% of patients did not have an interim PET/CT. At the completion of therapy, the Deauville scores were 1 to 3 in 75% of patients, 4 in 4%, 5 in 11%, and not available in 9%. Among the 50 patients who received a severely reduced CDB of 2.4 to 9.6 mg/kg, 70% had a Deauville score of 1 to 3 at the interim PET/CT; among them, only 1 patient had a disease relapse later. There was no statistically significant correlation between CDB and end-of-therapy Deauville score (*P* = .45). A further summary of responses, CDB, and relapses is described in Table 3.

Overall, disease progression occurred in 22 patients; 82% had stage IV and a median IPS of 3.5 (range, 0-6; with a median age of 32.5 years [range, 18-75 years]). These patients received a median CDB of 14.4 mg/kg (range, 3.6-14.4 mg/kg) and had additional therapy. Among them, 45% had a Deauville score of 1 to 3 at the interim PET/CT after 2 to 3 cycles of therapy, and 27% had a score of 1 to 3 at the end-of-therapy PET/CT.

The median PFS was not reached, and the 12-month PFS was 90.3% (95% confidence interval [CI], 85.9-95.0). The median follow-up time was 27.4 months (95% CI, 24.8-29). The impact of CDB on the PFS was not significant (*P* value = .15) when this variable was analyzed as a categorical or continuous variable (Figure 1A).

Alternatively, when comparing patients with full intended dose of BV with those with any dose reduction of BV, the latter had better PFS rates, and this difference in PFS was marginally significant (*P*

Table 2. Summary of adverse events

Variables	1 = yes; 0 = no	All patients		Cumulative received dose of BV (mg/kg)						
				Intended CDB 14.4 mg/kg		Moderately reduced CDB of 10.5-14.1 mg/kg		Severely reduced CDB of 2.4-9.6 mg/kg		
		N = 179	%	n = 81	%	n = 48	%	n = 50	%	*P* value
Neutropenia grade ≥3	0	93	52	51	63	23	48	19	38	**.0194**
	1	84	47	30	37	23	48	31	62	
Anemia grade ≥3	0	126	70	60	74	35	73	31	62	.2317
	1	51	28	21	26	11	23	19	38	
Increase of ALT grade ≥3	0	171	96	80	99	44	92	47	94	.2865
	1	6	3	1	1	2	4	3	6	
Increase of lipase grade ≥3	0	93	52	46	57	25	52	22	44	.1289
	1	4	2	1	1	0	0	3	6	
Thrombocytopenia grade ≥3	0	167	93	77	95	45	94	45	90	.2546
	1	10	6	4	5	1	2	5	10	
Constipation grade ≥3	0	159	89	68	84	41	85	50	100	.3515
	1	3	2	1	1	2	4	0	0	
Nausea grade ≥3	0	152	85	68	84	39	81	45	90	.4496
	1	11	6	3	4	3	6	5	10	
Vomiting grade ≥3	0	152	85	68	84	39	81	45	90	.2205
	1	9	5	2	2	2	4	5	10	
Diarrhea grade ≥3	0	150	84	68	84	38	79	44	88	.1187
	1	10	6	2	2	2	4	6	12	
Fatigue grade ≥3	0	155	87	70	86	39	81	46	92	.3785
	1	9	5	2	2	3	6	4	8	
Neuropathy grade ≥3	0	144	80	67	83	38	79	39	78	**.0073**
	1	22	12	3	4	8	17	11	22	
Pyrexia grade ≥3	0	158	88	69	85	39	81	50	100	.2516
	1	1	1	0	0	1	2	0	0	
Abdominal pain grade ≥3	0	145	81	67	83	36	75	42	84	.0854
	1	15	8	3	4	4	8	8	16	
Oral mucositis	0	155	87	67	83	39	81	49	98	1
	1	3	2	1	1	1	2	1	2	

ALT, alanine aminotransferase.

value = .06; supplemental Figure 1 in the supplemental Appendix). Other analyses comparing different dose groups, such as a third of intended CDB compared with more than a third of intended CDB, did not show statistically significant inferior PFS (supplemental Figures 1-4; supplemental Table 3 in the supplemental Appendix).

In a subgroup analysis, patients aged <60 years did not show statistically significant improved PFS compared with patients aged ≥60 years (12-month PFS was 89% [95% CI, 83-94] for patients aged <60 years vs 97% [95% CI, 91-100] for patients aged ≥60 years) (Figure 1B-C; supplemental Table 4 in the supplemental Appendix). In a univariate analysis, age at diagnosis did not show a statistically significant association with PFS ($P = .58$) or CDB ($P = .66$).

The 24-month OS was 98.5% (95% CI, 96.5-100). Overall, 4 patients died, 1 of stroke and retroperitoneal bleeding (aged 73 years at time of death; CDB of 9.6 mg/kg), 1 of acute myeloid leukemia (aged 69 years at time of death; CDB of 7.5 mg/kg), 1 of sepsis (aged 67 years at the time of death; CDB of 10.8 mg/kg; death possibly related to complication of a procedure and not associated with treatment or in the setting of febrile neutropenia), and 1 of unknown cause (aged 48 years at time of death; CDB of 6 mg/kg).

Discussion

This study presents an overview of the impact of CDB on the safety and efficacy of the A + AVD regimen in a real-world setting based on combined data from 9 US academic institutions. Our results show that reduced CDB neither compromises the efficacy of the

Table 3. Summary of PET/CT responses and relapses

Summary of responses		All patients			CDB received, mg/kg								
					Intended CDB of 14.4 mg/kg			Moderately reduced CDB of 10.5-14.1 mg/kg			Severely reduced CDB of 2.4-9.6 mg/kg		
		N = 179	%	Event(s)	n = 81	%	Event(s)	n = 48	%	Event(s)	n = 50	%	Event(s)
Interim PET/CT Deauville score	1-3	130	73	10	62	77	8	33	69	1	35	70	1
	4	30	17	8	15	19	6	7	15	2	8	16	0
	5	11	6	3	2	2	1	5	10	0	4	8	2
	NA	8	4	1	2	2	0	3	6	0	3	6	1
End-of-treatment PET/CT Deauville score	1-3	135	75	6	63	78	5	30	63	0	42	84	1
	4	8	4	2	3	4	2	4	8	0	1	2	0
	5	19	11	11	10	12	7	5	10	2	4	8	2
	NA	17	9	3	5	6	1	9	19	1	3	6	1

Event: relapse during follow-up.
NA, not available.

A + AVD regimen nor affects its safety based on a lack of statistically significant differences in the survival and adverse events rates between the study groups.

The 6-year follow-up data of the pivotal ECHELON-1 trial showed a survival advantage in patients treated with A + AVD over those who received ABVD (6-year OS, 93.9% in the A + AVD group vs 89.4% in the ABVD group).[1] The regimen A + AVD will possibly replace ABVD as the standard-of-care therapy in the treatment of advanced-stage cHL at many institutions. However, the impact of CDB on safety and efficacy was not presented for patients in the ECHELON-1 trial, which is needed to guide clinical decisions.

In the ECHELON-1 trial, among the 662 patients treated with A + AVD, the median number of doses of BV received was 12 (range, 1-12 doses), and 26% of patients received a dose reduction of BV.[2] Similarly, in our real-world setting study, the median number of doses of BV was 12 (range, 1-12 doses), and 30% of patients had at least 1 dose reduction of BV.

In our real-world study, 76% of patients who had an interim PET/CT had a Deauville score of 1 to 3, which increased to 83% at the completion of therapy. Compared with patients treated with A + AVD in the ECHELON-1 trial, 89% had Deauville score of 1 to 3 at the interim PET/CT, and 86% had this score at the completion of therapy.[2] The lower complete metabolic response rate in our study at the end of therapy could be due to the higher proportion of adults aged ≥60 years. Nevertheless, the patients in our study presented a 12-month PFS of 90.3% (95% CI, 85.9-95.0), which is comparable with the estimated 12-month PFS of 86% for the patients treated with A + AVD in the ECHELON-1 trial. The CDB did not show a statistically significant impact on PFS (P value = .15), even for patients with severe CDB reduction. More studies are needed to evaluate how to avoid overtreatment and identify which patients could benefit from a higher CDB.

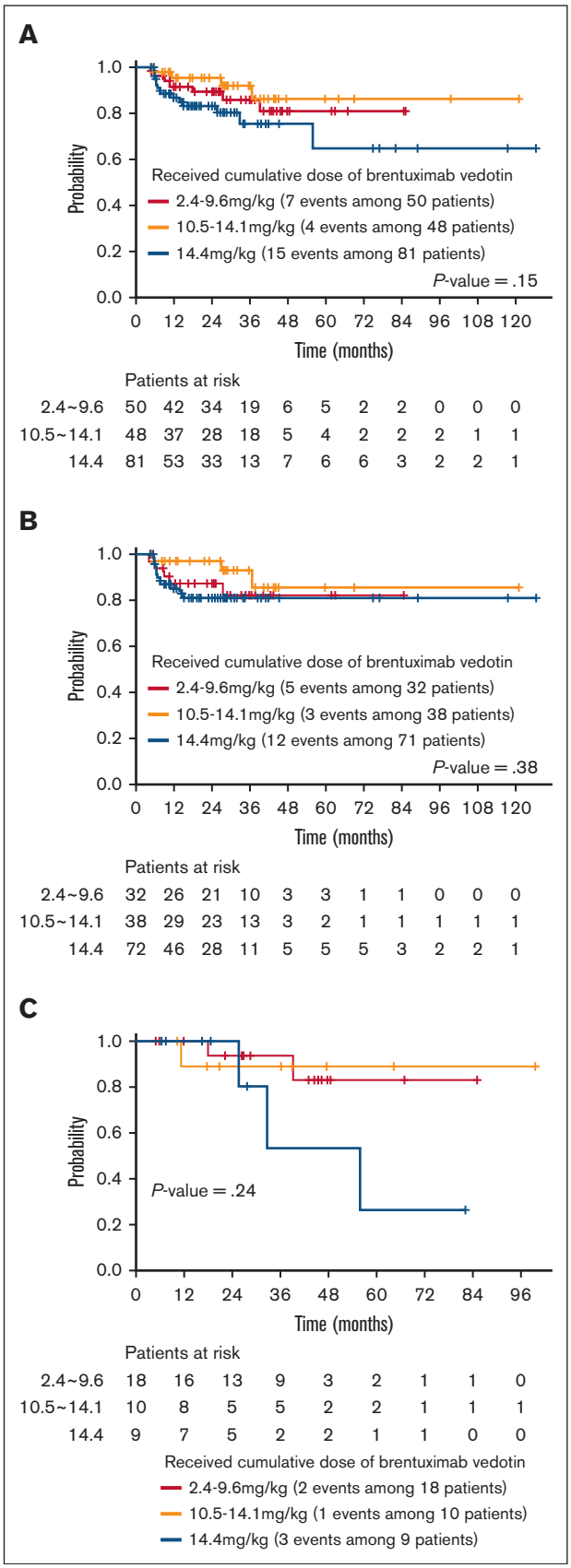
In the pivotal phase 2 study by Younes et al, with BV for patients with relapsed or refractory cHL, the median time to objective response was 5.7 weeks, and the median time to complete response was 12 weeks, suggesting that BV works rapidly and that extended BV may not be as critical.[13] cHL has a bimodal age distribution, peaking first in adolescence or early adulthood and again in older adults, usually >60 years of age.[11] Outcomes in adults aged ≥60 years with cHL have traditionally been poor, partly related to poor tolerance to standard chemotherapy. In the ECHELON-1 trial, 13% of patients treated with A + AVD were aged ≥60 years (median age was 35 years [range, 18-82 years]), which was lower than that in our study (21% of patients aged ≥60 years; median age, 37 years [range, 18-79 years]).

In a detailed analysis of an older patient (aged ≥60 years) subset of the ECHELON-1 study conducted by Evens et al, after a median follow-up of 60.9 months, the 5-year PFS was 67.1% with A + AVD vs 61.6% with ABVD (P = .443).[14] Overall, A + AVD showed similar efficacy to that of ABVD, with survival rates in both arms comparing favorably with those of prior series in older patients with advanced-stage cHL in the later study.[14] Compared with ABVD, A + AVD was associated with higher rates of neuropathy and neutropenia but lower rates of pulmonary-related toxicity.[14] Yet, in our study, patients aged ≥60 years did not show inferior PFS compared with younger patients.

Alternatively, sequential BV-AVD was studied for patients with cHL aged ≥60 years with an intended CDB of 10.8 mg/kg. Based on the intent to treat, the 2-year PFS and OS rates were 84%, and 93%, respectively.[15]

Neuropathy is a cumulative expected class effect of microtubule-binding drugs, such as the microtubule-disrupting agent monomethyl auristatin E covalently linked to the immunoglobulin G1 antibody–directed against CD30.

Increased risks of PN are possibly due to overlapping toxicity between BV and vinblastine.[16] Emerging data of BV plus adriamycin and dacarbazine without vinblastine suggest that this regimen may be efficacious in the frontline early-stage Hodgkin lymphoma with less hematotoxicity and neurotoxicity.[16] In an in vitro study, auristatin E was 52-fold more potent than vinblastine.[17] In addition, the single-center retrospective analysis by Mistry et al suggests that reduction or omission of vinca alkaloids from initial chemotherapy does not deleteriously affect outcomes in patients with lymphoma.[18] Consequently, vinblastine is unlikely to add to



therapeutic effectiveness, although it seems to be additive for toxicity. Studies are underway, investigating the substitution of vinca alkaloids with novel targeted agents.[19]

PN of any grade induced by BV occurred in 75% of the patients in our study and was the most common reason for dose modification or discontinuation of BV. In comparison, PN occurred in 67% of patients in the ECHELON-1 trial.[2]

In our study, 21% of patients aged ≥60 experienced grade ≥3 neuropathy (compared with 12% of all patients) despite decreased CDB. Similarly, in the study by Evens et al, grade ≥3 neuropathy occurred in 18% of patients.[14] In contrast, in the phase 2 trial with sequential administration of BV-AVD and an intended CDB of 10.8 mg/kg for older patients, only 4% of patients experienced grade ≥3 neuropathy.[15]

The inverse correlation of grade ≥3 neuropathy and CDB (P = .007) is possibly due to the limited tolerance of some patients who experienced severe early neuropathy requiring early dose reduction or omission of BV. Inversely, patients who did not have severe BV-induced neuropathy could tolerate high CDB. Moreover, some patients possibly had preexisting neuropathy, which worsened with BV and limited the CDB. Finally, severe neuropathy was more common in older patients, possibly because of more preexisting or risk factors for neuropathy.

The primary mitigation strategy for neurotoxicity consists of dose adjustments and treatment discontinuation. In standard-of-care and clinical trials, neurological symptoms related to BV are mainly self-reported by patients and not evaluated by electromyography. Moreover, some clinicians may not adjust doses or discontinue BV despite PN. Our study showed a dosing variation between the different institutions, as reported in supplemental Table 1 in the supplemental Appendix.

Moreover, 18% of our study patients presented at least 1 episode of febrile neutropenia despite the common use of pegfilgrastim prophylaxis. In particular, 29% of patients aged ≥60 years presented at least 1 episode of febrile neutropenia of any grade despite decreased CDB. In the study by Evens et al, any-grade febrile neutropenia occurred in 37% of patients aged ≥60 years treated with A + AVD.[14]

BV combinations have been studied for different cHL populations, including untreated patients with early stages[16,20,21] and pediatric patients,[22] as salvage therapy,[23,24] and consolidation therapy after autologous stem cell transplantation.[25] More studies are necessary to evaluate how to avoid overtreatment and to which extent our findings can be generalized to other therapeutic regimens that include BV. As a matter of fact, the retrospective study by Wagner et al showed that patients with relapsed/refractory cHL treated with BV maintenance after autologous stem cell transplantation, similar to the AETHERA[25] trial, did not show a statistically significant impact of CDB on PFS.[26]

Figure 1. PFS based on CDB during A + AVD frontline therapy. (A) All patients, (B) patients aged <60 years, and (C) patients aged ≥60 years.

In the Response Adapted Therapy in Advanced Hodgkin Lymphoma trial, the omission of bleomycin from the ABVD regimen after negative findings on interim PET resulted in a lower incidence of pulmonary toxic effects but not significantly lower efficacy than with continued ABVD.[27] A similar PET/CT-directed study[28] with BV instead of bleomycin could potentially allow for a dose reduction or omission of BV for early responders. In our study, 76% of patients who had an interim PET/CT scan presented a Deauville score of 1 to 3 (Table 2). Among the latter, 7.6% had a relapse after receiving a median CDB of 14.4 mg/kg (range, 4.8-14.2 mg/kg), and no deaths occurred. In comparison, 84% of patients in the Response Adapted Therapy in Advanced Hodgkin Lymphoma study presented a Deauville score of 1 to 3 at the interim PET/CT. Alternatively, in the ECHELON-1 trial, the 5-year PFS of patients with a Deauville score of 4 to 5 at the interim PET/CT was 60.6%.[3] Large prospective studies are needed.

Considering that neuropathy and hematotoxicity can be dose-limiting toxicities of BV, this study is the first, to our knowledge, to evaluate the impact of full vs reduced CDB because of dose reduction and/or dose omission on the efficacy and safety of A + AVD. The strengths of our study include the novelty of analyzing the CDB and its impact on the efficacy and safety of patients with cHL treated with A + AVD, the inclusion of patients from various centers, and the availability of granular data. We acknowledge some major limitations of this study, including its relatively small population size, with low power to detect the difference in PFS between the reduced CDB group and the full CDB group because of the limited number of events observed, short follow-up time, lack of central radiology review, and retrospective nature. Moreover, we could not fit the multivariate model because of the limited number of events. In addition, some clinicians might have omitted BV if the patients reached complete metabolic response at the interim PET/CT, creating a bias toward patients with lower CDB and good PFS.

Considering the increased frequency of neurotoxicity and hematotoxicity of A + AVD, our study provides insight into the impact of dose reduction/omission of BV on efficacy and safety. In this real-world experience, A + AVD was a highly effective treatment strategy for patients with advanced-stage cHL, even with dose reduction/omission of BV. Further studies are needed to refine the optimal dose of BV in the frontline setting to check whether toxicity can be reduced without compromising efficacy.

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Authorship

Contribution: R.E.S. and H.J.L. designed the research; R.E.S. performed the research; R.E.S., S.R.H., A.K., T.M.H., N.E., K.A., P.B.A., K.B., D.P., J.P.A., I.S.L., K.D., A.M.E., K.P., S.M.B., M.K., S.B.A., P.T., R.L., S.S., and M.N. collected the data; R.E.S., L.F., and H.J.L. analyzed and interpreted the data; L.F. performed statistical analysis; and R.E.S., N.E., J.P.A., I.S.L., A.M.E., S.M.B., P.T., R.L., S.S., L.F., S.A., R.N., F.V., S.W., P.F., C.C.P., J.R.G., B.S.D., and H.J.L. wrote the manuscript.

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References

1. Ansell SM, Radford J, Connors JM, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2022;387(4):310-320.
2. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378(4):331-344.
3. Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2021;8(6):e410-e421.
4. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016;128(12):1562-1566.
5. Straus D, Collins G, Walewski J, et al. Primary prophylaxis with G-CSF may improve outcomes in patients with newly diagnosed stage III/IV Hodgkin lymphoma treated with brentuximab vedotin plus chemotherapy. *Leuk Lymphoma*. 2020;61(12):2931-2938.
6. Steiner R, Cramer FM, Singh P, et al. Brentuximab vedotin with chemotherapy for advanced stage untreated classic Hodgkin's lymphoma in a real-world setting. *J Clin Oncol*. 2020;38(15_suppl):e20020.
7. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. *N Engl J Med*. 1998;339(21):1506-1514.
8. Repetto L, Fratino L, Audisio RA, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology study. *J Clin Oncol*. 2002;20(2):494-502.
9. Rodday AM, Parsons SK, Upshaw JN, et al. The advanced-stage Hodgkin lymphoma international prognostic index: development and validation of a clinical prediction model from the HoLISTIC consortium. *J Clin Oncol*. 2023;41:2076-2086.
10. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Accessed 1 October 2023. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
11. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;107(1):265-276.
12. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*. 2014;32(27):3048-3058.
13. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183-2189.
14. Evens AM, Connors JM, Younes A, et al. Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study. *Haematologica*. 2022;107(5):1086-1094.
15. Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. *J Clin Oncol*. 2018;36(30):3015-3022.
16. Abramson JS, Bengtson E, Redd RA, et al. Brentuximab vedotin plus adriamycin and dacarbazine in nonbulky limited-stage Hodgkin lymphoma: results of a phase 2 trial. *Blood Adv*. 2023;7(7):1130-1136.
17. Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. *Nat Biotechnol*. 2003;21(7):778-784.
18. Mistry N, Abbott D, Walker Wilkison J, Major A, Haverkos BM, Kamdar M. Dose reduction or omission of vinca alkaloids during initial chemotherapy treatment does not impact outcomes in patients with lymphoma. *Blood*. 2019;134(suppl_1):4126-4126.
19. PET adapted brentuximab vedotin and pembrolizumab in combination with doxorubicin and dacarbazine in classic Hodgkin lymphoma. ClinicalTrials.gov identifier: NCT05922904. Accessed 1 September 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05922904
20. Fornecker LM, Lazarovici J, Aurer I, et al. Brentuximab vedotin plus AVD for first-line treatment of early-stage unfavorable Hodgkin lymphoma (BREACH): a multicenter, open-label, randomized, phase II trial. *J Clin Oncol*. 2023;41(2):327-335.
21. Kumar A, Casulo C, Advani RH, et al. Brentuximab vedotin combined with chemotherapy in patients with newly diagnosed early-stage, unfavorable-risk Hodgkin lymphoma. *J Clin Oncol*. 2021;39(20):2257-2265.

22. Castellino SM, Pei Q, Parsons SK, et al. Brentuximab vedotin with chemotherapy in pediatric high-risk Hodgkin's lymphoma. *N Engl J Med*. 2022; 387(18):1649-1660.

23. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. *Blood*. 2021;138(6):427-438.

24. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132(1):40-48.

25. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015; 385(9980):1853-1862.

26. Wagner CB, Boucher K, Nedved A, et al. Effect of cumulative dose of brentuximab vedotin maintenance in relapsed/refractory classical Hodgkin lymphoma after autologous stem cell transplant: an analysis of realworld outcomes. *Haematologica*. 2023;108(11):3025-3032.

27. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016; 374(25):2419-2429.

28. Casasnovas RO, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol*. 2019;20(2):202-215.