

Bleomycin omission in limited-stage classic Hodgkin lymphoma with negative PET scan after two cycles of ABVD

Front-line therapies in early stage classic Hodgkin lymphoma (cHL) are associated with cure rates of $\geq 90\text{--}95\%$, with overall survival (OS) approaching 100% given the effectiveness of second-line therapy.¹ Thus, treatment strategies have evolved to minimize long-term treatment-associated morbidity and mortality. The phase III NCIC/CCTG HD6 study in early stage cHL evaluated doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) alone compared to standard therapy incorporating radiation therapy (RT).² In the experimental arm, those with a complete response (CR) by computed tomography (CT) scan after ABVD x 2 (CT2) received only two further cycles (total 4); while those with a partial response (PR) received a total of six cycles. Considering both favorable and unfavorable strata, there was a reduced progression-free survival (PFS) with RT omission (87% vs. 92%; $P=0.05$),² but improved OS (94% vs. 87%; $P=0.04$), largely due to the secondary complications from historically used subtotal RT.³ Importantly, for those in a CR by CT2 after ABVD x 2 and thus received four cycles total, the 5-year freedom from progression was 95%, suggesting that a response-adapted approach was feasible.² Collectively, subsequent early stage positron-emission tomography (PET)-adapted studies suggest an approximate 4–8% risk of relapse with RT omission.^{4–6} However, OS is not impacted, and thus PET2-adapted management is widely used.^{4–6}

Bleomycin pulmonary toxicity remains a concern with ABVD. As a cumulative toxicity, the UK RATHL study⁷ investigated bleomycin omission in patients with advanced stage cHL, with a negative PET scan after ABVD x 2 (PET2-negative Deauville 1–3). PFS was not impacted when bleomycin was omitted in the remaining four cycles (AVD), with long term follow-up meeting the pre-defined non-inferiority margin.⁸ Importantly, there was a decreased incidence of bleomycin pulmonary toxicity and improved lung function at 5 years.^{7,9} The GHSG HD13 trial evaluated the impact omitting components of ABVD in early stage favorable cHL and did demonstrate a small (3.9%), but statistically significant, increased risk of relapse comparing ABVD and AVD arms, both receiving involved field RT 30 Gy. However, this study was conducted prior to the use of PET scan for response assessment.¹⁰

Based on the excellent outcomes demonstrated in the HD6 study in those with an interim CT2 CR,^{2,3} a PET2-guided approach was adopted in British Columbia (BC) in 2005 for the management of limited stage cHL, defined as stage I or IIA with non-bulky disease ($<10\text{ cm}$), whereby only those with PET2-positive scan after two cycles of ABVD switched to involved nodal RT,¹¹ and those with a PET2-negative

scan completed therapy with two further cycles of ABVD alone¹² (total 4 cycles). Further, extrapolating from the RATHL study, bleomycin omission was endorsed by our provincial lymphoma tumor group (LYTG) on January 12, 2016, for the remaining two cycles (AVD) for limited-stage cHL patients with PET2-negative scan. Herein, we evaluated the impact on outcomes of this approach.

Patients aged 17–70 years with limited-stage cHL diagnosed between December 2011–June 2022 (follow-up to June 2024) were identified in the BC Cancer Lymphoid Cancer Database, encompassing an era where in addition to response assessment, staging PET scans were also routinely performed. Those planned for curative-intent therapy with ABVD and received at least one cycle were included. Up until 2014, FDG-PET scans were evaluated based on the International Harmonization Project (IHP),¹³ and subsequently by the Deauville criteria (for limited stage: D1–2, DX=PET-negative; D3–5=PET-positive),¹⁴ with ‘real time’ referring to the PET2 interpretation at the time of initial management. Earlier PET scans were re-reviewed and retrospectively assigned a Deauville score as previously described.¹² Patients were recommended to receive ABVD for two cycles. If PET2 was positive, patients switched to involved nodal RT; those with a PET2-negative scan were recommended to receive a further two cycles of ABVD (December 2011 to January 2016, ‘ABVD era’) or AVD x 2 (January 2016 onward [post LYTG meeting], ‘AVD era’) for a total of four cycles. Bleomycin pulmonary toxicity was determined by the treating physician based on clinical and/or radiographic features, resulting in permanent bleomycin discontinuation.

To evaluate the impact of PET-adapted bleomycin omission in limited stage cHL, two analyses were performed: (i) a comparison of outcomes in the ABVD *versus* AVD treatment eras, and (ii) an as-treated analysis evaluating only patients with a PET2-negative scan, who completed treatment with ABVD or ABVD/AVD alone, including a separate analysis of only those who received ABVD x 4 or ABVD x 2/AVD x 2. PFS, defined as the time from pathologic diagnosis to relapse, progression, or death from any cause, and OS were calculated. The University of British Columbia/BC Cancer Research Ethics Board approved this study.

A total of 188 patients treated across BC were identified; most had a staging PET scan ($N=179$, 95.2%). Overall, 17 (9.0%) received RT, primarily for PET2-positive disease as per our management algorithm (14/17, 82%). For all patients, the median follow-up by reverse censoring was 6.2 years (range, 1.3–12.4), and the 5-year PFS and OS were

93.8% and 99.3%, respectively. In total, 67 patients were managed in the ABVD era and 121 the AVD era with a median follow-up of 10.2 years (range, 1.3-12.4) and 4.9 years (range, 2.1-8.4) respectively. Baseline clinical features and involved nodal RT use (median dose 35 Gy; range, 30-40 Gy) were similar across the eras (Table 1) and RT use was also similar (11.9% vs. 7.4%; $P=0.30$). Staging PET scans were performed in all patients in the AVD era compared to 86.6% in the ABVD era, ($P<0.001$); however, this did not impact PFS ($P=0.75$; *data not shown*). Considering all 188 patients, the 5-year PFS was 92.3% in the ABVD era com-

pared to 94.9% in the AVD era ($P=0.50$) (Figure 1); 5-year OS was 98.4% compared to 100%, respectively ($P=0.22$) (*Online Supplementary Figure S1A*). There was only one death due to cHL which occurred during the ABVD era, and two additional deaths during the ABVD era, both due to pancreatic adenocarcinoma. There was one death in the AVD era due to cardiac disease.

In total, 186 patients had a PET2 scan as planned (*Online Supplementary Figure S2*), with 87.6% ($N=163$) 'real time' PET2-negative and 12.4% ($N=23$) PET2-positive. Review of earlier PET scans to assign a Deauville score did not

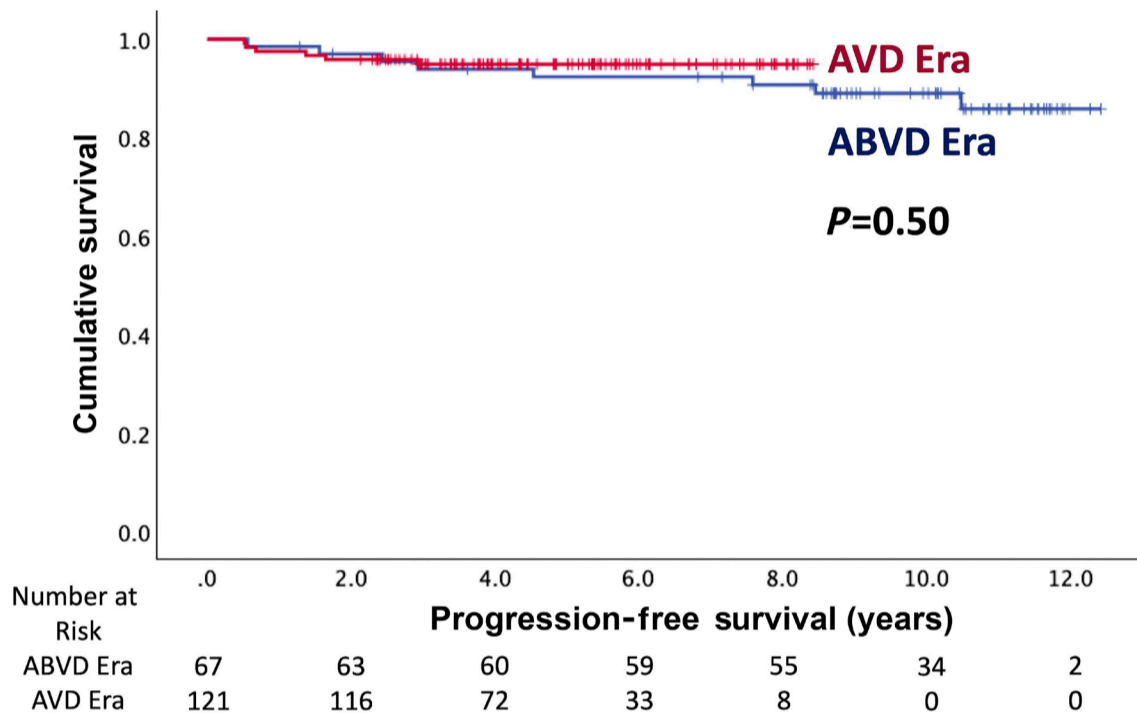


Figure 1. Progression-free survival of limited stage classic Hodgkin lymphoma patients managed in the ABVD era versus AVD era. ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AVD: doxorubicin, vinblastine, dacarbazine.

Table 1. Baseline characteristics, use of staging positron emission tomography scan and receipt of radiotherapy in all patients with limited-stage classic Hodgkin lymphoma, with comparison of those managed in the ABVD and AVD era.

Characteristics	All patients N=188	ABVD era N=67	AVD era N=121	P
Male, N (%)	90 (47.9)	34 (50.7)	56 (46.3)	0.56
Median age, years (range)	34 (17-68)	32 (17-67)	35 (18-68)	-
Age ≥60 years, N (%)	22 (11.7)	8 (11.9)	14(11.6)	0.94
Stage IIA, N (%)	154 (81.9)	57 (85.1)	97(80.2)	0.40
Extranodal involvement, N (%)	7 (3.7)	4 (6.0)	3 (2.5)	0.23
Median size of largest mass, cm (range)	4 (1-9)	4 (1-9)	4 (1-9)	-
Mass size, cm, N (%)				
<5	120 (63.8)	43 (64.2)	77 (63.6)	0.30
5-7	45 (12.2)	13 (19.4)	32 (26.4)	-
>7-9	179(95.2)	11 (16.4)	12 (9.9)	-
Hemoglobin <10.5 g/dL, N (%)	2 (1.1)	1(1.5)	1 (.8)	0.67
Staging PET scan, N (%)	179 (95.2)	58 (86.6)	121 (100)	<0.001
Involved nodal radiation therapy, N (%)	17 (9.0)	8 (11.9)	9 (7.4)	0.30

PET: positron emission tomography; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AVD: doxorubicin, vinblastine, dacarbazine.

alter PET2 response status: PET2-negative (87.6%) D1 N=41, D2 N=87, DX N=35; PET2-positive (12.4%) D3 N=13, D4 N=9, D5 N=1. 5-year PFS was 95.0% and 83.5% for patients with a PET2-negative and PET2-positive scan, respectively ($P=0.02$); 5-year OS estimates were 99.3% and 100%, respectively ($P=0.17$). All but four patients with a PET2-negative scan completed treatment with further chemotherapy; two patients switched to RT and two patients refused further therapy (*Online Supplementary Figure S2*). Thus, 159 patients continued chemotherapy alone (*Online Supplementary Figures S2 and S3*). In total, there were eight recurrences in the PET2-negative cases, two patients of which had refused further chemotherapy after two cycles of ABVD, and the remaining six relapses were all at the original disease site. Of the 23 PET2-positive cases (1 case with a PET scan after cycle 3A), 14 (60.9%) switched to RT as planned. Of these 14 patients, one had relapsed disease outside of the RT field, and one died of pancreatic cancer. The remaining nine PET2-positive cases completed treatment with ABVD (N=4, one of whom received 6 cycles) or a combination of ABVD/AVD (N=1) or AVD alone (N=4) (physician discretion N=8; patient refusal of RT N=1) (*Online Supplementary Figure S2*); two relapsed, one exclusively in sites that would have been included in a RT field, and one also relapsed in distant sites.

There were some management variations in each era, most commonly due to physician decision or toxicity (*Online Supplementary Figure S2*). In the ABVD era, two patients with PET2 D3 (i.e., PET2-positive) received a further ABVD x 2; and 13 with a PET2-negative scan did not complete two full cycles of ABVD, most commonly due to bleomycin pulmonary toxicity (N=11). The remainder of

the treatment variations (N=27) occurred in the AVD era; the most common reasons were failure to omit bleomycin despite a PET2-negative scan (N=19) and failure to switch to RT with D3 (N=5) (*Online Supplementary Figure S2*).

Of the 159 patients with a PET2-negative scan who completed treatment with further chemotherapy alone; 62 of 159 received a ABVD x 2 and 97/159 received AVD x 2 (N=84) as per protocol during the AVD era or, during the ABVD era received <2 subsequent cycles of ABVD (N=13) most commonly due to bleomycin toxicity (*Online Supplementary Figure S3*). In this ‘as treated’ analysis focusing only on PET2-negative cases, baseline clinical features were similar (*data not shown*). The 5-year PFS was 96.7% (ABVD4) and 95.7% (ABVD/AVD), respectively ($P=0.36$), and the 5-year OS 98.3% and 100% ($P=0.75$) (*data not shown*). Considering only patients who received a full four cycles of chemotherapy (N=146) (ABVD x 4 N=62 vs. ABVD x 2/AVD x 2 N=84) (*Online Supplementary Figure S3*), the results are similar: 5 year PFS 96.7% versus 95.0% respectively ($P=0.60$) (Figure 2); 5-year OS 98.3% versus 100% respectively ($P=0.32$) (*Online Supplementary Figure S1B*).

In total, 16 of 188 patients (8.5%) had bleomycin pulmonary toxicity. The majority of patients with bleomycin toxicity were female (11/16, 68.8%); median age was 47 years (range, 17-65) and four patients (25.0%) were 60 years of age or older, representing 18.2% of patients in the latter age group. Overall, 15 patients had clinical symptoms, and one had toxicity detected on PET2 scan; 12 of 16 patients had radiographic findings and seven had abnormal pulmonary function tests. Corticosteroids were used in nine patients (56.3%), and bleomycin was permanently discontinued in all patients. In total, 12 of 67 (17.9%)

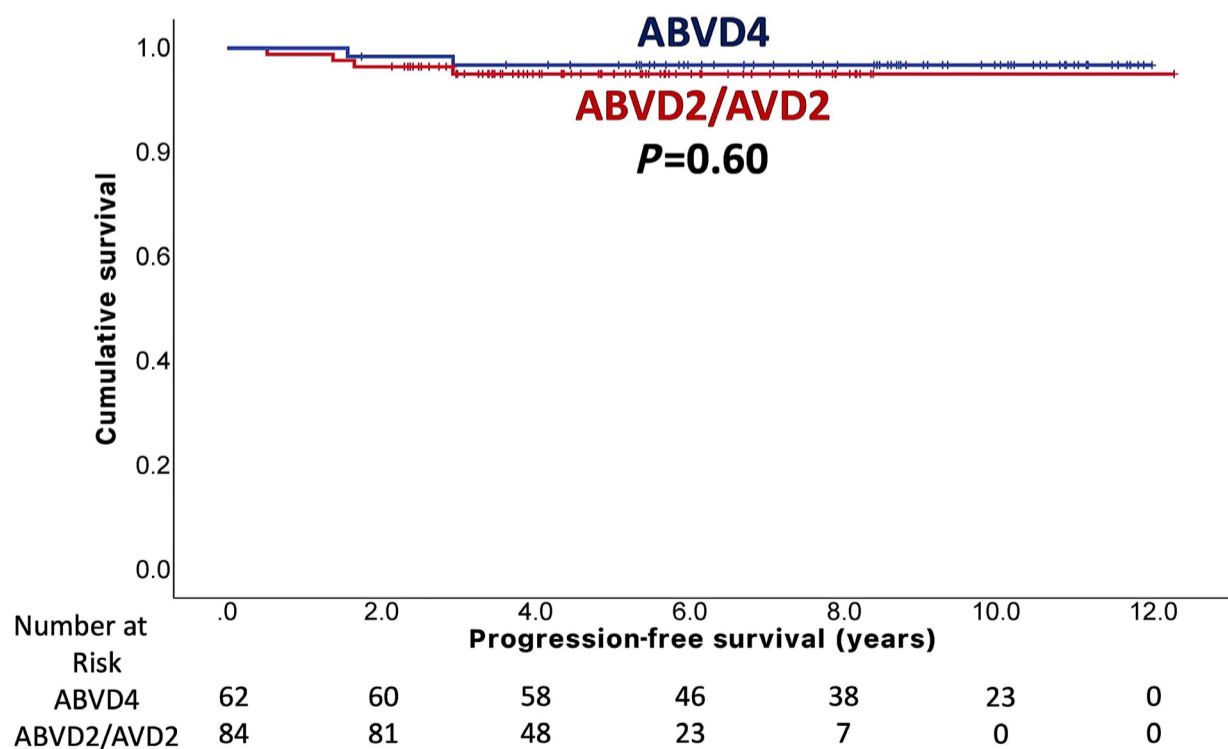


Figure 2. Progression-free survival of limited stage classic Hodgkin lymphoma patients with a PET2-negative scan (Deauville DX, D1-2) following two cycles of ABVD treated with ABVD x 4 versus ABVD x 2/AVD x 2. ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AVD: doxorubicin, vinblastine, dacarbazine; PET2-negative: second positron emission tomography-negative; x 4: 4 cycles; x 2: 2 cycles.

patients had bleomycin toxicity in the ABVD era, nine of which occurred during cycle 3 or 4, compared with only four of 121 (3.3%) in the AVD era ($P < 0.001$), all of which occurred during cycle 2.

We extrapolated the results of the RATHL study and introduced a similar management approach for limited stage cHL, a lower risk group than advanced stage. We confirm that outcomes are preserved in both an era-to-era comparison and considering only those with a PET2-negative scan treated with chemotherapy alone, thus supporting the adoption of this strategy more widely. Notably, bleomycin-associated pulmonary toxicity was lower in the AVD era, but across the study, rare pulmonary toxicity did occur during ABVD cycle 2, thus supporting ongoing studies investigating the omission of bleomycin altogether. Although not the focus of the current study, patients with a PET2-negative scan had a more favorable PFS, but not OS compared with those with a PET2-positive scan. Like the RAPID and H10 trials,^{4,6} we apply a conservative definition of PET2-negative (D1-2, DX) as RT is omitted. This difference in comparison to the RATHL study (PET2-negative D1-3) did lead to some variability in response interpretation by the treating physician. Regardless, for all patients with a PET2-negative scan, the 5-year PFS was 95% with chemotherapy alone.

There are some study limitations, including the retrospective nature and some non-adherence to our management policy, most commonly due to differences in PET2 CR definition in limited and advanced stage. However, strengths of our study include provincially implemented treatment guidelines, broad capture of patients in BC through our provincial database, in addition to both centralized PET reporting and hemato-pathology review. In summary, our data support that bleomycin can be safely omitted from subsequent treatment in limited stage patients with a negative PET scan following ABVD x 2 without compromising cure and may reduce overall bleomycin-related toxicity.

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Disclosures

JY reports honoraria from BeiGene and Sanofi. DV reports honoraria and advisory boards from/for AbbVie, Janssen, Kite/Gilead, AstraZeneca, Roche, BeiGene, Bristol Myers Squibb/Celgene, Merck, and Zetagen; and research funding (to the institution) from AstraZeneca and Roche. ASG reports honoraria from AbbVie, AstraZeneca, Janssen, and Beigene; and research funding (to the institution) from AbbVie, AstraZeneca, Janssen, Roche, and Loxo Oncology. CPV reports honoraria from Jansen, AbbVie, Pfizer, Sanofi, Forus, and Amgen. DWS reports consultancy for AbbVie, AstraZeneca, Chugai, GenMab, Incyte, Roche, and Veracyte; research funds from Janssen and Roche/Genentech; and is a named inventor on a patent describing the use of gene expression to subtype aggressive B-cell lymphomas, one of which is licensed to nanoString Technologies. LHS reports consulting and honoraria for/from AbbVie, Acerta, Amgen, Apbiologix, AstraZeneca, Celgene, Chugai, Gilead, Incyte, Janssen, Kite, Karyopharm, Lundbeck, Merck, Morphosys, Roche/Genentech, Sandoz, Seattle Genetics, Servier, Takeda, Teva, TG Therapeutics, and Verastem; and research funding from Roche/Genentech and Teva. KJS reports honoraria/consultancy for/from SeaGen and Roche; research funding from Bristol Myers Squibb; institutional research funding from Roche, Merck, Seagen and AstraZeneca; data safety monitoring committee for Regeneron; and steering committee for Corvus. The remaining authors have no conflicts of interest to disclose.

Contributions

KJS and JY conceived and designed the study. JY and KJS performed statistical analysis. RPT, DCW, and FB conducted the PET imaging review. GWS conducted the pathology review. ACL provided radiation oncology review. DV, ASG, CPV, DWS, and LHS participated in collecting and analyzing clinical data. JY and KJS wrote the manuscript; and all authors edited and approved the final version of the manuscript.

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Data-sharing statement

The original data are available upon request by contacting the corresponding author.

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