Incorporating novel agents into frontline treatment of Hodgkin lymphoma

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Classical Hodgkin lymphoma (cHL) is associated with excellent outcomes with standard frontline chemotherapy or combined modality therapy. However, up to 25% of patients will have relapsed or primary refractory (RR) cHL. Improving the cure rate with frontline treatment, treatment-related complications and late effects, and poor therapy tolerance with high relapse rates in older patients are unmet needs in the initial management of cHL. The introduction of novel therapies, including the CD30-directed antibody drug conjugate brentuximab vedotin and PD-1 blockade (ie, pembrolizumab or nivolumab), has transformed the treatment of RR cHL and has the potential to address these unmet needs in the frontline setting. Incorporation of these potent, targeted immunotherapies into frontline therapy may improve outcomes, may allow for de-escalation of therapy without sacrificing efficacy to reduce treatment complications, and may allow for well-tolerated and targeted escalation of therapy for patients demonstrating an insufficient response. In this article, we provide a case-based approach to the use of novel agents in the frontline treatment of cHL.

LEARNING OBJECTIVES

- Review the frontline treatment options with a focus on more recent studies incorporating brentuximab vedotin (BV) and PD-1 blockade
- Review the use of frontline BV and anti–PD-1 antibodies in managing older patients with classical Hodgkin lymphoma

Introduction

The frontline treatment of classical Hodgkin lymphoma (cHL) is determined according to stage and prognostic factors. In early-stage cHL, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with radiotherapy or positron emission tomography (PET)–adapted chemotherapy yields long-term progression-free survival (PFS) of 85% to 95%,[1-3] depending on disease bulk and other risk factors. In patients with advanced-stage cHL, PET-adapted approaches starting with ABVD or escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) are associated with 75% to 90% long-term PFS.[4-6] Standard therapy may result in acute and long-term toxicities such as bleomycin pulmonary toxicity (BPT), infertility (particularly with BEACOPP), secondary malignancies, and cardiovascular disease. Targeted, well-tolerated, and highly effective novel therapies may provide an opportunity to refine frontline therapy approaches, either improving or maintaining efficacy while potentially reducing toxicity.

Brentuximab vedotin (BV) is an ADC linking a CD30-targeting antibody with the potent microtubule inhibitor, monomethyl auristatin E. BV was initially approved in patients with relapsed or primary refractory (RR) cHL who progressed after autologous stem cell transplantation with an overall response rate (ORR) and complete response (CR) rate of 75% and 33%, respectively, and a median PFS of 9.3 months.[7] Nivolumab and pembrolizumab are anti–PD-1 antibodies that block interactions with PD-L1 and PD-L2 ligands, overexpressed in Hodgkin/Reed-Sternberg cells due to genetic alterations at chromosome 9p24.1.[8] Exploiting this genetic sensitivity, pembrolizumab and nivolumab produce an ORR of 69% to 72% and a CR rate of 16% to 28% in patients with RR cHL who failed prior autologous stem cell transplantation and/or prior BV with a median duration of response of ~16 months.[9-12] After their approval in RR cHL, the anti–PD-1 antibodies and BV were studied in earlier lines of therapy, including salvage treatment and ultimately frontline treatment.

Here, we review the data evaluating BV and PD-1 blockade in the frontline setting and discuss their current and possible future roles in early-stage and advanced-stage cHL.

CLINICAL CASE

A 24-year-old asymptomatic man presents with a supraclavicular mass, and excisional biopsy specimen reveals nodular sclerosing cHL. PET/computed tomography demonstrates an FDG-avid 1.9-cm right cervical lymphadenopathy (standardized uptake value [SUV] max 12.6), right supraclavicular lymphadenopathy measuring 2.3cm (SUV max 12.7), left supraclavicular lymphadenopathy measuring 1.2cm (SUV max 6.7), and a 4-cm mediastinal mass (SUV max 10.0). Laboratory values were as follows: white blood cells, 8.03; absolute neutrophil count, 5.99; hemoglobin, 14.4; platelets, 254; and ESR, 60.

Early-stage cHL

Combined-modality treatment

Conventional treatment of early-stage cHL has historically comprised combination chemotherapy and radiation, with duration of chemotherapy and dose of radiotherapy based on the presence of clinical risk factors that denote favorable or unfavorable disease (Table 1). The HD10 established ABVD×2 followed by 20 Gy of involved-field radiation therapy (IFRT) as the standard combined-modality treatment (CMT) for early-stage favorable cHL.[13] HD11 established ABVD×4 followed by 30 Gy IFRT as standard CMT for early-stage unfavorable cHL, with HD14 demonstrating in comparison superior PFS but comparable overall survival (OS) with escalated (esc)BEACOPP×4 followed by 30 Gy IFRT.[14,15]

PET-adapted therapy

PET-adapted therapy of early-stage cHL uses interim PET (iPET) results to omit radiation and/or shorten the duration of chemotherapy in PET-negative patients or escalate therapy in PET-positive patients (Table 1). In patients with early-stage nonbulky cHL, the RAPID study assessed the noninferiority of chemotherapy alone vs CMT among patients with a negative iPET scan.[1] While ABVD×3 alone in PET-negative patients resulted in 3-year PFS of 91%, noninferiority to CMT was not established, particularly in patients with tumors larger than 5cm.[1,16] CALGB 50604 also studied a PET-adapted approach in early-stage nonbulky patients using iPET Deauville score (DS) 1 to 3 as negative—after ABVD×2, an additional ABVD×2 resulted in an overall 3-year PFS of 89%, and 3-year PFS of 91% in PET after 2 cycles (PET2)-negative patients while escalating to escBEACOPP in PET2-positive patients resulted in a 3-year PFS of 66%.[3] Notably, patients with iPET DS 1 to 2 had a 3-year event-free survival of 94%, while iPET DS 3 patients had a 3-year event-free survival of 77%, raising the question of whether a shorter course of ABVD was appropriate for iPET DS 3 patients, although the number of patients in that subgroup was small.[3] In separate cohorts for early-stage favorable and unfavorable cHL, the H10 study evaluated a response-adapted strategy after ABVD×2, comparing 1 to 2 additional cycles of ABVD followed by involved node radiotherapy based on risk in the control arm compared with 2 to 4 additional cycles of ABVD without radiation depending on risk in the experimental arm. PET2-positive patients received escBEACOPP×2 followed by radiation. The study demonstrated that CMT improved 5-year PFS by 12% in favorable-risk patients and 3% in unfavorable-risk patients. For PET-positive patients, intensified therapy improved 5-year PFS by 13%.[2] In early-stage bulky patients, the CALGB 50801 study demonstrated excellent outcomes with omitting radiation in 78% of patients who were iPET negative (ABVD×6 total), and in iPET-positive patients (escalation to BEACOPP with consolidative radiation), outcomes were also excellent (3-year PFS 93.1% in PET negative, 89.7% in PET positive).[17]

These randomized trials have demonstrated a small but consistent detriment in PFS when radiation is omitted for iPET-negative patients and a benefit in PFS with escalation of therapy for iPET-positive patients. Despite the failure of RAPID and H10 studies to show noninferiority in PFS with PET-adapted omission of radiotherapy compared with CMT, there was no survival difference between PET-adapted approaches and CMT. Treatment selection for early-stage cHL should entail a balanced discussion with the patient of the potential late effects of radiation (secondary malignancies, cardiovascular/pulmonary complications) with the risks of PET-adapted radiotherapy omission (inferior disease control). In certain scenarios, the authors favor PET-adapted chemotherapy approaches (young, female patients with mediastinal/axillary involvement, 3+ areas of lymph node areas of involvement), but there are other patients in whom a CMT approach may be favored (eg, male patients with a single, peripheral site of involvement).

Using novel agents in frontline early-stage cHL

Studies incorporating BV into treatment of early-stage cHL have shown promising efficacy despite the omission of radiation (Table 2). A multicenter phase 2 study evaluating BV-AVD (doxorubicin, vinblastine, and dacarbazine) in stage I/II, nonbulky, favorable or unfavorable cHL that used a PET-adapted approach of BV-AVD for 4 cycles in PET2-negative patients and 6 cycles in PET2-positive patients demonstrated 3-year PFS of 94% and OS of 97%.[18] Another multicenter study evaluated the role of consolidative radiation after BV-AVD in early-stage unfavorable cHL, with the majority of enrolled patients having bulky disease (defined as >7cm). Patients received BV-AVD×4 cycles followed by either 30 Gy or 20 Gy involved-site radiotherapy, consolidation-volume radiotherapy, or no radiotherapy. Across the cohorts, the overall 2-year PFS and OS rates were 94% and 99%, respectively, with a 2-year PFS of 97% in the cohort of patients who received BV-AVD×4 without radiation.[19] A multicenter phase 2 study evaluated BV as consolidation after frontline ABVD for nonbulky, early-stage favorable and unfavorable cHL, stratifying patients to 3 arms with varying duration of ABVD based on risk and iPET followed by 6 cycles of BV consolidation, resulting in a 3-year PFS of 92% and 3-year OS of 97%.[20] In all of these studies, the incorporation of BV into frontline therapy of early-stage cHL was generally well tolerated, with higher rates of peripheral neuropathy observed and more febrile neutropenia/sepsis observed when BV was combined with AVD.

PD-1 blockade has also been studied in the frontline setting for early-stage cHL either sequentially or concurrently with chemotherapy (Table 2). In early-stage unfavorable cHL patients, the phase 2 randomized NIVAHL trial of 109 patients compared 4 cycles of concomitant nivolumab (N) and AVD to sequential

Table 1. Selected clinical trials in early-stage Hodgkin lymphoma without the use of novel agents

Trial	N	Clinical disease features	Median age, y	Therapy received/arms of treatment	Median follow-up, y	Response	PFS	OS
Combined-modality treatment								
HD10[13]	1370	Favorable, stage I or II	38.8	1. ABVD×4+30 Gy IFRT 2. ABVD×4+20 Gy IFRT 3. ABVD×2+30 Gy IFRT 4. ABVD×2+20 Gy IFRT	7.5	CR rates 1. 96.3% 2. 96.6% 3. 97.3% 4. 96.3%	8-year PFS 1. 88.4% 2. 90.0% 3. 85.4% 4. 86.5%	8-year OS 1. 94.4% 2. 94.7% 3. 93.6% 4. 95.1%
HD11[14]	1395	Unfavorable, stages IA, IB IIA, IIB	33	1. ABVD×4+30 Gy IFRT 2. ABVD×4+20 Gy IFRT 3. $BEACOPP_{baseline}$×4+30 Gy IFRT 4. $BEACOPP_{baseline}$×4+20 Gy IFRT	7.6	CR rates Overall 94.1% 1. 94.7% 2. 92.8% 3. 94.4% 4. 94.6%	5-year PFS 1. 87.2% 2. 82.1% 3. 87.9% 4. 87%	5-year OS 1. 94.3% 2. 93.8% 3. 94.6% 4. 95.1%
HD14[15]	1528	Unfavorable, stages IA, IB, IIA, IIB	32	1. ABVD×4+30 Gy IFRT 2. escBEACOPP×4+30 Gy IFRT	3.6	CR rates Overall 95.4%	5-year PFS 1. 89.1% 2. 95.4%	5-year OS Overall 97.0% 1. 96.8% 2. 97.2%
PET-adapted treatment								

RAPID[1]	602	Stage IA or IIA, nonbulky	34	ABVD×3 → PET
				If PET−, then
				1. IFRT or
				2. No further treatment
				If PET+, then
				3. ABVD×1+30 Gy IFRT
					5		3-year PFS
							1. 94.6%
							2. 90.8%
							3. 87.6%
								3-year OS
								1. 97.1%
								2. 99.0%
								3. 87.6%

CALGB 50604[3]	164	Stage I or II, favorable or unfavorable, nonbulky only	31	ABVD×2 → PET 1. If PET−, then ABVD×2 2. If PET+, then escBEACOPP×2+IFRT	3.8	EOT CR rate 1. 97% 2. 85%	3-year PFS PET− DS 1–3 Overall 89% 1. 91% 2. 66% PET− DS 1–2 Overall 94%	
EORTC H10[2]	1950	Stage I or II, favorable or unfavorable	30	Favorable 1. ABVD×2 → ABVD×1+INRT or ABVD×2 → PET 2. If PET−, then ABVD×2 3. If PET+, then escBEACOPP×2+INRT Unfavorable 4. ABVD×2 → ABVD×2+INRT or ABVD×2 → PET 5. If PET−, then ABVD×4 6. If PET+, then escBEACOPP×2+INRT	4.5		PET+ Favorable and unfavorable Group 1 or 4: 5-year PFS 77.4% Group 3 or 6: 5-year PFS 90.6% PET− Favorable Group 1: 5-year PFS 99.0% Group 2: 5-year PFS 87.1% Unfavorable Group 4: 5-year PFS 92.1% Group 5: 5-year PFS 89.6%	PET+ Favorable and unfavorable Group 1 or 4: 5-year OS 89.3% Group 3 or 6: 5-year OS 96.0% PET− Favorable Group 1: 5-year OS 100% Group 2: 5-year OS 99.6% Unfavorable Group 4: 5-year OS 96.7% Group 5: 5-year OS 98.3%
CALGB 50801[48]	94	Stage IA-IIB, bulky only	30	ABVD×2 → pET 1. PET−, then ABVD×4 2. PET+, then escBEACOPP×4+30 Gy ISRT	5.5		3-year PFS 1. 89.7% 2. 92.3%	3-year OS 1. 94.4% 2. 97.7%

RATHL[24]	1203	Stage IIB to IV or IIA with adverse features	33	ABVD×2 → PET
				If PET−, then
				1. ABVD×4 or
				2. AVD×4
				If PET+, then
				3. BEACOPP×4
					3.4		3-year PFS
							1. 85.7%
							2. 84.4%
							3. 67.5%
								3-year OS
								1. 97.2%
								2. 97.6%
								3. 87.8%

INRT, involved node radiotherapy; pET, positron emission tomography.

Table 2. Selected clinical trials in early-stage Hodgkin lymphoma using novel agents

Trial	N	Clinical disease features	Median age, y	Therapy received/arms of treatment	Median follow-up, y	Response	PFS	OS
BV-AVD[18]	34	Stage I/II, favorable and unfavorable, nonbulky only	36	BV-AVD×2 → PET 1. If PET−, then BV-AVD×2 (total 4) 2. If PET+, then BV-AVD×4 (total 6)	3.2	ORR and CR at EOT 91.2%	3-year PFS 94%	3-year OS 97%
ABVD followed by BV consolidation[20]	41	Stage I/II, favorable and unfavorable non-bulky only	29	ABVD×2 → PET 3. If favorable and PET−, then BV consolidation 4. If favorable and PET+ or unfavorable and PET−, then ABVD×2+BV consolidation 5. If unfavorable and PET+, then ABVD×4+BV consolidation	3.9	CR rate 95%	3-year PFS 92%	3-year OS 97%
BV-AVD[19]	117	Stage I/II, unfavorable only	32	BV-AVD×4 → PET If PET−, then 1. 30 Gy ISRT 2. 20 Gy ISRT 3. 30 consolidation volume radiotherapy 4. No radiotherapy	3.8	EOT CR rates for 4 cohorts 1. 93% 2. 100% 3. 93% 4. 97%	Overall 2-year PFS 94% 2-year PFS for 4 cohorts 1. 93.1% 2. 97% 3. 90% 4. 97%	Overall 2-year OS 99.1%
NIVAHL[21]	109	Stage I/II, unfavorable only	27	1. Nivo-AVD×4+30 Gy ISRT 2. Sequential therapy: nivo×4 doses → nivo-AVD×2 → AVD×2+30 Gy ISRT	1.2 in group 1 and 1.1 group 2	Group 1: ORR 100%, CR 83% Group 2: ORR 98%, CR 84%	12-month PFS: Group 1: 100% Group 2: 98%	12-month OS 100% in both groups
Sequential pembrolizumab and AVD[22]	30	Stage I/II unfavorable only, stage III/IV	29	Pembro×3 → AVD×4–6 (4 cycles for early stage, 6 cycles for advanced stage or early-stage bulky)	1.9	CMR after pembro 37%, CMR after AVD 100%, EOT CMR 100%	Median PFS not reached, 2-year PFS 100%	Median OS not reached, 2-year OS 100%
Pembrolizumab and AVD[23]	30	Stages I, II, III, IV	32	Pembro+AVD (2–6 cycles)	0.86	68% PET2−, 78% EOT PET−	1-year PFS 96%	1-year OS 100%

CMR, complete metabolic response.

treatment with 4 doses of nivolumab, 2 cycles of N-AVD, and 2 cycles of AVD followed by a 30-Gy involved-site radiotherapy in both groups. The CR rate at end of treatment (EOT) was 90% in the concomitant arm and 94% in the sequential therapy arm, with a 12-month PFS of 100% for patients receiving concomitant treatment and 98% for patients receiving sequential therapy.[21] Another phase 2 study of 30 patients evaluated frontline sequential pembrolizumab monotherapy for 3 cycles followed by AVD 4 to 6 cycles in both early-stage unfavorable and advanced-stage cHL. In the early-stage unfavorable patients (n=12), the CR rate after 3 cycles of pembrolizumab was 42%, and with a median follow-up of 22.5 months, the median PFS and OS were not reached (2-year PFS and OS 100%).[22] Another ongoing 30-patient study is evaluating concurrent pembrolizumab with AVD treatment in untreated cHL of any stage that has included 40% early-stage patients. With a median follow-up of 10.3 months, 1-year PFS and OS were 96% and 100%, but outcomes in the early-stage group have not yet been reported separately.[23]

There are several ongoing studies, including large randomized phase 3 trials, evaluating the incorporation of BV and/or PD-1 blockade into frontline treatment of early-stage cHL (Table 3). While the results of smaller phase 2 studies have been promising thus far, these randomized studies will determine whether novel agents can improve outcomes in early-stage cHL or allow for the safe omission of radiation therapy. Currently, in the absence of randomized evidence, PET-adapted chemotherapy or CMT remains the standard treatment approach for early-stage cHL.

Table 3. Ongoing trials with novel agents in early-stage and advanced-stage cHL

Trial	Clinical trials.gov identifier	Clinical disease features	Therapy received/arms of treatment	Phase	Anticipated enrollment
Brentuximab vedotin and nivolumab in treating patients with early-stage cHL	NCT03712202	Early stage (favorable, unfavorable, bulky, nonbulky)	ABVD×2 → PET– 1. ABVD×2→ nivo×6 or 2. BV×nivo×6 PET+ 3. BV-AVD×4 → nivo×6 *Bulky patients all randomized to arm 1	2	264
Brentuximab vedotin in early-stage Hodgkin lymphoma (RADAR)	NCT04685616	Early stage (favorable, unfavorable, bulky, nonbulky)	1. ABVD±ISRT ABVD×2 → PET DS 1–3 ABVD×2 DS 4 ABVD×2+ISRT DS 5 withdraw 2. BV-AVD±ISRT BV-AVD×2 → PET DS 1–3 BV-AVD×1 DS 4 BV-AVD×2+ISRT DS 5 withdraw	3	1042
BV-AVD+nivolumab in stage I/II cHL	NCT03233347	Early stage (favorable, unfavorable, nonbulky)	BV-AVD×3 → PET 1. If PET+, → BV+nivo×4 →If PET+, → nivo×8 2. If PET–, → nivo×8	2	82
Avelumab+ABVD in advanced-stage cHL (AVENuE)[50]	NCT03617666	High risk stage II, stage II, stage IV cHL	Avelumab×4 → ABVD×2 → PET PET+, → escBEACOPP×4 PET–, → AVD×4	2	49
Pembrolizumab and chemotherapy in advanced-stage cHL (KEYNOTE-C11)	NCT05008224	Unfavorable risk stage I/II, stage III, or stage IV	Pembro×3 → AVD×2 → PET 1. PET–, → AVD×4 → pembro×4 2. PET+→ escBEACOPP×4 → pembro×4	2	140
Immunotherapy (nivolumab or BV) plus chemotherapy (S1826)[35]	NCT03907488	Stage III or IV cHL	1. Nivolumab+AVD×6 (with interim PET2) 2. BV-AVD×6 (with interim PET2)	3	987
Brentuximab vedotin, nivolumab, doxorubicin, and dacarbazne (AN+AD) for advanced-stage cHL (SGN35–027 Part B)[50]	NCT03646123	Bulky stage I/II, stage III, or stage IV	(BV+nivolumab+doxorubicin+dacarbazine)×6	2	240

CLINICAL CASE 1 (Continued)

This patient with newly diagnosed unfavorable stage IIA cHL was treated with 4 cycles of ABVD (PET2 was negative) based on the CALGB 50604 study given nonbulky disease and the patient's desire to avoid radiation. He achieved CR at EOT.

CLINICAL CASE 2

A 28-year-old man presents with new-onset chest pain, pruritus, and diffuse lymphadenopathy with ultrasound-guided biopsy of the left supraclavicular lymph node consistent with cHL. PET/computed tomography showed a 11.8-cm superior mediastinal mass (SUV 15.5), an 8-cm right pulmonary mass (SUV 14.3), a 2.3×1.4-cm left supraclavicular lymphadenopathy (SUV 12.5), and a 1.1×0.8-cm left retroperitoneal lymphadenopathy (SUV 13.1). Laboratory values were as follows: white blood cells, 18; hemoglobin, 9; platelets, 150; albumin, 2.0; and ESR, 40.

Advanced stage

Frontline advanced-stage cHL management without novel agents

Standard-of-care frontline treatment for advanced-stage cHL in North America for over 20 years has been a full course of ABVD-based therapy for 6 cycles. The RATHL study evaluated dropping bleomycin after 2 cycles using a PET-adapted approach, with the aim of reducing the cumulative bleomycin dose and minimizing the risk of BPT. Omitting bleomycin after 2 cycles (AVD) in PET2-negative patients was noninferior to ABVD×6, with a 3-year PFS of 84.4% vs 85.7%, respectively, and a 3-year OS of 97.6% vs 97.2%, respectively, with fewer respiratory adverse events observed in the AVD arm, thus validating PET-adapted A(B)VD as the standard frontline treatment approach for advanced-stage cHL.[24] The PET-adapted SWOG S0816 established the role of escalating therapy from ABVD to escBEACOPP for PET2-positive patients with a 5-year PFS of 66%.[25] EscBEACOPP is a more intensive regimen primarily used in Europe that is associated with superior disease control in advanced-stage cHL.[26] However, BEACOPP is associated with more toxicity, including

myelosuppression, increased risk of secondary malignancies, infertility, and prolonged fatigue, among other adverse effects.[26] Given the excess toxicities associated with escBEACOPP, 2 studies established the feasibility of de-escalating escBEACOPP therapy for early responders based on iPET2 either to reduced number of cycles in the HD18 study (5-year PFS of 90.8% vs 92.2% in standard and reduced-cycle arms, respectively)[27] or to ABVD in the AHL2011 trial (5-year PFS of 86.2% vs 85.7% in standard and de-escalation arms, respectively).[28] Despite improved disease control, BEACOPP is not associated with a survival advantage over ABVD; thus, use of one regimen or the other in advanced-stage cHL depends on provider and patient prioritization of efficacy and toxicity (Table 4).

Novel agents in frontline advanced-stage cHL

The randomized phase 3 ECHELON-1 trial compared BV-AVD with non-PET-adapted ABVD as frontline treatment of advanced-stage cHL, resulting in a modest improvement in the primary end point of independently assessed 2-year modified PFS with BV-AVD (82.1% vs 77.2%, $P = .04$),[29] as well as investigator-assessed 3-year PFS with BV-AVD (83.1% vs 76.0%, $P = .005$) (Table 5).[30] A post hoc subgroup analysis showed that patients from North America, patients with involvement of ≥1 extranodal site, patients with a high-risk International Prognostic Score, stage IV patients, and younger patients appeared to derive greater benefit from BV-AVD.[30] The 5-year follow-up of ECHELON-1 demonstrated ongoing benefit of BV-AVD over ABVD, with a 5-year PFS rate of 82.2% vs 75.3%, respectively ($P = .0017$), with the benefit maintained across prespecified subgroups, including age, International Prognostic Score risk group, and disease stage. The benefit of BV-AVD over ABVD was observed irrespective of the PET2 status but statistically significant in the PET2-negative group (5-year PFS of 84.9% vs 78.9%, $P=.0035$) compared with the PET2-positive group (5-year PFS of 60.6% vs 45.9%, $P=.23$).[31] Importantly, there was increased toxicity observed with BV-AVD compared with ABVD, including higher rates of neuropathy (all grades, 67% vs 43%; grade 3, 11% vs 2%), febrile neutropenia (19% vs 8%), and grade ≥3 infection (18% vs 10%), except for pulmonary toxicity (2% vs 7%) in BV-AVD and ABVD arms, respectively.[29,31] Prophylactic granulocyte colony-stimulating factor (G-CSF) with BV-AVD reduced the rate of grade ≥3 neutropenia to 29% from 70% and febrile neutropenia to 11% from 21%.[32] Peripheral neuropathy improvement or resolution was observed in most patients in both arms (85% vs 86%).[31] While fertility was not formally assessed in ECHELON-1, there was no significant difference in the number of pregnancies after either treatment in long-term follow-up.[31] The recent ASCO 2022 abstract demonstrated that at a median follow-up of 73 months, the 6-year OS rates were 93.9% vs 89.4% with BV-AVD vs ABVD, respectively, with comparable long-term safety profiles.[33] BV-AVD treatment resulted in a statistically significant 41% reduction in the risk of death vs ABVD,[33] which makes a compelling case for the preferred use of BV-AVD over ABVD for previously untreated advanced-stage cHL.

Multiple studies have evaluated PD-1 blockade in combination with chemotherapy in the frontline setting for advanced-stage cHL (Table 5). The CheckMate 205 phase 2 trial assessed frontline nivolumab monotherapy followed by nivolumab plus AVD in patients with advanced-stage cHL, resulting in acceptable tolerability with few immune-related adverse events, as well as an EOT CR rate of 67% per independent radiology review committee, a CR rate of 80% per investigator, and 9-month modified PFS 92%.[34] Two separate studies have incorporated pembrolizumab into frontline therapy of cHL. One evaluated sequential pembrolizumab followed by AVD chemotherapy,[22] and the other studied concurrent pembrolizumab and AVD chemotherapy.[23] Both studies included a mix of early-stage and advanced-stage cHL and yielded similar results, with 2-year PFS 100% in the sequential study and 1-year PFS of 96% in the concurrent study.

The ongoing SWOG S1826 study is a phase 3 randomized study comparing N-AVD with BV-AVD to determine the best immunotherapy partner for AVD in patients with newly diagnosed advanced-stage cHL.[35] There are several other ongoing trials evaluating nivolumab and BV in frontline therapy for advanced-stage cHL (Table 3).

CLINICAL CASE 2 (Continued)

This patient has high-risk disease with an IPI score of 5 (points given for sex, albumin, hemoglobin, stage, and leukocytosis) with extranodal involvement. He was treated with 6 cycles of BV-AVD with G-CSF support per ECHELON-1 and achieved CR. He developed grade 1 peripheral neuropathy, which resolved after completion of treatment.

CLINICAL CASE 3

A 70-year-old man presents with fatigue, night sweats, and diffuse palpable nontender adenopathy. Excisional lymph node biopsy specimen of the left supraclavicular node is consistent with cHL mixed cellularity type. Staging PET shows diffuse hypermetabolic disease, including bilateral hilar and retroperitoneal adenopathy, with the largest node being 5.8cm (SUV 17.9). Patient has history of heart failure with ejection fraction of 45% and prior smoking history.

Elderly/frail patients

Combination chemotherapy is associated with increased toxicity and poor outcomes in older, frail patients with cHL.[36,37] In the E2496 study comparing Stanford V with ABVD in advanced-stage cHL, patients ≥60 years old had higher treatment-related mortality (9% vs 0.3%), lower 5-year failure-free survival (48% vs 74%), and lower 5-year OS (58% vs 90%) compared with the younger patients.[36] An analysis of the older patients from ECHELON-1 demonstrated that BV-AVD has similar efficacy to ABVD (5-year PFS of 67.1% vs 61.6%) but poorer outcomes compared with the overall cohort.[38] BV-AVD in older patients was associated with higher rates of neuropathy and neutropenia compared with ABVD and compared with those reported with BV-AVD in the overall cohort.[38] Given the increased toxicity observed, novel therapies have been studied in older/frail patients as an alternative to traditional therapy, including BV and PD-1 blockade (Table 6).

Table 4. Selected clinical trials in advanced-stage Hodgkin lymphoma without the use of novel agents

Trial	N	Clinical disease features	Median age, y	Therapy received/arms of treatment	Median follow-up, y	Response	PFS	OS
Stanford V[49]	142	Stage III or IV or locally extensive mediastinal stage I or II	28	Stanford V: vinblastine, doxorubicin, vincristine, bleomycin, etoposide, and prednisone followed by 36 to 44 Gy RT	5.4		5-year freedom from progression 89%	5-year OS 96%
S0816[25]	331	Stage III or IV	31	ABVD×2 → PET 1. If CR, then ABVD×4 2. If not in CR, then switch to escBEACOPP×6	5.9	PET2− 82%	5-year PFS Overall 74% PET2− 76% PET2+66%	5-year OS Overall 94% PET2− 96% PET2+86%
RATHL[24]	1214	Stage IIB to IV or stage IIA with adverse features	33	ABVD×2 → PET 1. If PET−, then AVD×4 2. If PET+, then switch to escBEACOPP	3.4	PET− 83.7%	3-year PFS PET2− 85.7% PET2+67.5%	3-year OS PET2− 97.2% PET2+87.8%

HD18[27]	2101	Stage III or IV, stage II with B symptoms or bulky	32	escBEACOPP×2 → PET
				If PET−, then
				1. escBEACOPP×6 (later amended to escBEACOPP×4) or
				2. escBEACOPP×2
				If PET+, then
				3. escBEACOPP×6
					5.5		Overall 5-year PFS 89.4%
							PET− Overall 5-year PFS 91.4%
							escBEACOPP×8 (or×6) 5-year PFS 90.8%
							escBEACOPP×4 5-year PFS 92.2%
							PET+ 5-year PFS 88.3%
								Overall 5-year OS 95.6%
								PET− Overall 5-year OS 96.3%
								escBEACOPP×8 (or×6) 5-year OS 95.4%
								escBEACOPP×4 5-year OS 97.7%
								PET+ 5-year OS 95.5%

AHL2011[28]	826	Stage III or IV, high-risk IIB	30	escBEACOPP×2 → PET (2) Standard group: 1. escBEACOPP×2 → PET (4) If PET−, then escBEACOPP×2 If PET+, then salvage or PET-adapted approach: 2. If PET+, then escBEACOPP×2 → PET (4) If PET−, then escBEACOPP×2 If PET+, then salvage or 3. If PET−, then ABVD×2 → PET (4) If PET−, then ABVD×2 If PET+, then salvage	4.2		Overall standard arm: 5-year PFS 86.2% PET-adapted arm: 5-year PFS 85.7% PET2 and PET4− 5-year PFS 92.5% PET2+ and PET 4− 5-year PFS 75.4% PET 4+ 5-year PFS 46.5%	Overall Standard Arm: 5-year OS 95.2% PET-adapted arm: 5-year OS 96.4%

RT, radiotherapy.

Table 5. Selected clinical trials in advanced-stage Hodgkin lymphoma using novel agents

Trial	N	Clinical disease features	Median age, y	Therapy received/arms of treatment	Median follow-up, y	Response	PFS	OS
ECHELON 1[31]	1334	Stage III or IV	36	1. ABVD×6 2. BV-AVD×6	5.1		BV-AVD 5-year PFS 82.2% ABVD 5-year PFS 75.3%	
CHECKMATE 205[34]	51	Stage III, IV, or IIB with unfavorable risk factors	37	Nivo×4 → nivo+AVD×6	0.93	84% ORR, 67% CR	9-month PFS 92%	9-month OS 98%
Sequential Pembro and AVD[22]	30	Stage I/II unfavorable only, stage III/IV	29	Pembro×3 → AVD×4–6 (4 cycles for early stage, 6 cycles for advanced stage or early-stage bulky)	1.9	CMR after pembro 37%, CMR after AVD 100%, EOT CMR 100%	Median PFS not reached, 2-year PFS 100%	Median OS not reached, 2-year OS 100%
Pembro+AVD[23]	30	Stages I, II, III, IV	32	Pembro+AVD (2–6 cycles)	0.86	68% PET2–, 78% EOT PET–	1-year PFS 96%	1-year OS 100%

CMR, complete metabolic response.

Table 6. Selected clinical trials in elderly patients using novel agents

Trial	N	Clinical disease features	Median age, y	Therapy received/arms of treatment	Median follow-up, y	Response	PFS	OS
BV	27	≥60 years cHL	78	BV monotherapy×16 cycles		ORR 92%, CR 73%	Median PFS 10.5 months	Median OS not reached
BV (BREVITY)[40]	38	Stage II with B-symptoms or bulky disease, stage III, stage IV unfit for standard chemotherapy	77	BV monotherapy×16 cycles	3	ORR 83.9%, CR 25.8%	Median PFS 7.3 months	Median OS 19.5 months
BV+bendmaustine (HALO)[42]	59	Stages III, IV, elderly HL	70.3	BV+bendamustine	1.7		2-year PFS 54%	2-year OS 83%
BV+DTIC[41,43]	19	Stages I-IV, aged ≥60 years	69	BV+dacarbazine	4.83	ORR 100%, CR 68%	Median PFS 46.8 months	Median PFS 64 months
BV+bendamustine[41,43]	20	Stages I-IV, aged ≥60 years	75	BV+bendamustine	4.3	ORR 100%, CR 88%	Median PFS 40.3 months	Median OS 46.9 months
BV+nivo (≤16 cycles[43]	21	Stages I-IV, aged ≥60 years	72	BV+nivolumab for up to 16 cycles	1.6	ORR 95%, CR 79%	Median PFS not reached	Median OS not reached
Sequential BV → AVD in elderly[47]	69	Stages I, II, III, IV, aged ≥60 years	69	BV×2 → AVD×6 → BV×4	0.52	ORR 82%, CR 36%	2-year PFS 84%	2-year OS 93%
BV+nivolumab (8 cycles) (ACCRU RU051505I)[46]	46	Stages I, II, III, IV, aged ≥60 years or unsuitable for standard chemo-therapy	71.5	BV+nivolumab for 8 cycles	1.8	ORR 64%, CR 52%	Median PFS 18.3 months	Median OS not reached

DTIC, dacarbazine; HL, Hodgkin lymphoma.

BV monotherapy demonstrated an ORR of 84% to 92% and CR rates of 26% to 73% in newly diagnosed elderly/frail patients with cHL with a median PFS of 7.3 to 10.5 months, with the primary toxicity being neuropathy.[39,40] BV-based doublets, both BV+chemotherapy and BV+PD-1 blockade, have demonstrated efficacy in the frontline setting for elderly patients with cHL. BV+dacarbazine and BV+bendamustine have resulted in similar 100% ORR and similar CR rates of 62% to 69% vs 88%, respectively. However BV+bendamustine is associated with increased toxicity in elderly patients.[41] The durability of responses is improved when single-agent chemotherapy is added to BV, with a median PFS of 46.8 months and a 3-year PFS of 52% with BV+dacarbazine and a median PFS of 40.3 months and a 3-year PFS of 60.3% with BV+bendamustine.[41-45] Frontline BV+nivolumab has also been evaluated in 2 phase 2 studies and is associated with best ORR of 91% to 95% and CR rates of 65% to 79%. More grade ≥3 adverse events were observed in elderly patients, most commonly elevated lipase (19%), neutropenia (17%), and peripheral neuropathy (11%-14%, 48% all grades).[43] A fixed duration of 8 cycles of BV+nivolumab was found to have an ORR of 61%, a CR of 48%, and a median PFS of 18.3 months in the ACCRU RU051505I study, but it was closed to accrual after interim analysis failed to meet prespecified efficacy criteria.[46]

Many older patients with cHL are candidates for combination chemotherapy, but BPT remains an important risk. One multicenter phase 2 study evaluated omission of bleomycin, in favor of sequential brentuximab followed by AVD in treatment-naive patients with cHL aged ≥60 years. Patients were treated with 2 cycles of BV followed by AVD×6, followed by BV×4 in responding patients. This approach yielded an ORR of 95% and a CR rate of 90% after 6 cycles of AVD with a 2-year event-free survival, PFS, and OS rates of 80%, 84%, and 93%, respectively. The most common high-grade adverse event was neutropenia (44%), and 33% patients had grade 2 peripheral neuropathy.[47] Although only about half of patients completed all planned therapy and 20% of patients did not complete a full curative intent course of AVD chemotherapy, 75% of patients who did not receive a full course of AVD remained in CR, suggesting that outcomes were similar among patients who discontinued early.[47]

The use of novel agents has transformed the frontline management of elderly, frail patients. Patients who can tolerate chemotherapy should be treated with a sequential BV-AVD regimen due to curative potential with the administration of full systemic course of therapy but minimization of BPT and less toxicity compared with concurrent BV-AVD, given the sequential nature of chemotherapy administration.[47] If a patient cannot tolerate combination chemotherapy, BV doublets represent an effective and well-tolerated option, and BV monotherapy can be used in those who are more frail. Patients whose performance status improves with treatment can be transitioned to combination chemotherapy.

CLINICAL CASE 3 (Continued)

Given this patient's smoking history, age, and heart failure history, both bleomycin and doxorubicin were avoided, and the patient received BV+dacarbazine for 12 cycles followed by BV monotherapy and achieved CR.

Conclusion

Several clinical trials have evaluated the use of BV and PD-1 blockade in the frontline treatment of cHL. The incorporation of these agents into frontline cHL treatment provides opportunities to potentially improve outcomes, reduce short- and long-term toxicities of therapy, or escalate/de-escalate therapy in a targeted way. While studies using BV and PD-1 blockade for initial treatment of early-stage cHL have yielded promising results, randomized studies to establish these approaches as a standard option are ongoing, and novel agents remain investigational in that setting. For advanced-stage cHL, omitting bleomycin and substituting with BV in combination with AVD is a standard-of-care approach that improves efficacy but is associated with some added toxicity. The ongoing randomized S1826 study will further clarify the role of PD-1 blockade in frontline advanced-stage cHL. Finally, novel agents have a clear role in the frontline management of older/frail patients with cHL who are unable to tolerate combination chemotherapy and are at higher risk for BPT. With ongoing and upcoming studies potentially cementing the role of novel agents in frontline cHL management, future research will be needed to identify ways to overcome resistance to BV and PD-1 blockade, optimally salvage patients who progress after frontline regimens by incorporating novel agents, and understand what role newer agents (eg, CD30 chimeric antigen receptor T cell therapy) may play and how to sequence these therapies.

Conflict-of-interest disclosure

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Off-label drug use

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