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REVIEW ARTICLE

Therapeutic Roles of Antibody Drug Conjugates (ADCs) in Relapsed/Refractory Lymphomas

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Abstract

Relapsed or refractory lymphoma is commonly treated with combination chemoimmunotherapy and cellular immunotherapy. Modest response rates and associated toxicities are obstacles to achieving durable remission using traditional cytotoxic chemotherapy, especially in frail patients with advanced disease. Antibody drug conjugates represent a new class of novel targeted agents with significant improvement in therapeutic efficacy in the treatment of lymphomas. Several of these agents, which offer improved targeting, greater potency, and better therapeutic index over traditional chemotherapy, are changing the treatment landscape for lymphomas and other hematological malignancies. Despite the therapeutic potential of these agents, the delivery and release of cytotoxic agents to malignant cells through the combination of a monoclonal antibody, payload, and linker represents a complex design challenge. This article reviews the clinical data on currently available antibody drug conjugates and the ongoing development of novel antibody drug conjugates. Antibody drug conjugates constitute an important armamentarium for treatment of lymphomas and their evolving roles in the treatment spectrum are discussed.

Keywords: Antibody drug conjugate, Relapse refractory, Non-Hodgkin lymphoma

Malignant lymphomas are a heterogeneous family of lymphoid malignancies which typically develop in lymphoid organs but may occur in almost any tissue. Both Hodgkin and non-Hodgkin lymphoma (NHL) are common cancers in the United States and affect all ages. Most cases of NHL (85%-90%) are of B-cell origin, with 10−15% derived from T-cells or natural killer-cells. There are 61 subtypes of NHL recognized in the 2016 World Health Organization classification [1]. The majority of Hodgkin lymphoma (HL) patients are cured with front-line therapy and a minority require salvage chemotherapy and hematopoietic cell transplantation (HCT) [2]. The disease course of NHL is more variable. While some NHL exhibit indolent behavior, with a long disease course of repeated relapses and progression, others are extremely aggressive and require treatment with multi-agent chemoimmunotherapy [3,4].

Lymphomas can express a wide variety of surface antigens depending on which immune cell they are derived from. Surface antigens including CD19, CD20, CD22 and CD79a are expressed on all B lymphocytes except pre-pro B lymphocytes and mature plasma cells. These antigens play a wide range of vital roles in B-cell biology including regulation of cell activation, proliferation, differentiation, migration, anergy, and apoptosis [5]. Rates of expression of these antigens in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are as high as 90−100%. CD30 is expressed on the surface of activated B-cells and plays a critical role in B-cell isotype switching. It is expressed in about 25% of DLBCL cases [5]. Because CD30 expression is

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often high on lymphoma cells and relatively limited in normal tissues, abrogation of CD30 signaling via antibody drug conjugates [ADC] has been used as a promising treatment strategy.

1. Current treatment approaches in relapsed/refractory lymphoma

A detailed description on all available chemotherapy options for relapsed/refractory (R/R) lymphoma is beyond the scope of this review. Treatment decisions for R/R HL and NHL take into account the patient's histological subtype, extent of disease, age, and comorbidities. Multi-agent chemotherapy regimens remain the mainstay of the therapeutic armamentarium with an overall response rate (ORR) of 20–85% and complete remission (CR) seen in one-quarter to two-thirds of patients [6]. However, these agents are rather nonspecific with significant hematological and non-hematological toxicities. Hence, they are poorly tolerated in patients with advanced disease, comorbidities, and poor performance status. An emerging therapeutic option that has shown success is CD19 chimeric antigen receptor (CAR) T-cell therapy, available to patients who failed two or more prior lines of therapy. However, the cost and toxicities associated with CAR T-cell therapy remain a significant burden [7]. Despite recent therapeutic advances in lymphoid malignancies, treatment challenges remain for the management of both HL and NHL and many novel approaches are being pursued. ADCs are a novel drug delivery concept which offer precision drug delivery to target tissues, thus minimizing potential toxicities and improving therapeutic indices. Here, we review the current status and future treatment implications of ADCs in lymphomas.

2. Antibody drug conjugates (ADC)

The essential function of the ADC is to promote the internalization of a cytotoxic drug into malignant cells while minimizing toxic effects on neighboring healthy tissue (Fig. 1). This requires high specificity of the monoclonal antibody for the target antigen, high penetrance, and high expression of the target antigen on the tumor cells with a limited expression in healthy tissues [8].

The development of ADCs led to the introduction of targeted agents with an improved therapeutic index and better tolerability [9]. An ADC is comprised of a monoclonal antibody conjugated with a cytotoxic agent via a linker (Fig. 1) [9]. Early generation ADCs experienced several limitations related to immunogenicity, potency, target selection, and tumor selectivity [9]. Newer generations of ADCs have several novel features that are designed to address these limitations. With advances in bioengineering techniques, newer ADCs have chimeric or fully humanized antibodies, which have decreased immunogenicity compared with their earlier counterparts, longer circulation times, and improved antibody dependent cellular cytotoxicity [10]. Cytotoxic agents used in modern ADCs for the treatment of NHL include microtubule inhibitors (maytansinoids 1 [DM1], maytansinoids 4 [DM4], monomethyl auristatin E [MMAE], and monomethyl auristatin F [MMAF]) or DNA synthesis inhibitors (calicheamicins, duocarmycins, pyrrolobenzodiazepine dimers, and doxorubicin) which are much more potent than doxorubicin and methotrexate used in early generation ADCs [11].

The effectiveness of an ADC may be limited by insufficient expression of antigens on tumor cells, inappropriate or low-affinity binding, or a lack of internalization following binding [12]. However, there is evidence of certain ADC designs, particularly those with cleavable linkers, resulting in "bystander killing." In this phenomenon, the cytotoxic portion of the ADC is released after uptake by a tumor cell that expresses the target antigen or by proteases or pH differences in the tumor microenvironment. The released cytotoxic agent can then damage neighboring tumor cells that do not express the target antigen. This may allow for durable responses despite intratumoral variation in target antigen expression [13]. Site-specific conjugation has been useful for overcoming low expression of target antigens and slow tumor cell internalization kinetics, while achieving a high therapeutic index [12].

Given their efficacy and safety profile, multiple ADCs have been approved by the FDA for clinical use in hematological malignancies in the U.S. which include: gemtuzumab ozogamicin (a CD33-targeting agent approved for acute myeloid leukemia), brentuximab vedotin (a CD30-targeting agent approved for HL and anaplastic large cell lymphoma), inotuzumab ozogamicin (a CD22-targeting agent approved for acute lymphoid leukemia) and polatuzumab vedotin (a CD79-targeting agent approved for NHL). In the following section, we will review the current data on clinically available ADCs and novel ADCs in development. Table 1 provides a summary of novel ADCs for B-Cell, T-Cell Non-Hodgkin and Hodgkin Lymphoma. Table 2.

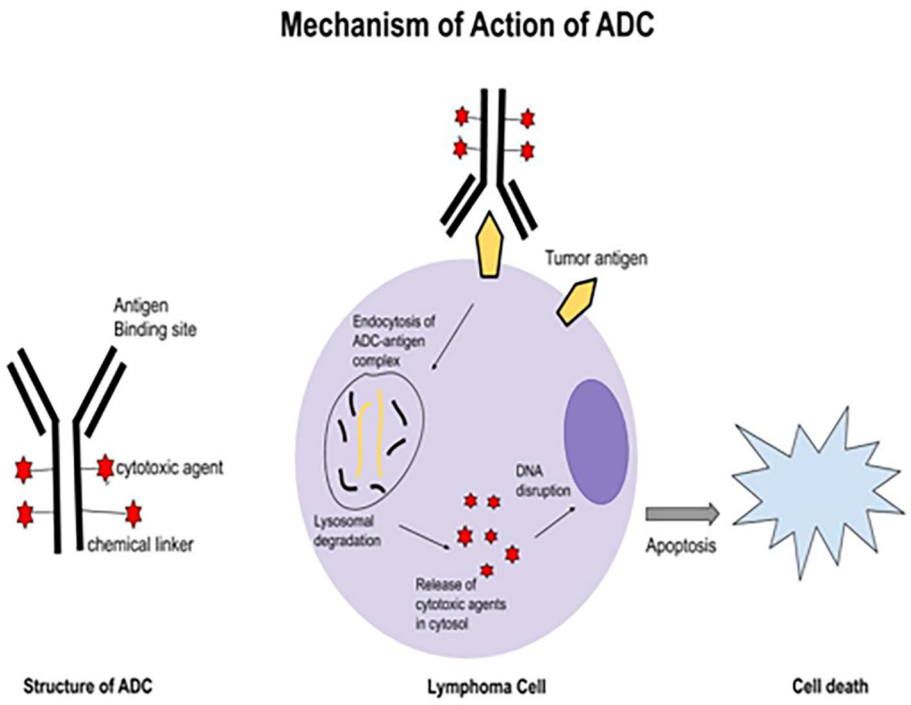

Fig. 1. Structure and Mechanism of action of Antibody Drug Conjugate.

3. Hodgkin's lymphoma

ADCs are currently being used in both R/R and early stage HL settings, either alone or in combination with chemotherapy and have shown overall better responses than chemotherapy alone. ADCs have become important therapeutic option for patients with HL.

4. Anti-CD30 ADCs in HL

CD30 is a member of the tumor necrosis factor (TNF) receptor superfamily and is primarily expressed in Hodgkin Reed-Sternberg cells in HL, anaplastic large-cell lymphoma, and a subset of DLBCL [14]. Brentuximab vedotin (BV or AdcetrisTM) is an ADC composed of a chimeric anti-CD30 monoclonal antibody attached to MMAE, a synthetic microtubule disrupting agent, via a dipeptide linker. In a pivotal phase II trial, 102 patients with R/R HL who failed autologous HCT were treated with intravenous BV 1.8 mg/kg every 3 weeks at a maximum of 16 cycles in the absence of disease progression or unacceptable toxicity [15]. The ORR was 75% with 34% CR and a median duration of response (DOR) of 6.7 months. The most common adverse events were peripheral sensory neuropathy (42%), nausea (35%), fatigue (34%), and neutropenia (19%). Grade $\geq$ 3 adverse events were experienced by 55% of patients, with the most common being neutropenia (20%) and peripheral sensory neuropathy (8%). Most adverse events were manageable with dose reductions and/or delays [15].

The AETHERA trial was a randomized multicenter open label phase III study that evaluated BV as maintenance therapy following HCT. A total of 329 patients with HL received BV 1.8 mg/kg for 16 cycles, starting 30–45 days after HCT [16]. At 5-year follow-up, BV continued to provide patients with a sustained progression-free survival (PFS) benefit; 5-year PFS was 59% (95% confidence interval [CI], 51–66) with BV versus 41% (95% CI, 33–49) with placebo (hazard ratio [HR], 0.521; 95% CI, 0.379–0.717). Upfront post-HCT consolidation with BV significantly delayed time to subsequent therapy, an indicator of ongoing disease control, versus placebo. Peripheral neuropathy; the most common adverse event in patients receiving BV (56% in BV vs. 16% placebo), improved and/or resolved in 90% of patients [16]. Based on the AETHERA findings, BV has been FDA approved for post-HCT maintenance for high risk HL patients, i.e. patients with primary refractory disease, relapsed disease less than 12 months after completion of frontline therapy, or extra-nodal disease at the time of relapse.

The ECHELON-1 trial, a randomized multicenter open label phase III study enrolled 1334 newly diagnosed HL stage III/IV patients. Patients were

Table 1. Summary of Novel Antibody Drug Conjugates [FDA Approved]

	Disease Setting	Combination Agents	Study Phase	# of Patients	Line of Therapy	ORR (CR)	PFS (months)	Median OS (months)	Adverse Events (G3 +)	Reference #
Brentuximab vedotin, CD30, Monomethyl auristatin E	R/R DLBCL (NHL)	None	II	48	>1	44% (17%)	4.0	NR	Neutropenia (37%), nausea (12%), fatigue (12%)	[26]
	R/R DLBCL (NHL)	Rituximab	I/II	16	>1	NR	NR	NR	Neutropenia (19%), pyrexia (6%)	[26]
FDA Approved Indications: •HL after failure of ASCT or failure of ≥2 lines of treatment in pts who are not ASCT candidates	DLBCL (NHL)	RCHOP	II	73	1st line	84.9% (69.9%)	NR	NR	Febrile neutropenia (24%), diarrhea (5.5%), bacteremia (4.1%), pneumonia (4.1%)	[52]
	R/R PMBL (NHL)	None	II	6	>1	17% (17%)	NR	NR	NR	[26]
	R/R FL (NHL)	None	II	3	>1	0% (0%)	NR	NR	NR	[26]
	R/R ALCL (NHL)	None	II	58	>1	86.2% (57.0%)	13.3	NR	Neutropenia (20.7%), thrombocytopenia (13.8%), peripheral neuropathy (12.1%),	[53]
•Systemic anaplastic large cell lymphoma after failure of ≥ 1 line of treatment	PTCL (NHL)	CHP	III	226	1st line	83.2% (67.7%)	48	NR	Neutropenia (34.5%), anemia (13.5%), diarrhea (5.8%)	[49]
	PTCL (NHL)	CHEP	II	28	1st line	95% (90%)	NR	NR	Neutropenia (29%), anemia (21%), febrile neutropenia (21%)	[21]
	CTCL (NHL)	None	III	64	>1	54.7% (17.2%)	16.7	NR	Peripheral sensory neuropathy (5%), fatigue (5%), diarrhea (3%), skin infection (3%)	[50,51]
	HL (Stage III-IV)	AVD	III	664	1st line	85.7% (73.5%)	NR	NR	Neutropenia (53.9%), peripheral sensory neuropathy (4.7%), peripheral neuropathy (4.1%)	[17,18]
	HL (Stage I-II)	Adriamycin and dacarbazine	II	34	1st line	(94%)	NR	NR	Neutropenia (6%), nausea/vomiting, pneumonia, and thromboembolic event (3%)	[22]
	R/R HL	BV + Bendamustine ± ASCT ± BV maintenance	I/II	53	>1	92.5% (73.6%)	NR	NR	Lymphopenia (10.9%), maculopapular rash (9.1%), hypotension (7.3%)	[54]
	R/R HL	None	II	102	>1	72% (33%)	9.3	40.5	Specific AEs NR, 54.9% experienced ≥ G3 AE	[15]
	R/R HL	Nivolumab	I/II	61	>1	82.0% (60.7%)	NR	NR	Immune related reaction (3.3%), fatigue, pruritis, diarrhea, myalgia, constipation, and urticaria (1.6%)	[21]

Polatuzumab vedotin, CD79b, Monomethyl auristatin E **FDA Approved Indications:** •R/R DLBCL after failure of $\geq$ 2 lines of treatment	R/R NHL	None	I/II	68	>1	54.8% (16.7%)	5.7	NR	Neutropenia (40%), anemia (11%), peripheral neuropathy (9%)	[31]
	R/R DLBCL	Bendamustine, rituximab (pola-BR)	Pola-BR: II	Pola-BR: 40	>1	Pola-BR: 45.0% (40.0%)	Pola-BR: 9.5	Pola-BR: 12.4	Pola-BR: neutropenia (46.2%), thrombocytopenia (41.0%), anemia (28.2%)	[32]
				Pola-BG: 27		Pola-BG: 40.7% (29.6%)				
		Bendamustine, obinutuzumab (pola-BG)	Pola-BG: I/II				Pola-BG: 6.3	Pola-BG: 10.8		
	R/R FL or DLBCL (NHL)	Rituximab	II	39	>1	53.8% (20.5%)			Neutropenia (23%), anemia (8%), diarrhea (8%)	[33]
	DLBCL (NHL)	R-CHP	I/II	45	1st line	91% (78%)	NR	NR	Neutropenia (27%), febrile neutropenia (11%)	[55]
	R/R FL (NHL)	Obinutuzumab and lenalidomide	I/II	52 (interim analysis)	>1	89% (61%)	NR. Study (NCT02600897) ongoing. Interim results presented.		Neutropenia (46%), thrombocytopenia (17%), anemia (12%), infections (12%)	[56]
	R/R FL or DLBCL (NHL)	Atezolizumab, obinutuzumab, rituximab	I/II	36	>1	NR. Recruitment was stopped due to unexpected toxicity and atezolizumab was discontinued in all treated patients. 2 patients developed severe refractory immune-mediated toxicities.				[57] NCT02729896
	R/R B-cell NHL and HL	ASCT (followed by polatuzumab)	I/II	NR	>1	NR. Study not yet recruiting.				NCT04491370
	Aggressive B-cell NHL	DA-EPCH-PR	I	NR	1st line	NR. Study not yet recruiting.				NCT04231877
	DLBCL (NHL) (elderly/frail pts)	R-mini-CHP	III	NR	1st line	NR. Study not yet recruiting.				NCT04332822
	DLBCL (NHL)	R-CHP	III	NR	1st line	NR. Study enrollment ongoing.				NCT03274492
	R/R DLBCL (NHL) (Chinese pts)	Bendamustine and rituximab	III	NR	>1	NR. Study enrollment ongoing.				NCT04236141
	R/R DLBCL (NHL)	R-GEMOX	III	NR	>1	NR. Study enrollment ongoing.				NCT04182204
	R/R FL or DLBCL (NHL)	Mosenetuzumab	I/II	NR	>1	NR. Study enrollment ongoing.				NCT03671018
	R/R B-cell NHL	Mosenetuzumab and CHP	I/II	NR	>1	NR. Study enrollment ongoing.				NCT03677141
	R/R FL or DLBCL (NHL)	Obinutuzumab, venetoclax, and rituximab	I/II	133	>1	NR. Study ongoing, not recruiting.				NCT02611323

Table 2. Summary of Novel Antibody Drug Conjugates [under study]

Inotuzumab ozogamicin, CD22, Calicheamicin	R/R B-cell NHL	Rituximab	I/II	118	>1	64.0% (48.6%)	NR	NR	Thrombocytopenia (30.9%), neutropenia (21.8%), infections and infestations (10.9%)	[29]
FDA Approved Indications: •R/R B-cell precursor acute lymphoblastic leukemia (ALL) in adults	R/R indolent NHL (FL, MZL, SLL)	None	II	81	>1	66.7% (30.9%)	12.7	NR	Thrombocytopenia (56%), neutropenia (36%), lymphopenia (14%)	[58]
	R/R B-cell NHL	R-GDP	I	55	>1	53% (20%)	Aggressive NHL: 6.1 Indolent NHL: 12.0	NR	Thrombocytopenia (75%), neutropenia (62%), leukopenia (24%)	[59]
	R/R NHL (pts not candidates for high-dose chemotherapy)	Rituximab	III	338. Study terminated enrollment d/t futility.	>1	41% (15%)	3.9	8.6	Thrombocytopenia (48%), neutropenia (24%), lymphopenia (9%)	[60]
	R/R B-cell NHL	Temsirolimus	I	25	>1	NR. Study completed, no results posted.				NCT01535989
	R/R DLBCL (NHL)	R-GEMOX	I/II	11	>1	NR. Study completed, no results posted.				NCT01562990
	CD22 + hematologic malignancies including lymphoma	Fludarabine ± bendamustine, melphalan, rituximab. Pre- and post-stem cell transplant.	II	NR	NR	NR. Study enrollment ongoing.				NCT03856216
	R/R FL (NHL)	Rituximab	III	29	>1	Study terminated due to poor enrollment.				NCT00562965
	R/R DLBCL (NHL) (pts not candidates for anthracyclines)	R-CVP	II	132	1st line	NR. Study completed, no results posted.				NCT01679119
Loncastuximab tesirine, CD19, Pyrrolobenzodiazepine (PBD) dimer toxin	R/R B-cell NHL	None	I	183	>1	45.6%	3.1	8.3	NR	[61,62] NCT02669017
	R/R DLBCL (NHL)	None	II	52 (interim analysis)	>1	46.2% (19.2%)	NR. Study ongoing. Futility requirements met, not recruiting.		Decreased neutrophil count (32.7%), elevated GGT (25%), decreased platelet count (21.2%)	[63] NCT03589469
	R/R DLBCL (NHL)	Rituximab	III	NR	>1	NR. Study enrollment ongoing.				NCT04384484
	R/R DLBCL or MCL (NHL)	Ibrutinib	I/II	NR	>1	NR. Study enrollment ongoing.				NCT03684694
	R/R DLBCL, MCL, FL (NHL)	Durvalumab	I	NR	>1	NR. Study ongoing, not recruiting.				NCT03685344
Coltuximab ravtansine, CD37, Maytansinoid derivative (DM1)	R/R B-cell NHL	None	II	61	>1	43.9% (14.6%)	4.7	4.4	Neutropenia (24.6%), lymphopenia (21.3%), leukopenia (14.8%)	[36]

Naratuximab emtansine, CD37, Maytansinoid derivative (DM1)	R/R B-cell NHL	None	I	49	>1	12.8% (2.6%)	NR	NR	Neutropenia (32.7%), febrile neutropenia (14.3%), thrombocytopenia (14.3%)	[47]
Milatuzumab doxorubicin, CD74, Doxorubicin	R/R B-cell NHL	None	I/II	13	>1	NR. Study was terminated due to lack of efficacy.				[44]
STRO-001, CD74, Dibenzocyclooctyne	R/R B-cell NHL	None	I	11 (interim analysis)	>1	NR. Study (NCT03424603) enrollment ongoing.			Thromboembolic event (9.1%)	[64]
Camidanlumab tesirine, CD25, Pyrrolobenzodiazepine (PBD) dimer toxin	R/R HL	None	I	61	>1	69.1% (43.6%)	6.7	NR	Elevated GGT (16.7%), maculopapular rash (13.3%), anemia (8.3%), GBS/radiculopathy (8.2%)	[24,25]
	R/R HL	None	II	NR	>1	NR. Study enrollment ongoing.				NCT04052997
	R/R HL and NHL	None	I	37 (interim analysis)	>1	NR. Study ongoing, enrollment completed.			Anemia (5.4%), neutropenia (5.4%), elevated GGT (5.4%), hypercalcemia (5.4%), back pain (5.4%), pruritis (5.4%), maculopapular rash (5.4%)	[65] NCT02432235

AE: adverse event.
ALCL: anaplastic large cell lymphoma.
ASCT: autologous stem cell transplant.
AVD: doxorubicin, vinblastine, dacarbazine.
CHEP: cyclophosphamide, doxorubicin, etoposide, prednisone.
CHP: cyclophosphamide, doxorubicin, prednisone.
CTCL: cutaneous T-cell lymphoma.
DA-EPCH-PR: dose adjusted rituximab, prednisone, etoposide, doxorubicin, cyclophosphamide.
DLBCL: diffuse large B-cell lymphoma.
FL: follicular lymphoma.
GBS: Guillain-Barre syndrome.
GGT: gamma glutyl transferase.
HL: Hodgkin lymphoma.
MCL: mantle cell lymphoma.
MZL: marginal zone lymphoma.
NHL: non-Hodgkin lymphoma.

randomly assigned to frontline treatment with up to 6 cycles of either BV + doxorubicin, vinblastine, and dacarbazine (A + AVD), or doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) [17,18]. With a median follow-up of 37.1 months, the 3-year PFS was 83.1% (95% CI, 79.9–85.9) in the A + AVD arm and 76.0% (95% CI, 72.4–79.2) in the ABVD arm, for a difference of 7.1% favoring the A + AVD arm; the HR was 0.704 (95% CI, 0.550–0.901; P = .005). A PFS improvement with A + AVD at 3 years in patients < 60 years was also observed (HR = 0.69; P = .008). Seventy eight percent of patients with peripheral neuropathy on A + AVD had either complete resolution or improvement compared with 83% on ABVD [18]. The results of the ECHELON-1 trial suggested that the addition of BV to AVD was a tolerable and successful approach to increase the efficacy of initial therapy, particularly among patients with the highest-risk disease. In March 2018, BV was approved in combination with AVD by the FDA for the frontline treatment of stages III and IV HL. The NCCN guidelines have now incorporated BV-AVD as a category 2B option for stages III and IV HL and a category 2A option for select patients without baseline neuropathy and International Prognostic Score (IPS) of 4–7 or inability to tolerate bleomycin [19].

However, there are few limitations of this trial which must be clearly outlined. In contrast to a standard definition of PFS, the primary end point of this study was a modified progression-free survival (mPFS) defined as the time to disease progression, death, or a modified progression event (lack of a CR [Deauville 3–5]) after completion of frontline therapy. This contrasts with most clinical studies, and everyday clinical practice, where a score of Deauville 3 post treatment is considered CR. It is also unclear why patients treated in the regions identified as Americas and North America achieved a greater mPFS benefit from A + AVD compared to patients in Europe and Asia. This may be an important question, provided investigators are certain that the drugs were infused at the correct doses and schedules. Questions remain on the cost consideration for A + AVD regimen and the guidance on appropriate use of growth factor use with this regimen.

A multicenter phase II study investigated the effect of BV sequentially before and after standard AVD for untreated patients with HL age 60 years or older. After 2 lead-in doses of single-agent BV (1.8 mg/kg once every 3 weeks), patients received 6 cycles of AVD followed by 4 consolidative doses of BV in responding patients. ORR and CR were 95% and 90%, respectively, after 6 cycles of AVD among

NR: not reported.
PTCL: peripheral T-cell lymphoma.
R/R: relapsed or refractory.
RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.
R-CHP: rituximab, cyclophosphamide, doxorubicin, prednisone.
R-CVP: rituximab, cyclophosphamide, vincristine, prednisone.
R-GDP: rituximab, gemcitabine, cisplatin, oxaliplatin.
R-mini-CHP: rituximab, cyclophosphamide, doxorubicin, prednisone.
SLL: small lymphocytic lymphoma.

42 response-evaluable patients. Forty two percent of patients experienced a grade 3–4 adverse event, most commonly neutropenia (44%), febrile neutropenia and pneumonia (8%), or diarrhea (6%). One-third of patients had grade 2 peripheral neuropathy, which was reversible in a majority of patients. By intent-to-treat, the 2-year EFS, PFS and overall survival (OS) rates were 80%, 84%, and 93%, respectively [20].

The combination of BV and nivolumab was active and well tolerated as salvage therapy in a study of 62 patients with R/R HL, showing an ORR of 82% with CR in 61% of the patients [21]. Infusion related reactions were seen in 44% of patients. There is an ongoing phase II multicenter trial evaluating the role of combination nivolumab and BV for patients with previously untreated HL with age > 60 years or those unable to receive standard ABVD chemotherapy [NCT02758717].

For non-bulky limited stage HL, BV 1.2 mg/kg in was studied in combination with doxorubicin and dacarbazine. CR at interim PET/CT after 2 cycles of chemotherapy and at the end of therapy PET/CT after 4–6 cycles was seen in 94% and 100%, respectively. Most toxicities were low-grade, with only 15% of the patients experiencing grade 3 toxicities [ASH 2018 abstract 1654] [22].

5. Anti-CD25 ADCs in HL

CD25, also known as interleukin-2 receptor-α, is a type I transmembrane protein that comprises the α-subunit of the IL-2 receptor. Except for regulatory T-cells and activated T-cells, CD25 is rarely expressed in normal cells. However, it is found in Reed-Sternberg cells and adjacent cells in the microenvironment in HL and in many B-cell and T-cell malignancies [23]. An ADC targeting CD25, camidanlumab tesirine (ADCT-301, CAMI), consists of an anti-CD25 antibody linked to a pyrrolobenzodiazepine (PBD) dimer payload by a protease-sensitive linker. A phase 1/2 dose-escalation study of ADCT-301, in 60 patients with R/R HL demonstrated ORR of 70% with CR seen in 44% [ASH 2018 abstract 0928] [24]. Responses were seen in all subgroups including patients with prior BV, checkpoint inhibitor (CPI), or HCT. Median DOR and PFS were 7.7 and 6.7 months, respectively. Most common treatment emergent adverse events included Gamma-Glutamyl-Transferase (GGT) elevation (17%), maculopapular rash (13%), and Guillain-Barré syndrome/radiculopathy (8%) [24]. Although an increased ORR in patients with previous exposure to CPI could suggest a possible immunological interaction, it did not appear to increase autoimmune and neurologic adverse events [25]. Hence, it remains unclear whether this neurological toxicity is related to the immunological mode of action of CAMI and synergy with immune CPI or a direct effect of PBD.

6. B-cell Non-Hodgkin's lymphomas

6.1. Anti-CD30 ADCs in B-cell NHL

Based on phase II study data, use of BV in patients with R/R DLBCL resulted in ORR of 44% including 17% CRs and a median DOR of 16.6 months in those achieving CR. One out of 6 patients with primary mediastinal B-cell lymphoma also achieved CR (17%). There was no correlation between the response and CD30 expression but all responding patients had quantifiable CD30 identified by immunohistochemistry. Most common adverse events included fatigue (55%), diarrhea (43%), neutropenia (41%) and peripheral sensory neuropathy (29%) [26].

7. Anti-CD22 ADCs in B-cell NHL

CD22, also known as Siglec-2, is a type I transmembrane sialoglycoprotein expressed on the cell surface of mature B-lymphocytes, with limited expression elsewhere. Based on one study, CD22 was expressed in 100% of acute lymphoblastic leukemia (ALL) cases, of which 95% showed expression in $\geq$ 90% of blasts [27]. Inotuzumab ozogamicin is a humanized anti-CD22 monoclonal antibody attached to calicheamicin via hydrazone linker. Clinical studies have shown encouraging activity for inotuzumab ozogamicin in R/R adult ALL patients when used alone or combined with chemotherapy [28]. A phase 1/2 study of inotuzumab ozogamicin in patients with relapsed FL and DLBCL showed that at the maximum tolerated dose of 1.8 mg/m2 every 3 weeks, ORR was 87% (CR rate 62%) and 74% (CR rate 50%) in patients with relapsed FL and relapsed DLBCL, respectively. Two-year PFS and OS for relapsed FL was 68% and 91%, respectively. For patients with relapsed DLBCL, two-year FPS and OS was 41% and 69%, respectively [29]. The most common grade 3 to 4 adverse events were thrombocytopenia (31%) and neutropenia (22%). Common low-grade toxicities included hyperbilirubinemia (25%) and increased aspartate aminotransferase (AST)(36%).

8. Anti-CD79b in B-cell NHL

CD79b is a component of the B-cell receptor (BCR) complex. It is a promising therapeutic target

because of its restricted expression on mature B-cells and B-cell malignancies [30].

Polatuzumab vedotin (pola) is an anti-CD79b monoclonal antibody conjugated to MMAE, a microtubule toxin. A phase I study in R/R NHL revealed promising results with the most common grade $\geq$ 3 toxicities being hematologic and neuropathy (9%), and an ORR of 55% with a median PFS of 5.7 months [31]. Sehn et al. published a study exploring the role of pola in combination with chemoimmunotherapy for patients with R/R DLBCL who were considered ineligible for transplant [32]. Safety and efficacy of pola with bendamustine and obinutuzumab (pola-BG) was evaluated in a single-arm cohort (phase Ib/II). Pola combined with bendamustine and rituximab (pola-BR) was compared with bendamustine and rituximab (BR) in a randomly assigned cohort of patients with transplantation-ineligible R/R DLBCL. Pola-BG and pola-BR had a tolerable safety profile. The phase Ib/II pola-BG cohort (n = 27) had a CR rate of 29% and a median OS of 10.8 months (median follow-up, 27.0 months). In the randomly assigned cohort (n = 80; 40 per arm), pola-BR patients had a significantly higher CR rate (40.0% vs 17.5%; P = .026) and longer PFS (median, 9.5 vs 3.7 months; HR, 0.36, 95% CI, 0.21 to 0.63; P < .001) and OS (median, 12.4 vs 4.7 months; HR, 0.42; 95% CI, 0.24 to 0.75; P = .002; median follow-up, 22.3 months), versus the BR group. Pola-BR patients had higher rates of grade 3–4 neutropenia (46.2% vs 33.3%), anemia (28.2% vs 17.9%), and thrombocytopenia (41% vs 23.1%), but similar grade 3–4 infections (23.1% vs 20.5%), versus the BR group. Peripheral neuropathy associated with pola (43.6% of patients) was grade 1–2 and resolved in most patients [32]. Based on the results of this phase II trial, the FDA granted accelerated approval to pola in combination with BR for the treatment of adults with R/R DLBCL who have received at least 2 prior therapies. Given significant grade 3 and higher side effects, guidelines for the management of peripheral neuropathy, infusion-related reactions, and myelosuppression are provided in the manufacturer's prescribing information, as are recommendations pertaining to the use of prophylactic medications (e.g. granulocyte colony-stimulating factor for neutropenia).

The ROMULUS trial is a multicenter, open-label, phase II study that compared rituximab plus pola (R-pola) or Pinatuzomab (ADC targeting CD79b) (R-pina) in patients with R/R DLBCL and FL [33]. Of the 42 patients with DLBCL who received R-pina, ORR was 60% (95% CI 43–74) and 26% (95% CI 14–42) achieved CR. Of the 39 patients in this cohort who received R-pola, ORR was 54% (95% CI 37–70) and 21% (95% CI 9–36) achieved CR. Of the 21 patients in the FL cohort who received R-pina, ORR was 62% (95% CI 38–82) and 5% (95% CI 0·1–24) achieved CR. Of the 20 patients in this cohort who received R-pola, ORR was 70% (95% CI 46–88) and 45% (95% CI 23–68) achieved CR. Polatuzumab vedotin was selected by the study funder for further development in NHL, partly because of longer durations of response than pina, and an overall risk–benefit favoring R-pola. Given promising results seen in patients with R/R NHL, a phase 1/2 study is underway to evaluate combination obinutuzumab, atezolizumab, and pola in patients with R/R FL, as well as rituximab, atezolizumab, and pola in patients with R/R DLBCL [NCT 02729896]. Similarly, a phase III, randomized, double-blind, placebo-controlled trial is comparing the efficacy, safety, and pharmacokinetics of pola plus rituximab-cyclophosphamide, doxorubicin, and prednisone (R-CHP) versus rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with previously untreated DLBCL [NCT03274492].

The CD79b monoclonal antibody component of pola makes it an ideal therapeutic strategy in B-cell NHL. The FDA approval of pola in combination with BR is an exciting addition to the treatment options for patients with R/R DLBCL including bridging therapy to CAR T-cell therapy, or for those who may be ineligible for cellular therapy. Whether the BR chemoimmunotherapy is the most optimal partner for pola in the treatment of DLBCL patients remains to be answered by ongoing trials. Although evaluations of the safety and efficacy of pola have mostly focused on DLBCL in a R/R setting, early studies of various pola combinations have shown antitumor activity and a manageable safety profile in FL and in front-line NHL settings.

9. Anti-CD19 ADCs in B-cell NHL

CD19 is a type I transmembrane protein expressed in both normal and neoplastic B-cells and in follicular dendritic cells. It functions as a co-stimulator of the B-cell receptor (BCR) complex and also has BCR-independent effects [34].

Tafasitamab is an Fc enhanced, humanized anti-CD19 monoclonal antibody designed to have increased antibody dependent cellular cytotoxicity and antibody dependent cellular phagocytosis with increased cell killing. In a phase II trial involving 92 patients with various histologies of NHL [25 DLBCL, 24 FL, 12 MCL, 11 other NHL], tafasitamab was given a dose of 12 mg/kg/day 1, 8, 15 and 22 of cycle 1 and 2 then every 2 weeks onwards [35]. The ORR

in R/R DLBCL, FL, and other NHL were 26%, 29% and 27%, respectively. Most common adverse events were infusion related reactions and neutropenia. Most common grade 3 or higher adverse events were neutropenia, mainly occurring during the first 2 cycles. Combination of tafasitamab and lenalidomide was studied in a phase II study of 72 patients with R/R NHL, not eligible for transplant [36]. Lenalidomide was dosed at 25 mg 21/28 days. The ORR with the combination was 58% with CR of 41%, and median DOR of 34.6 months. The regimen was overall well-tolerated with major adverse events being neutropenia without infections. Non-hematologic toxicities included rash, diarrhea, asthenia, peripheral edema, but grade 3 or worse toxicities were uncommon. Most of the toxicities were attributed to lenalidomide.

ADCT-402 (loncastuximab tesirine) is an ADC comprised of a humanized antibody directed against human CD19 conjugated to a PBD dimer toxin. Based on the results of a phase I study, loncastuximab tesirine has demonstrated potent anti-tumor activity and tolerable toxicity against R/R NHL [37]. Among 59 patients with DLBCL, ORR was 57% with a 34% CR rate and a median PFS 3.5 months. The study is ongoing at doses 120 ug/kg and 150 ug/kg [37].

Coltuximab ravtansine is a humanized anti-CD19 monoclonal antibody conjugated to the antimitotic agent DM4 via a disulfide linker. A phase II study evaluated a single agent coltuximab ravtansine in patients with CD19-positive R/R DLBCL who were ineligible for HCT after at least one standard rituximab-based therapy [38]. ORR was 44% with a 12% CR rate. Grade 3–4 hematological toxicities included neutropenia (26%) and thrombocytopenia (10%) [38].

Denintuzumab mafodotin is a humanized anti-CD19 monoclonal antibody conjugated to the toxin MMAF via a non-cleavable linker. Based on the results of a phase I study in patients with B-cell NHL, this ADC was associated with an ORR of 56% (40% CR rate) across dosing schedules. Common adverse events included blurry vision, dry eyes, fatigue and keratopathy [ASH 2015 Abstract 182] [39]. A randomized, phase 2 trial of denintuzumab mafodotin and rituximab, ifosfamide and etoposide (RICE) versus RICE alone in treatment of patients with R/R DLBCL who are candidates for autologous HCT is underway [40].

10. Anti-CD74 ADCs in B-cell NHL

CD74 is a type II transmembrane glycoprotein involved in major histocompatibility complex class II antigen presentation, B-cell maturation, T-cell responses, and macrophage migration inhibitory factor-induced signaling [41]. Based on immunohistochemical analysis, CD74 expression is seen in more than 90% of cell lines in DLBCL, FL, and mantle cell lymphoma [42]. STRO-001 is an anti-CD74 monoclonal antibody conjugated to a non-cleavable dibenzocyclooctyne (DBCO) linker. In preclinical studies, this ADC has demonstrated potent in vitro cytotoxicity in multiple NHL cell lines and anti-tumor activity in DLBCL and mantle cell lymphoma xenograft models [43]. Clinical studies of this novel ADC for the treatment of B-cell malignancies are under development [44]. Milatuzumab doxorubicin is composed of milatuzumab, a humanized anti-CD74 monoclonal antibody, conjugated to doxorubicin via a hydrazine linker which has been explored in malignancies with CD74 expression [45]. Milatuzumab doxorubicin was evaluated in the phase 1/2 study [NCT01585688] in patients with relapsed chronic lymphocytic leukemia and NHL. The study was terminated due to lack of efficacy [46].

11. Anti-CD37 ADCs in B-cell NHL

CD37 is a member of the tetraspanin family found on pre-B and mature B-cells, which mediates apoptotic cell signaling and is important for B-cell and T-cell interactions [47]. CD37 antigen is a transmembrane protein highly expressed in malignant B-cells in patients with NHL and chronic lymphocytic leukemia [CLL]. Naratuximab emtansine is a humanized anti-CD37 antibody conjugated to the maytansinoid derivative DM1 via non-cleavable linker. A phase I study of naratuximab in patients with R/R NHL and CLL completed enrollment in July 2016. Based on early data, grade 3–4 adverse events included neutropenia (30%) and fever (27%) [48,49].

12. T-cell lymphomas

12.1. AntI-CD30 ADCs in T-cell NHL

BV has been studied in a phase II trial with R/R CD30-positive T-cell lymphoma [50]. Of 34 evaluable patients, ORR was 41% (8 CRs, 6 partial remissions (PR)); ORR was 54% in angioimmunoblastic T-cell Lymphoma (5 CRs, 2 PRs) with a median PFS of 6.7 months. Interestingly, degree of response did not appear to correlate with CD30 expression.

ECHELON-2, a phase III randomized controlled trial, evaluated the substitution of BV [A + CHP group] for vincristine in CHOP chemotherapy for

patients with previously untreated CD30-positive mature T-cell lymphomas [51]. Median PFS was 48 months in the A + CHP group and 20 months in the CHOP group. The efficacy of A + CHP seemed to be greatest in the systemic anaplastic large cell lymphoma (sALCL) subgroup and lowest in patients with angioimmunoblastic T-cell lymphoma, although these histological subgroup analyses were underpowered. Adverse events, including febrile neutropenia (18% in the A + CHP and 15% in the CHOP group] and peripheral neuropathy (52% in the A + CHP and 55% in the CHOP group), were similar between groups. Overall, the trial showed that A + CHP in comparison to standard of care CHOP more than doubled the median PFS and reduced risk of death by 34%. A + CHP had a manageable toxicity profile that was similar to that of CHOP, with comparable rates of grade $\geq$ 3 adverse events (66% versus 65%), treatment discontinuation (6% versus 7%) and treatment-related deaths (3% versus 4%). These promising efficacy and safety results supported approval of A + CHP for the first-line treatment of CD30 positive PTCL via the FDA's Real-Time Oncology Review Pilot Program. FDA Approval was granted in November 2018, rapidly transforming a treatment landscape that had for decades remained unchanged.

A phase III randomized controlled trial of BV evaluated 131 patients with R/R CD30 positive cutaneous T-cell lymphoma including mycosis fungoides and primary cutaneous anaplastic large cell lymphoma [52]. At median follow-up of 22.9 months, ORR was 56.3% with BV versus 12.5% with physician's choice (methotrexate and bexarotene). A published update showed ORR of 69% (CR 18.8%) in the BV group versus. 22% (CR 0%) in physician's choice groups. Median PFS was 15.8 months versus 3.6 months, respectively [ASH 2017 Abstract 1509] [53].

13. Evolving therapeutic roles of ADCs

BV has been demonstrated to produce durable response in HL and NHL. The success of BV had expanded the use of ADCs in various hematologic malignancies. Most recently, polatuzumab vedotin was approved by the FDA for its use in R/R NHL. A growing number of clinically available ADCs are reshaping the treatment algorithm in many lymphoid malignancies. Particularly in B-cell NHL, the availability of CD19-directed CAR T-cell therapy has further advanced the treatment landscape in refractory lymphoid diseases. Emerging ADCs have provided physicians with more therapeutic options to either bridge patients to CD19 directed CAR T-cell therapy or for further treatment with ADCs after CAR T-cell therapy failure. Though adoptive cellular therapy options have revolutionized the treatment of NHL, there remain patients who may not be able to receive cellular therapy while waiting for their engineered cells to be produced or have disease relapse after receiving CAR T-cell therapy. Incorporation of ADCs either in sequence or combination with adoptive cellular therapy may further improve the outcomes of R/R lymphoma patients. ADCs may also produce responses that were not previously achievable with conventional chemotherapy, allowing some refractory patients to become autologous HCT candidates. Future research is needed to overcome current challenges in ADCs to limit off-target adverse events and improve efficacy.

14. Conclusions

R/R disease in NHL and HL has traditionally been treated with chemoimmunotherapy followed by consolidation with high-dose chemotherapy and HCT for more aggressive histology, provided patients achieve adequate response to salvage chemotherapy and are fit to undergo HCT. Chemoimmunotherapy is associated with a modest response rate and significant hematological and non-hematological toxicities. Given comparable response rates and better toxicity profiles, ADCs offer alternative options for patients who have chemo-refractory disease or those who are unable to undergo intensive treatment. Similarly, the addition of ADCs to traditional chemoimmunotherapy has led to better response rates than chemoimmunotherapy alone with minimal additional toxicities. This helps improve not only the ability of patients to achieve deeper response prior to HCT but also long-term survival. Several early phase studies are under way to evaluate the feasibility and efficacy of newer ADCs for both indolent and aggressive NHLs. For patients with R/R NHL, enrollment in clinical trials exploring the potential role of ADCs should be encouraged. With improved targeting and greater potency in new-generation ADCs, these agents have the potential to dramatically alter the treatment landscape for lymphoma and other hematological malignancies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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