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REVIEW ARTICLE

Bispecific antibodies in relapsed / refractory diffuse large B-cell lymphoma

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Abstract

Modern immunochemotherapy protocols allow 60–70% of diffuse large B-cell lymphoma (DLBCL) patients to be cured by first-line therapy. Those with primary resistance or early relapse have a poor prognosis, and classical salvage regimens are effective in less than 20% of these patients. Targeted chemotherapy and immunotherapy protocols are considered the current standard of care. Chimeric antigen receptor T cell (CAR-T cell) therapy and bispecific antibodies (BsAbs) are regarded as the two most effective methods. Epcoritamab and glofitamab are novel BsAbs approved for the treatment of DLBCL after two lines of systemic therapy. Their high efficacy and safety have been confirmed in phase II multicenter studies. BsAbs are an alternative to CAR-T cell therapy in patients who do not qualify for it or who cannot wait for CAR-T cell preparation due to rapidly progressing disease. Although BsAbs are approved as monotherapy, combinations with chemotherapy and immunomodulatory agents are being explored in ongoing clinical studies. The high efficacy of BsAbs has prompted further research into their potential role in earlier lines of treatment, including first line and debulking before CAR-T cell therapies.

Key words: bispecific antibodies, diffuse large B-cell lymphoma, epcoritamab, glofitamab, refractory, relapsed

Introduction

The R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) regimen has been for the last 20 years the undisputed standard of care (SOC) in first line diffuse large B-cell lymphoma (DLBCL) therapy, allowing 60–70% of patients to be cured [1]. POLARIX was the first randomized study to demonstrate this improvement: the addition of polatuzumab vedotin to R-CHP (rituximab, cyclophosphamide, doxorubicine and prednisone) immunochemotherapy significantly prolonged event-free survival (EFS) and progression-free survival (PFS) in intermediate and high-risk DLBCL patients [2]. However, 20–45% of patients still relapse or are refractory to the initial therapy [3]. Traditional salvage regimens with autologous stem cell transplantation (ASCT) have been considered the standard of second-line treatment [4]. However, their efficacy is moderate, especially in patients with primary resistant disease [5], early relapse [6], or an unfavorable prognostic score calculated by the secondary age-adjusted International Prognostic Index (aaIPI) [7]. In practical terms, ASCT may only be recommended in late, chemosensitive relapses [8–11]. Targeted chemotherapy and modern immunotherapy methods are emerging as the SOC in relapsed / refractory (R/R) DLBCL.

Treatment options in second line of therapy

The two most important questions in DLBCL patients with primary resistance or early relapse are: 1) are they eligible for chimeric antigen receptor T cell (CAR-T cell) therapy; and 2) is CAR-T cell therapy available?

The results of randomized phase III trials comparing anti-CD19 CAR-T cell therapy to chemoimmunotherapy salvage regimens consolidated by ASCT (the historical standard of care) led, in 2022, to the approval of axicabtagene ciloleucel (axi-cel) and lisocabtagene mataleucel (liso-cel) both by the US FDA (Food and Drug Administration) and the EMA (European Medicines Agency) [12, 13]. As we write this paper, the potential reimbursement of these methods by the Polish National Health Fund is being considered.

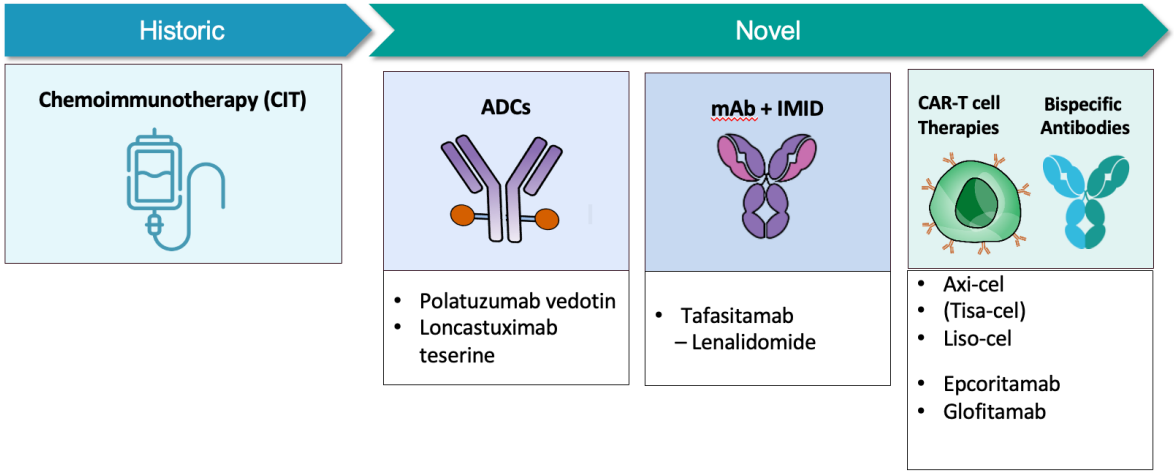
When patients are not eligible for CAR-T cell therapy or when CAR-T cell therapy is not available, modern treatment options are based on targeted chemotherapy or alternative immunotherapy protocols. An anti-CD79b antibody-drug conjugate (ADC) polatuzumab vedotin [14] in combination with rituximab-bendamustine (BR) is effective and well tolerated. However, it should be used cautiously in patients planning for CAR-T cell therapy in the third line, as bendamustine given six months before the procedure can interfere with T cell collection. A regimen with the immunomodulatory drug lenalidomide and the anti-CD19

monoclonal antibody tafasitamab is an alternative for elderly and comorbid patients, but its efficacy has never been tested in primary refractory patients [15]. It should be noted that palliative immunochemotherapy regimens (e.g. gemcitabine-based) are available for unfit and frail patients, and classical salvage regimens should be considered in early-relapsing, transplant-eligible patients. In the latter, early positron emission tomography computed tomography (PET-CT)-based response assessment is recommended for poor-risk patients to change relatively early therapy plans for non-responding patients [16].

Treatment options in third + line: role of bispecific antibodies

All methods listed as second line treatments are also available in subsequent lines (Figure 1). Additionally, we can use loncastuximab tesirine, an anti-CD19 ADC with a different 'warhead' to that of polatuzumab vedotin [17]. However, the most significant improvement, which perhaps could even be regarded as a breakthrough, has been related to the introduction CAR-T cell therapy and T-cell-engaging bispecific antibodies (BsAbs). BsAbs are full-length monoclonal antibodies that simultaneously target both tumor antigens and effector T cells, most commonly through CD3 antigens. A stable immunological synapse initiates T-cell activation and proliferation [18]. Blinatumomab, the first bispecific T-cell engager (BITE), targets CD3/CD19 and is approved in R/R B-cell acute lymphoblastic leukemia [19]. It is a small (55-kDa) single-chain peptide connecting two variable antibody fragments directed against CD3 and CD19 [19]. However, the development of all CD3/CD19 BITEs in DLBCL was discontinued due to the high frequency of severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Figure 1. Protocols approved in third and subsequent lines of diffuse large B-cell lymphoma (DLBCL) therapy



ADCs — antibody drug conjugates; mAb — monoclonal antibody; IMID — immunomodulatory drug; CAR-T — chimeric antigen receptor T cell

All other BsAbs developed for the treatment of peripheral B cell lymphomas, i.e. epcoritamab, glofitamab, mosunetuzumab, and odronextamab, are CD3/CD20 BsAbs with high activity and manageable safety profiles [20–23]. CRS was identified as an important adverse effect of BsAbs. Therefore, various strategies were implemented to reduce its occurrence i.e. step-up dosing during the first cycle, steroid prophylaxis, or obinutuzumab infusion before the first dose of the BsAbs.

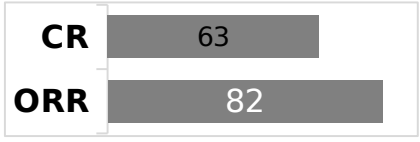
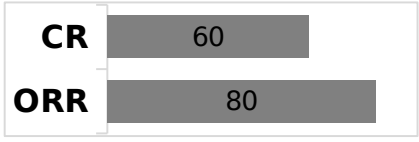
Mosunetuzumab, the first-in-class CD20xCD3 IgG-like BsAb (IgG1) approved for treating R/R follicular lymphoma, is not being developed as a single agent in DLBCL.

A phase II study with glofitamab (NCT03075696), CD20xCD3 IgG1 BsAb included 154 DLBCL patients after a minimum of two lines of prior treatment. All were heavily pretreated, high-risk patients; 58% were primary refractory, 86% were refractory to the last line of treatment, and 33% had failed CAR-T cell therapy. After fixed-duration treatment with glofitamab (maximum 12 cycles), objective responses were observed in 52% of patients, including 39% of complete remissions (CRs). The probability of achieving complete remission (CR) was independent of prior CAR-T cell exposure and the number of previous therapy lines. In 61 patients with CR, the PFS rate at 12 and 24 months was 93% and 79%, respectively. Treatment with glofitamab was well tolerated with mostly mild adverse events (AEs) (Common Terminology Criteria for Adverse Events, CTCAE, grades 1–2). CRS was observed in 63% of patients, usually after the priming dose. Severe CRS (CTCAE grade >3) was observed only in 3.9% of patients. AEs leading to discontinuation of treatment were uncommon, occurring in 14/154 patients (9%); five patients (3%) had a glofitamab-related AE leading to treatment discontinuation (gastrointestinal hemorrhage in one

patient, myelitis in one, CRS in one, and neutropenia in two). Grade 3 or higher adverse events occurred in 62% of the patients. Grade 5 (fatal) adverse events (not including progressive disease) occurred in eight patients (5%; COVID-19-related pneumonia or COVID-19 in five, sepsis in two, and delirium in one) [24]. Glofitamab was granted accelerated approval by the FDA in June 2023, and conditional marketing authorization by the EMA the following month.

Epcoritamab is a novel CD20xCD3 IgG1 bispecific antibody administered subcutaneously in aggressive lymphoma patients until progression. The results of a phase II study (NCT03625037, EPCORE NHL-1) demonstrated efficacy and safety in a high-risk, heavily pretreated population of DLBCL patients after a minimum of two lines of previous treatment. 61% of patients were primary refractory, 83% of patients were refractory to the recent line of treatment, and 39% had failed the CAR-T cell therapy. Objective responses were observed in 63% of patients, including 39% of CRs; achieving CR did not depend on prior CAR-T cell exposure or the number of previous therapies. Most responses were durable, with PFS at 12 months observed in >80% of complete responders. CRS occurred mainly during the first cycle and was mostly mild (CTCAE grade >3 occurred only in 2.7% of patients). The safety profile was as expected from the initial reports of this trial. The most common treatment-emergent AE was CRS (49.7% grade 1, 47.1% grade 2, 2.5% grade 3), pyrexia (23.6%) and fatigue (22.9%). ICANS occurred in 6.4% of patients with one fatal event [25]. Based on the EPCORE NHL-1 study results, epcoritamab was granted accelerated approval by the FDA in May 2023, and conditional marketing authorization by the EMA in September 2023. A comparison of registration trials of glofitamab and epcoritamab in R/R DLBCL is set out in Table 1.

Table 1. Comparison of registration trials of glofitamab and epcoritamab in R/R DLBCL

	Glofitamab [24] NCT03075696 (N = 154) Median F/U: 12.6 months	**Epcoritamab** [25] NCT03625037, EPCORE NHL-1 (N = 157) Median F/U: 10.7 months
Trial population	58% primary refractory 33% prior CAR-T cell exposure Median 3 prior LOTs	61% primary refractory 39% prior CAR-T cell exposure Median 3 prior LOTs
Efficacy		

	mPFS: 4.9 months	mPFS: 4.4 months
	mDOR: 18.4 months	mDOR: 12 months
Safety (in parentheses: grade 3–4)	CRS: 63% (4%)[a]	CRS: 49.7% (2.5%)
	ICANS: 8% (0%)	ICANS: 6.4% (0,6%)
	Neutropenia: 38% (27%)	Neutropenia: 21.7% (14.6%)
	9% discontinuation	7.6% discontinuation
Dosing	i.v. FTD	s.c. TTP
	SUD (mg): 2.5 / 10 / 30	**SUD** (mg): 0.16 / 0.8 / 3 / 48
	C1: Weekly; **C2–12**: Once every 3 weeks	**C1–3**: Weekly; **C4–9**: Biweekly; **C10+**: Monthly

F/U — follow-up; LOT — line of treatment; CR — complete response; ORR — overall response rate; mPFS — median progression-free survival; mDOR — median duration of response; CRS — cytokine release syndrome; ICANS — immune effector cell-associated neurotoxicity syndrome; s.c. — subcutaneous; i.v. — intravenous; SUD — step-up dosing

The results of a phase II study with odronextamab, CD20xCD3 IgG4 BsAb, have not been published yet as a full-text publication. The first analysis of this study (NCT03888105, ELM-2 study) was presented at the American Society of Hematology's annual meeting in December 2023. It confirmed the highly encouraging clinical activity of odronextamab in R/R DLBCL patients, including high-risk cases (57% of patients were primary refractory, and 86% refractory to the most recent treatment line) [26]. ORR and CR rates were 52% (66/127) and 31% (39/127), respectively, and were consistent across high-risk subgroups. The median duration of response (DOR) was 10.2 months, and the median duration of CR was 17.9 months; the probability of maintaining CR for 24 months was 48%. Safety was generally consistent with previous reports. Treatment-related AEs led to odronextamab interruption/delay in 75 (53%) patients and discontinuation in 14 (10%) patients. The most common treatment-emergent AEs (>30% of all grades) were CRS (55%), anemia (43%), and pyrexia (42%). With the optimized 0.7/4/20 mg step-up regimen (n = 74), 98% of CRS events were grade 1 or 2 CTCAE, and only one grade 3 CTCAE CRS (confounded by pancreatitis) was reported. CRS events were resolved with supportive measures. No ICANS events were reported with the optimized step-up regimen. However, despite continuous treatment until progression, more than half of the CRs were lost within 18 months. In March 2024, the FDA denied approval of odronextamab in R/R DLBCL.

The presented registration studies for epcoritamab and glofitamab confirm not only the high efficacy and safety of BsAbs, but also constitute an alternative to CAR-T cell therapy. They should be considered when CAR-T cell therapy is unavailable, including patients with rapidly progressive disease who cannot wait for CAR-T cell preparation. As readily available 'off the shelf' compounds, they are potentially the best debulking option before CAR-T cell therapy. The more favorable safety profile of BsAbs allows the treatment of severely comorbid patients who are not eligible for CAR-T cell approaches.

However, as repeated infusions lead to severe and long-lasting B cell depletion, one must be aware of infectious complications, which are also observed in CR patients. All prophylactic approaches, including anti-viral prophylaxis with acyclovir, screening for hepatitis B virus reactivation risk in all patients, universal *pneumocystis jirovecii* pneumonia prophylaxis, and anti-COVID-19 vaccinations are recommended [27]. BsAbs are also the most effective therapeutic option in patients relapsing after CAR-T cell therapy.

Although Richter's transformation of the DLBCL type should not be regarded as *de novo* DLBCL, using BsABs in this rare entity is a possible clinical option [28]. Epcoritamab, glofitamab, and mosunetuzumab as single agents have demonstrated their efficacy with predictable and manageable toxicity profiles in relapsed/refractory settings [21, 29, 30].

BsAb-containing combination therapy

Although BsAbs are approved in monotherapy in R/R large B cell lymphomas (LBCL), many ongoing phase 1b and 2 trials are exploring the safety and efficacy of epcoritamab and glofitamab in various combination regimens. including combinations with standard-of-care therapies. The results in R/R LBCL are favorable, with response rates exceeding 90% and acceptable toxicity. One of the few protocols to mention epcoritamab was tested with rituximab, dexamethasone, cytarabine, oxaliplatin (R-DHAX) (NCT04663347, EPCORE NHL-2 trial), while both epcoritamab and glofitamab with rituximab, gemcitabine, oxaliplatin (R-GemOx) — NCT04663347 and NCT04408638 studies respectively). Both mosunetuzumab and glofitamab have been combined with ADC polatuzumab vedotin with high response rates; the overall response rate (ORR) and the CR rate were 65% and 48%, 80% and 51%, respectively, for mosunetuzumab (NCT03671018) and glofitamab (NCT03533283). Initial observations of BsAbs combined with checkpoint inhibitors (atezolizumab) confirmed their safety, but not increased efficacy compared to BsAbs monotherapy (NCT03533283). Other potentially interesting combinations of BsAbs include immunomodulatory agents and immune agonists, i.e. combinations of glofitamab with bispecific CD19/4-1BBL and

bispecific CD19/CD28 antibodies (NCT04077723, NCT05219513). Epcoritamab combined with the immunomodulatory drug lenalidomide showed promising antitumor activity in patients with R/R DLBCL and a tolerable safety profile (NCT05283720, EPCORE NHL-5). The BsAbs-containing combination studies are set out in Table 2.

Table 2. BsAbs combination studies

Trial ID	Drugs	Route of BsAb
NCT04663347	epcoritamab-R-CHOP epcoritamab-R-DHAX epcoritamab-GemOx	s.c. s.c. s.c.
NCT04408638	glofitamab-GemOx vs R-Gemox	i.v.
NCT03671018	mosunetuzumab-polatuzumab	i.v.
NCT03533283	glofitamab-polatuzumab glofitamab-atezolizumab	i.v. i.v.
NCT04077723	glofitamab-RO7227166	i.v.
NCT05219513	glofitamab-RO7443904	i.v.
NCT05283720	epcoritamab-lenalidomide	s.c.

R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAX — rituximab, dexamethasone, cytarabine, oxaliplatin; R-GemOx — rituximab, gemcitabine, oxaliplatin; s.c. — subcutaneous; i.v. — intravenous

Benefits of treatment with BsAbs

There are several other issues that indicate the benefits of using BsAbs:

1. Pharmacoeconomic point of view. In CAR-T cell therapy, the whole cost is paid in advance, even if the procedure is eventually not performed. Treatment with BsAbs is cost-effective, as we pay only for the administered doses. Furthermore, the responses to BsAbs are observed relatively early, mostly in the first two months of therapy, allowing for the identification of patients who will benefit the most.
2. Treatment with BsAbs requires a ramp-up with the first doses, so although the drug is already available when the patient is qualified for treatment, its full efficacy is not expected during the first two weeks.
3. Both CAR-T cell and BsAbs engage cytotoxic T cells. Although there is a potential concern about T cell depletion (so-called “exhaustion”), it remains theoretical, as effectiveness has been observed so far in both sequences (BsAbs after CAR-T cells and CAR-T cells after BsAbs).

4. BsAbs involve the patient's own immune system. The treatment is more effective when the immune system is relatively intact and not exhausted by subsequent lines of therapy. Therefore, the potential role of BsAbs is being investigated in the first-line treatment of aggressive B-cell lymphomas.
5. CAR-T cells are recommended as a single procedure, so their efficacy does depend on tumor burden. The smaller the tumor mass, the better the result. This is not observed in patients treated with BsAbs. Furthermore, BsAbs, although not formally tested in this setting, are probably the best cytoreduction method before CAR-T cell therapies.

Conclusions

The prognosis for patients with R/R DLBCL has improved significantly. Progress is not related to the improvement of ASCT, the slowly-being-forgotten standard of care, but to the introduction of targeted chemotherapy and modern immunotherapy methods such as CAR-T cells and BsAbs. It is likely that both methods will soon be recommended in the earlier stages of treatment. The efficacy of molecularly targeted therapies (such as Bruton's tyrosine kinase inhibitors) has not yet been confirmed in randomized clinical studies. It is probable that their role depends on identifying properly eligible patients, which is unlikely unless we upgrade lymphoma classification to correctly address cytogenetic abnormalities.

Article information and declarations

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Authors' contributions

All authors have fully participated in the concept of the article, wrote and accepted the final version of the manuscript.

Conflicts of interest

MD declares no conflict of interest. WJ declares research funding, honoraria and an advisory role for AbbVie, Genmab, Morphosys, Roche and Sobi.

Ethics statement

Authors declare that informed consent for publication was not obtained, as published data does not allow for patient identification.

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Supplementary material

None.

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