REVIEW ARTICLE

Bispecific antibodies in the treatment of follicular lymphoma

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ABSTRACT

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma. The course of the disease is recurrent with varying periods of remission among individual patients. Treatment in the second and subsequent lines poses a therapeutic challenge, especially in patients with early disease recurrence. Using standard rituximab-based therapy, the progression-free survival (PFS) after the second line of treatment averages 10 months. Currently, new therapeutic options are being sought in this indication. One of the strategies under investigation in the FL treatment is chimeric antigen receptor T-cell therapy and bispecific antibodies. The second ones, by simultaneously binding to the CD3 antigen present on T-lymphocytes and CD20 on B lymphocytes, create an immunological synapse leading to neoplastic cell death. So far, after promising results of the clinical trials, the most extensively studied FL bispecific antibody, mosunetuzumab, has been registered for use in the third and further lines in relapsed and refractory FL. In the phase 2 study, the overall response rate was 80% and the median PFS was 17 months, despite the inclusion of patients with poor prognosis factors. Studies regarding the application of this drug in the first-line treatment are ongoing. Clinical trials have been also conducted with the use of antibodies such as epcoritamab and odronextamab. The aim of this work is an attempt to summarize the current knowledge regarding the effectiveness and safety of the investigated bispecific antibodies.

Keywords: bispecific antibodies, follicular lymphoma, B-cell lymphoma

INTRODUCTION

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) in Western populations and the second most common NHL overall, following diffuse large B-cell lymphoma (DLBCL). Furthermore, a significant increase in its incidence is expected in the coming years [1]. With a typical indolent course and a prognosis that poorly predicts a complete cure, FL has become a subject of research for new therapeutic strategies.

Prognostic evaluation in FL commonly employs the Follicular Lymphoma International Prognostic Index (FLIPI), created before the introduction of rituximab, and its revised version — FLIPI2. Determining the disease stage at diagnosis and identifying adverse prognostic factors are crucial for choosing the optimal treatment strategy. Observation is an option in asymptomatic cases. For advanced stages' treatment, radiation therapy or immunochemotherapy is used [2, 3]. The introduction of rituximab into the standard treatment significantly prolonged progression-free survival (PFS) and overall survival (OS) and improved the overall response rate (ORR) to first-line treatment. At advanced stages of FL treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) or R-lenalidomide, the rate of complete remission (CR) was 53% and 48%, respectively, with a 6-year PFS reaching 59% and 60% [4, 5]. However, a relatively large group of patients still experiences resistance or relapses (R/R), with a poor prognosis in these cases.

In general, patients treated with second-line immunochemotherapy have a median OS of 11.67 years, with a median PFS of

just 10 months. With each subsequent line of treatment, both parameters sharply decline [6]. Results are even worse for early relapse after the first line, with a 5-year OS of 50% for patients who relapsed within 24 months of completing therapy (POD24). These are mainly individuals diagnosed with advanced-stage disease and identified as having high risk according to the FLIPI score [7]. A 12-month PFS has also been proposed as a particularly important prognostic factor for patient survival [8].

Due to the need to optimize FL treatment strategies in subsequent lines, research is ongoing on new drugs. Some focus on molecular changes occurring in neoplastic cells, such as the EZH mutation. However, advanced immunotherapy, mainly the use of bispecific antibodies (BsAbs) or CAR T-cell therapy, is becoming an increasingly explored direction in hematologic malignancies. BsAbs are used in various B-cell NHLs, binding simultaneously to CD3 antigen on T-cell surfaces and forming part of the T-cell receptor complex, as well as CD20 present on B-cell surfaces. By creating a specific immunological synapse, they lead to T-cell activation, resulting in B-cell destruction and the generation of specific inflammatory cytokines [9]. BsAbs in FL treatment have been used mainly in clinical trials.

MOSUNETUZUMAB

Mosunetuzumab is a fully humanized IgG1 class BsAb targeting CD3 and CD20 antigens. In the phase 1 study conducted on patients with R/R B-NHL, promising efficacy data were obtained. The ORR was 19.4% in aggressive lymphomas and 48.5% in indolent lymphomas, with a median duration of response slightly exceeding 20 months, longer in the aggressive lymphoma group. The most common adverse events were hematologic toxicity and cytokine release syndrome (CRS). The last one occurred in over half of the participants, but in most cases, it did not exceed grade 2 according to Common Terminology Criteria for Adverse Events (CTCAE). Interestingly, pharmacokinetic studies demonstrated a half-life of up to 21 days, significantly longer than other IgG1 antibodies, indicating a potential prolonged therapeutic effect. Encouraging data from the phase 1 study prompted further investigations. Current phase 1 and 2 trials are taken in DLBCL, FL, mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL), mostly combining mosunetuzumab with immunotherapy and comparing it with Rituximab-based or glofitamab-based treatments [10].

In the phase 1/2 study, GO29781, 90 patients with FL grade 1–3a were enrolled, with inclusion criteria such as resistance or relapse after at least two lines of treatment involving anti-CD20 antibodies and an alkylating agent. The average age of included patients was 60 years, and the majority of them were assessed as stage III–IV according to Ann Arbor. Adverse prognostic factor — POD24, was identified in 47% of patients. Mosunetuzumab was administered as monotherapy through intravenous injections every 3 weeks. Similar to other BsAbs, the dose was gradually increased during cycle 1 to avoid severe CRS (step-up dosing). In cycle 2 a dose of 60 mg was used, reduced to the target 30 mg from cycle 3 onwards. Treatment was completed after 8 cycles and extended to 17 cycles in cases of partial response. Importantly, the administration of mosunetuzumab did not require hospitalization which is important for the cost-effectiveness of the drug. The primary endpoint was CR assessed by an independent review committee (IRC), which was observed in 60% of participants, significantly higher than in the historical control group treated with copanlisib. An ORR of 80% was noted, and the median PFS was 17.8 months. The most common adverse event was CRS, occurring in 44% of participants, generally assessed as Grade 1 or 2 according to CTCAE. The most common grade 3–4 adverse event (AE) was neutropenia which occurred in 27% of participants [11]. Efficacy and safety data from the phase 2 trial compared to below below-mentioned BsAbs is summarized in Table 1. In the recent 3-year update of those results, it was shown that 57.1% of responders remained progression-free, with a PFS of 24 months in this group [12].

In the next stage, a cohort was added, in which mosunetuzumab was administered subcutaneously, assuming that this might reduce the number of adverse events. The optimal dosing turned out to be the step-up dose of 5/45/45 mg. As expected, a reduction in the frequency of CRS was observed. CRS in any grade was diagnosed in 27% of patients and the most frequent adverse event was injection-site reaction. The efficacy results were similar to those in the intravenous administration group [13].

One limitation of this trial is the absence of a current control group. However, in another study, the results were compared with data from the US nationwide Flatiron Health (FH) electronic health record (EHR)-derived de-identified database. Patients meeting key inclusion criteria for the GO29871 study and treated within a similar timeframe were selected for analysis. It is not surprising that these were patients with, on average, fewer lines of treatment than those enrolled in the clinical trial, thus in a more favorable clinical situation. Nevertheless, both the CR and PFS proved to be significantly higher in the group treated with mosunetuzumab compared to standard treatment (CR 60% vs. 33%; PFS 17.8 months vs. 10.1 months respectively) [14].

The results of the clinical trial GO29871 became the basis for the approval of mosunetuzumab by the Food and Drug Administration (FDA) and subsequently the European Medicines Agency (EMA) for the indication of R/R FL after at least two lines of treatment [15].

Currently, a multicenter phase 2 study is underway to assess the efficacy and safety of mosunetuzumab in the first-line treatment of patients with FL. The drug is administered subcutaneously according to a previously established step-up dosing. A preliminary data presentation from the study is scheduled for this year at the American Society of Hematology (ASH) conference. So far, 43 patients have been

Tabela 1. Safety and efficacy of bispecific antibodies as monotherapy in follicular lymphoma (FL) due to available data from clinical trials

Phase	Trial population	FL patients [n]	POD24 [%]	ORR[a] [%]	CR[a] [%]	PFS, median [months]	CRS [%] (total/grade 3–4)	ICANS-like syndromes [%] (total/grade 3–4)	Ref.
Mosunetuzumab									
2	R/R FL ≥ 2 lines	90	52	80	60	17.8	44.4/2.2	3/0	[11]
Glofitamab									
1	R/R B-NHL ≥ 1 line	44	nd	70.5	47.7	11.8	35.7[b]/3.5[b]	5.3[b]/nd	[17]
Odronextamab									
1	R/R B-NHL ≥ 2 lines	32	nd	91	72	17.1	61[b]/7.0[b]	12[b]/3[b]	[19]
2	R/R FL ≥ 2 lines[c]	128[d]/140	50	80	72	20.7	55/2	0.7/0	[21]
Epcoritamab									
1/2	R/R B-NHL ≥ 2 lines	10	nd	90	50	Not evaluable	59.0[b]/0[b]	6.4[b]/0.6[b]	[22]
1/2	R/R FL ≥ 2 lines[c]	128	42	82	63	15.4	66/2	6/0	[23]

[a]Assessed by an independent review committee; [b]in all population, regardless of diagnosis, [c]preliminary data from conference reports dpatients evaluable for efficacy; CR — complete response; CRS — cytokine release syndrome; ICANS — immune effector cell-associated neurotoxicity syndrome; i.v. — intravenously; nd — no data; ORR — overall response rate; PFS — progression-free survival; POD24 — relapse in 24 months after treatment; R/R — refractory/relapsed; s.c. — subcutaneously

Table 2. Mosunetuzumab in follicular lymphoma in active clinical trials (acc. to https://clinicaltrials.gov/)

Clinical trial	Phase	Agent	Primary endpoints
First-line			
NCT05389293	2	Mosunetuzumab s.c. monotherapy	CR rate
NCT05994235	2	Mosunetuzumab s.c. + tazametostat	CR rate
NCT04792502	2	Mosunetuzumab s.c. + lenalidomide	CR rate
NCT05169658	2	Mosunetuzumab s.c. ± obinutuzumab and poltuzumab vs. mosunetuzumab s.c. + glofitamab and obinutuzumab	CR rate
R/R lymphoma			
NCT05315713	1b/2	Mosunetuzumab s.c. + tiragolumab vs. mosunetuzumab s.c. + tiragolumab, atezolizumab	AEs rate; ORR
NCT04712097 (CELESTIMO)	3	Mosunetuzumab i.v. + lenalidomdie vs. enalidomide + rituximab	PFS
NCT05464329	1b	Mosunetuzumab s.c. + DHAX regimen vs. mosunetuzumab s.c. + ICE regimen	TEAEs rate, grades
NCT04246086	1b/2	Mosunetuzumab i.v., vs., s.c. ± lenalidomide	DLTs rate; AEs rate; AUC 1–3; $C_{trough4}$
NCT05169658	2	Mosunetuzumab s.c. ± obinutuzumab and poltuzumab vs. mosunetuzumab s.c. + glofitamab and obinutuzumab	CR rate
NCT04889716	2	Mosunetuzumab i.v. monotherapy vs. glofitamab + obinutuzumab	CMR rate; DLTs rate

AEs — adverse events; AUC1–3 — area under the concentration cycles 1–3; CMR — metabolic complete response; CR — complete response; $C_{trough4}$ — serum trough concentration at steady state approximated by cycle 4; DHAX — dexamethasone, cytarabine and oxaliplatin; DLTs — dose-limiting toxicity; FL — follicular lymphoma; ICE — ifosfamide, carboplatin, etoposide; i.v. — intravenously; ORR — overall response rate; PFS — progression-free survival; s.c. — subcutaneously; TEAEs — treatment-emergent adverse events

enrolled, with 40% having bulky disease and 27% having a FLIPI score of at least 3. The most common adverse events included injection site reactions, CRS in grades 1–2 in about 50% of patients, and rash. Neutropenia was observed in only 10% of the participants. In 26 patients, a response was possible, with 81% achieving CR and an ORR of 96% [16]. Therefore, the drug in this indication seems to have a fairly high efficacy with a good safety profile. Active clinical trials with mosunetuzumab in FL have been summarized in Table 2.

GLOFITAMAB

Glofitamab is a bispecific full-length BsAb targeting both CD3 and CD20, containing an Fc fragment devoid of the Fc gamma receptor. Due to the configuration of binding domains in a 2:1 ratio, it binds bivalently to the CD20 antigen and monovalently to CD3, significantly enhancing its efficacy compared to antibodies configured in a 1:1 manner. In the phase 1 NP30179 study, glofitamab was administered to patients with B-cell NHL for whom no other therapeutic option was feasible. Patients diagnosed with FL grade 1–3a comprised 25.7% of the participants (Table 2). In this group, 47.7% of patients achieved CR, and the ORR was 70.5%. PFS reached 11.8 months, with the consideration that heavily pretreated patients were intentionally included. CRS was observed in slightly over 70% of those receiving the drug at escalated doses of 2.5 mg–10 mg–30 mg and 50% of patients overall, including those in groups with lower drug doses [17]. In the second phase of the study, the inclusion criteria were limited to the diagnosis of DLBCL, high-grade B-cell lymphomas (HGBL), and primary mediastinal large

Table 3. Epcoritamab, glofitamab, and odronextamab in follicular lymphoma (FL) in active clinical trials (acc. to https://clinicaltrials.gov/)

Clinical trial	Phase	Agent	Indication	Primary endpoints
NCT06112847	2	Epcoritamab monotherapy	Untreated	CR rate
NCT05783609	2	Epcoritamab monotherapy	Untreated	CMR at EOT
NCT05451810	2	Epcoritamab monotherapy outpatient	R/R	CRS rate, ICANS rate, grade 3 neurotoxicity rate
NCT05409066 (EPCORE 1-FL)	3	Epcoritamab + R2 vs. R2	R/R	PFS 5 years
NCT04663347 (EPCORE NHL-2)	1b/2	Epcoritamab + BR regimen Epcoritamab + R2 Epcoritamab + lenalidomdie (POD24)	Untreated; R/R	Number of DLTs, AEs; ORR rate
NCT06091254 (OLYMPIA_1)	3	Odronextamab vs. rituximab + physician's choice	Untreated	DLTs rate, TEAEs rate and severity, CR at 30 months
NCT06097364 (OLYMPIA-2)	3	Odronextamab + CHOP ± maintance vs. R-CHOP	Untreated	DLTs rate, TEAEs rate and severity, CR at 30 months
NCT06149286 (OLYMPIA-5)	3	Odronextamab + lenalidomdie vs. lenalidomide	R/R	DLTs rate, TEAEs rate and severity, PFS in 5 years
NCT02290951 (ELM-1)	1	Odronextamab monotherapy i.v., v.s., s.c.	R/R	AEs rate, DLTs rate, ORR
NCT05783596	2	Glofitamab + obinutuzumab	Untreated	CMR rate at EOT

AEs — adverse events; BR — bendamustine, rituximab; CHOP — cyclophosphamide, doxorubicin, vincristine, prednisolone; CMR — metabolic complete response; CR — complete response; DLTs — dose-limiting toxicity; EOT — end of treatment; ICANS — immune effector cell-associated neurotoxicity syndrome; i.v. — intravenously; ORR — overall response rate; OS — overall survival, PFS — progression free survival; POD24 — relapse in 24 months after treatment; R-CHOP — rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R — resistant/refractory; R2 — rituximab, lenalidomide; s.c. — subcutaneously; TEAEs — treatment-emergent adverse events

B-cell lymphoma (PMBCL), and this formed the basis for the drug's registration in patients with refractory or relapsed DLBCL not qualifying for chimeric antigen receptor T-cell (CAR-T) therapy [18].

Currently, phase 1 and 1b trials are ongoing for glofitamab in the treatment of relapsed/refractory NHL, including FL, either as monotherapy or in combination with obinutuzumab, standard chemotherapy, or other novel molecules [18].

ODRONEXTAMAB

Odronextamab is a hinge-stabilized, human IgG4 bispecific antibody targeting CD20 and CD3. Currently, it is investigated in a few clinical trials, either in monotherapy or combined with other drugs (Table 3). In the phase 1, ELM-1 study, whose preliminary results were published last year, patients with relapsed/refractory (R/R) NHL previously treated with anti-CD20 antibodies were included. Odronextamab was administered once a week intravenously, to continue until disease progression or unacceptable toxicity. In the first cycle, the drug doses were escalated to the target dose, which in the FL cohort was established at 80 mg. CRS and neurological adverse events were recorded at a maximum grade of 1 or 2. The most common significant complications were anemia and neutropenia. All of the above-mentioned adverse events occurred surprisingly rarely, in less than 30% of patients each. However, serious adverse events (SAE) were observed cumulatively in 61% of patients, including CRS in 28% of all SAEs. However, considering that CRS did not occur at grade 3 or higher, these CRS were not life-threatening events. In the FL patient group receiving at least 5 mg of the drug, the ORR was 91%, and the CR was 72% [19].

Currently, a phase 2 study is ongoing in patients with R/R NHL. An analysis of data from the DLBCL cohort has been published [20], but preliminary results from an interim analysis of data from the FL group have been reported only in an oral presentation at the ASH 2023 conference. As of January 2023, 140 patients have been enrolled, with efficacy data available for 128 of them. Half of the patients had POD24. Odronextamab was administered intravenously every week for 4 cycles of 21 days. After cycle 4, maintenance therapy with the drug was administered every two weeks, to continue until progression. The ORR and CR were 80% and 71%, respectively. The median PFS exceeded 20 months, and the median OS has not been reached at 24 months [21]. This represents one of the longest PFS durations reported in R/R FL, but the final analysis is still under development. Available data from both phase 1 and phase 2 trials is summarized in Table 1.

EPCORITAMAB

Epcoritamab is a bispecific antibody targeting CD20 and CD3. It was investigated in the phase 1/2 dose-expansion study EPCORE-NHL-1, including patients with R/R NHL after multiple lines of treatment. Subcutaneous injections were administered, with the dose escalated to a final dose of 48 mg, and 12 treatment cycles were planned. No CRS grade 3 or higher was observed, and the overall toxicity profile was generally favorable. In the FL cohort, despite the presence of patients with adverse prognostic factors such as POD-24 and multiple lines of treatment, an ORR of 90% and a CR rate of 50% were achieved [22]. Preliminary follow-up results suggest a PFS of 15.4 months in this cohort, significantly correlating with minimal residual disease (MRD) negativity after epcoritamab treatment [23].

In 2022, partial results of the phase 1b/2 study, EPCORE-NHL-3, were published. Several arms were designed in the study, for varying patient diagnoses and clinical situations. Arm 6 included patients with previously untreated

Table 4. Bispecific antibodies in follicular lymphoma (FL) in early phases active clinical trials (acc. to https://clinicaltrials.gov/)

Clinical trial	Phase	Agent	Target	Additional agents	Indication	Primary endpoints
NCT04082936	1/2	Imvotamab	CD20, CD3	–	R/R B-NHL	Number of AEs; ORR
NCT0357182	1	AMG-562	CD19, CD3	–	R/R DLBCL, MCL, FL	Incidence of: DLTs, AEs, changes in physical examination, vital signs, ECG, laboratory tests
NCT04594642	1	AZD0486	CD19, CD3	–	R/R B-NHL	Number of DLTs, AEs; C_{max}; AUClast; apparent terminal half-life
NCT02568553	1	Blinatumomab	CD19, CD3	Lenalidomide	R/R B-NHL	Incidence of toxicity
NCT00889408	1	DT2219ARL	CD19,CD22	–	R/R lymphoma, leukemia	MTD
NCT04806035	1b	TG-1801	CD19, CD47	None/ublituximab	R/R B-NHL	RP2D
NCT04763083	1	NVG-111	ROR1, CD3	–	R/R B-NHL, malignant melanoma, non-small cell lung cancer	Number of TEAEs, SAEs, DLTs, AESI, abnormalities in physical examination, lab tests, ECG
NCT02924402	1	Plamotamab	CD20, CD3	–	R/R B-NH	Number of participants with trAEs; MTD; RD; schedule for dosing

AEs — adverse events; AESI — AE of special interest; AUClast — area under the concentration versus time curve from time 0 to the point before the next dose; B-NHL — B-cell non-Hodgkin lymphoma; C_{max} — max serum concentration; DLTs — dose-limiting toxicity; ECG — electrocardiography; MCL — mantle cell lymphoma; MTD — maximum tolerated dose; ORR — overall response rate; R/R — relapsed/refractory; RD — recommended dose; RP2D — recommended phase-2 dose; SAEs — severe AEs; TEAEs — treatment-emergent adverse events; trAEs — treatment-related AEs

FL who met generally accepted criteria for starting treatment. The most common adverse event associated with epcoritamab was grade 1 or 2 CRS, occurring in slightly over half of the patients (Table 1). Other frequent complications included neutropenia, fever, and injection site reactions. At the time of publication, the average observation time for these patients was 4.4 months, making it impossible to present efficacy data. In another arm involving R/R FL patients, epcoritamab was combined with rituximab administered once a month for 5 cycles and lenalidomide in a 12-cycle schedule (R2). Epcoritamab was administered weekly for the first 2 cycles and then every 4 weeks. The immunomodulatory action of lenalidomide was intended to enhance the BsAb's efficacy. Based on data as of 2022, a remarkable 100% ORR and 97% CR were reported in a 7-month observation [24].

Such excellent results prompted further research. In the ongoing phase 3 study, EPCORE FL-1, the efficacy of 12 treatment cycles with the epcoritamab + R2 regimen is planned to be compared to the standard R2 regimen in FL patients after the first line of treatment. The treatment is scheduled for 2 years, with the primary endpoint established on PFS, and secondary endpoints include OS, ORR, and MRD negativity [25]. The first patients were enrolled in 2022, so unfortunately, there are no study results yet. Few other trials in both the first and subsequent lines of treatment are ongoing (Table 3).

EARLY-PHASE CLINICAL TRIALS IN FL

Numerous BsAbs are investigated in the early-phase clinical trials. To date, most of them do not have even preliminary results, however, one should expect it in the next years. The most promising, imvotamab (IGM2323) is an IgM antibody against CC20 and CD3 characterized by high avidity. In the phase 1 study, 13 patients with advanced R/R FL were included. Total number of patients was 29. Results from that first-in-human study showed a good tolerability profile of imvotamab with less than 50% of patients who developed CRS [26]. Active trials, both, still recruiting and not, are listed in Table 4.

DISCUSSION

Resistance to treatment or disease recurrence after two lines of therapy is a significant challenge in patients with FL. While the efficacy of first-line treatment is usually satisfactory, subsequent lines of standard immunochemotherapy yield progressively less favorable outcomes. For patients with R/R FL, modern therapies, such as CAR-T cell therapy, are investigated, with BsAbs being increasingly explored in this context.

CAR-T cell therapy represents a groundbreaking treatment for hematologic malignancies, including lymphomas. In the case of R/R FL after at least two lines of therapy, the FDA and EMA have approved two products: tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) [27].

In the phase 2 ELARA trial, the use of tisa-cel in R/R FL led to a CR rate of 69% and an ORR of 86%, ZUMA-5 trial presented even better results for axi-cel, which in the FL group (n = 84) were 80% for CR and 94% for ORR. PFS in ZUMA-5 was nearly 40 months, and the median OS was not reached [28, 29]. In the registration study, patients with R/R FL treated with mosenutuzumab achieved slightly worse results with a mean ORR of 80%, CR of 60%, and PFS of 17.8 months [11]. Preliminary data from studies of epcoritumab and odronextamab administered in the subsequent lines of treatment in FL patients appear to be similar to mosunetuzumab. However, considering the effects of standard treatment with immunochemotherapy, these results still remain satisfactory.

A distinguishing complication in T-cell-engaging therapies compared to conventional immunochemotherapy regimens are CRS and ICANS. The incidence of these AEs

in selected FL cohorts for the best-studied BsAb has varied between approximately 40–60% and 3–6% respectively. However, grade 3–4 CRS in these groups was observed in only about 2% of patients, and grade 3–4 ICANS-like AEs in none of them [11, 21, 23], allowing BsAb to be considered relatively safe drugs. In tisa-cel treatment, CRS occurred in 48.5% of patients, with no cases in grade 3 or higher and ICANS occurred in 4.1%, with 1% having a grade ≥ 3 [28]. In the clinical trial of axi-cel, CRS was observed in more than 80% of the entire group. Despite such a high incidence of AE in general, CRS of grade 3 or higher occurred in only 6% of FL patients. Neurologic adverse events were observed in 15% of that cohort which is which is a significantly higher frequency than in the case BsAb. Neutropenia of at least grade 3 were noted in about 30% of both axi-cel and mosunetuzumab-treated groups [11, 29].

Compared to CAR-T therapy, the advantages of BsAb treatment seem to be a better safety profile and lower toxicity, evidenced by a lower percentage of complications such as CRS. Additionally, the drug's availability is significantly better, understood as independent from patient-related factors and the state of their disease, as well as involving a smaller number of highly qualified personnel. On the other hand, in favor of CAR-T, there is the time-limited nature of the therapy, as most BsAbs are administered in several-week cycles. Also, and perhaps most importantly, CAR-T therapy likely exhibits better efficacy with a higher percentage of CR and ORR.

SUMMARY

Regarding BsAb, mosunetuzumab is currently the only registered drug for FL treatment. However, several BsAb are in the early stages of investigation in NHL patients. Partial data from cohorts involving FL appear promising. Despite the lack of randomized comparative studies between CAR-T therapy and BsAb treatment in FL, an analysis of registration trial data suggests that, in many cases, BsAb may provide similar therapeutic responses with a comparable, if not more favorable, toxicity profile and potentially lower treatment costs. However, the short observation time hinders the assessment of the durability of achieved remissions. It seems that in certain clinical situations, the use of BsAb may be an alternative to CAR-T therapy or an additional option after the failure of tisa-cel or axi-cel treatment.

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