Review

Developing New Strategies for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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Review

Developing New Strategies for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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Abstract: Diffuse large B-cell lymphoma (DLBCL) is an aggressive but potentially curable disease. However, approximately 40% of patients with DLBCL will experience disease relapse or will be refractory to first line chemoimmunotherapy. In recent years there have been several new therapeutic agents approved for the treatment of relapsed/refractory (R/R) DLBCL. These agents include anti-CD19 chimeric antigen receptor T-cell therapies (CAR T-cells) and monoclonal antibodies as polatuzumab and tafasitamab. Nevertheless, despite the high efficacy of all these new therapies, there are still patients who do not respond or relapse, representing an unmet clinical need. This review describes new promising therapies that are under investigation to treat R/R DLBCL.

Keywords: diffuse large B-cell lymphoma. relapsed/refractory; therapy; efficacy; toxicity

1. Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin lymphoma, is a heterogeneous disease. Since the late 1990s, six to eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been the standard of care for first line therapy [1], with which more than 60% of patients are cured. Different studies have been published whose objective was to improve the results of this regimen, without success. However polatuzumab-R-CHP, a modified regimen of R-CHOP in which vincristine is replaced by polatuzumab vedotin (anti-CD79b antibody-drug conjugate), demonstrated recently an improvement in progression-free survival (PFS) when compared with the standard R-CHOP (76.7% vs. 70.2% at 2 years, hazard ratio 0.73), without increased toxicity, although overall survival (OS) did not differ significantly [2].

Salvage high-dose chemotherapy followed by autologous stem cell transplant (ASCT) has been the standard second-line treatment for relapsed or refractory (R/R) DLBCL patients. However, few patients are cured with this intensive approach, and applicability is limited by comorbidities and advanced age [3]. Moreover, patients with refractory disease or relapsed within 12 months after first line therapy have very poor outcomes even with this strategy, as it is shown in the SCHOLAR-1 multicenter retrospective study, in which the objective response rate (ORR) to the next line of therapy in such patients was 26%, and the complete remission (CR) rate was 7%, with a median overall survival (OS) of 6.3 months [4].

Recent novel therapy approaches have changed the treatment landscape of R/R DLBCL patients. Three different constructs of CD19 chimeric antigen receptor T-cells (CAR T-cells): axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel), have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of R/R DLBCL following 2 or more lines of systemic therapy, showing high response rates with durable remissions [5–7]. The most up-to-date data with axi-cel demonstrates an OS at 5 years of 42.6%, without new serious adverse events or deaths after additional follow-up [8]. CAR T-cells have also been assayed as second line therapy in high risk patients with DLBCL, defined as refractory to first line or in early relapse less than 12 months after completing first line treatment [9–11]. In 2 phase 3 trials, axi-cel and liso-cel showed an improvement in event-free survival (EFS)

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compared with ASCT, and, as a result of these data, they have been approved by EMA and FDA [9,10].

Another targeted approaches for R/R DLBCL have been approved in the last years, as the combination of tafasitamab (anti-CD19 nude monoclonal antibody) and lenalidomide [12], the combination of polatuzumab vedotin (anti CD79b conjugated monoclonal antibody) with bendamustine and rituximab [13], and selinexor, an oral inhibitor of exportin 1 (approved by the FDA but not by the EMA) [14]. Each of these options should be considered for patients who are poor candidates for ASCT or for CAR T-cell therapy.

Nevertheless, despite the high efficacy of all these new therapies, there are still patients who do not respond or relapse, representing an unmet clinical need. This review describes some of the new promising therapies that are under investigation to treat DLBCL.

2. Results

2.1. Small molecules

The B-cell receptor (BCR) signaling pathway is crucial for the development of malignant B cells, making it one of the targets for small molecule inhibitors in B cell non-Hodgkin Lymphoma (NHL). Constitutive activation of the BCR pathway is implicated in the pathogenesis of activated B-cell (ABC)-DLBCL subtype, which is associated with NF-κB activation. Drugs targeting this pathway include Bruton's tyrosine kinase (BTK) inhibitors. These drugs have also immunomodulatory effects on their own, as they've been shown to skew T-cell differentiation towards the inflammatory Th1 subtype. Four BTK inhibitors have been used for the treatment of lymphomas: ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib. Some of these drugs are approved to treat other B-cell lymphoproliferative diseases, as chronic lymphocytic leukemia or mantle cell lymphoma, however, its efficacy as monotherapy in DLBCL is limited. A phase 1/2 trial of the single-agent ibrutinib reported an ORR of 25% (CR, 10%), median PFS and OS of 1.6 and 6.4 months, respectively. Results were better in ABC DLBCL subtype compared to germinal center B-cell (GCB-) DLBCL, with ORR of 37% vs. 5%, median PFS of 2 vs. 1.6 months and median OS of 10.3 vs. 6.4 months [15]. When ibrutinib is combined with other targeted drugs, better results are reported. The combination of ibrutinib with venetoclax, prednisone, obinutuzumab, and lenalidomide (ViPOR), and ViPOR with polatuzumab vedotin, have shown ORRs of 56% (CR, 37%) and 64% (CR 36%), respectively [16,17]. There are also other trials ongoing thatevaluate BTK inhibitors in combination with other drugs in DLBCL (as examples: NCT02077166, NCT04436107). An important point is that BTK inhibitors can cross the blood-brain barrier, and have demonstrated activity in primary central nervous system (CNS) lymphoma [18].

Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is another essential component of the NF-κB pathway. MALT1 inhibition could be a good target in ABC-DLBCL. There are several phase 1 trials that are testing different agents that target MALT1, however, no clinical data are currently available (NCT03900598, NCT05618028).

Immunomodulatory imide drugs (IMIsDs) as lenalidomide have shown modest activity as monotherapy in R/R DLBCL. Several next-generation compounds termed cereblon E3 ligase modulators (CELMoDs) are in development, including avadomide, iberdomide, and golcadomide. The most promising results have been reported with iberdomide. In a phase 1/2 trial, 18 patients were treated with iberdomide with or without rituximab. Among the 7 who received the combination of iberdomide and rituximab, the ORR was 71% (CR, 29%). The most common grade 3/4 adverse event was neutropenia in 49% of patients [19]. Golcadomide has been assessed in a phase1 trial in patients with R/R NHL, including 30 with R/R DLBCL, with ORR of 40% (CR, 12%) [20]. These trials are still recruiting patients.

Interleukin-1 receptor-associated kinase 4 (IRAK4) is a protein that is part of the toll-like receptor pathway, that is downstream of MYD88 and enables activation of the NF-κB and MAPK pathways. IRAK4 inhibition results in lymphoma cell death in vitro. Around 40% of ABC-DLBCL has MYD88 mutations, and IRAK4 inhibition results in lymphoma cell death in vitro. Emavusertib is an IRAK4

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inhibitor that is being explored in monotherapy and in combination with ibrutinib, in an ongoing phase 1 trial in different lymphomas (NCT03328078). Preliminary safety and efficacy results in different NHL have been reported [21].

2.2. Conjugated monoclonal antibodies

Loncastuximab tesirine is a CD19 directed humanized monoclonal antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin. In the phase 2 LOTIS-2 trial, 145 patients with R/R DLBCL with a median of 3 previous lines of treatment were included (17% primary refractory, 9% after CAR T-cell failure). Therapy was given intravenously every 21 days until disease progression or unacceptable toxicity. ORR was 48% and CR 24%, with a median duration of response (DOR) of 13.4 months [22]. Concerns have been expressed that using an anti-CD19 agent may compromise subsequent CAR T-cell therapy, in which the same anti-CD19 antigen is used as target . There are preliminary experience with 14 patients who were identified from the phase 1 and phase 2 trials, who successively received CAR T-cell therapy, achieving an ORR of 50% (CR, 43%), similar to those without a previous anti-CD19 therapy **[**23]. However, 13 patients treated with loncastuximab after CD19 directed CAR T-cell failure, had an ORR of 46.2% and a lower CR of 15.4% [24].The most common adverse events identified were increased gamma-glutamyl transferase (40%), neutropenia (40%), and fatigue (37%) . An adverse event of special interest was edema (peripheral 20% or pleural 10%) which is related to the pyrrolobenzodiazepine toxin. Dexamethasone was used to relieve edema. New trials with loncastuximab in combination are now recruiting patients. LOTIS 5 is a phase 3 randomized trial for elderly frail patients with R/R DLBCL that compares 8 cycles of R-locastuximab vs 8 cycles of R-GemOx (NCT04384484); LOTIS 9 is a phase 2 trial with R-loncastuximab for elderly frail patients with previously untreated DLBCL. (NCT05144009).

Zilovertamab vedotin (MK-2140), is an antibody–drug conjugate comprising a monoclonal antibody recognizing the extracellular receptor tyrosine kinase like orphan receptor 1 (ROR1), a cleavable linker, and the anti-microtubule cytotoxin monomethyl auristatin E. ROR1 is a fetal protein highly expressed during early embryonic development but expressed at very low levels in adult tissues. Pathologic expression of ROR1 is seen in some hematologic and solid tumors cancers. In the phase 1 trial in which patients with different NHL were included, 17 had DLBCL, with a median of 4 prior lines of therapy, 71% had received prior CAR T-cells or CAR Natural Killer (NK)-cells and 47% had GCB-DLBCL subtype. The most frequent grade 3/4 treatment-related adverse events were neutropenia (32%) and thrombocytopenia (11%). ORR was 29% (CR, 18%) in patients with DLBCL [25]. There is a phase 2 trial ongoing for R/R DLBCL with zylovertamab until disease progression, unacceptable toxicity, or withdrawal (WAVELINE-004). So far, 40 patients have been enrolled, 24 (60%) with ≥3 prior lines of therapy, 25% with prior ASCT and 28% had failed to prior CAR T-cell therapy. ORR was 30%. The most common grade 3/4 toxicities were neutropenia (18%) and anemia (15%). Treatment-related peripheral neuropathy occurred in 15% of patients, and none was grade ≥3 [26]. There are different trials ongoing using zilovertamab in combination with other drugs for R/R DLBCL (NCT05139017) and even in first line DLBCL (NCT05406401).

Brentuximab vedotin is an anti-CD30 antibody–drug conjugated also with the anti-microtubule cytotoxin monomethyl auristatin E. It is indicated for the treatment of Hodgkin lymphoma and CD30+ T-cell lymphomas. About 15-25% DLBCL express CD30, therefore, trials have been performed in this setting. In a phase 2 trial, 49 patients with R/R DLBCL CD30+ (defined as >1% expression) were treated with brentuximab. The majority of patients were refractory to first-line (76%) and most recent therapies (82%). The ORR was 44% (CR, 17%), the median DOR was 16.6 months and median PFS was 4 months. It is important to remark that the degree of CD30 expression did not correlate with responses. Adverse events were consistent with known toxicities [27]. In a phase 1 study, the combination of brentuximab with lenalidomide were used in 37 patients, achieving an ORR of 57% (CR, 35%), median PFS and OS were 10.2 and 14.3 months, respectively [28]. Enrollment in the phase 3 trial named ECHELON-3 of R-Lenalidomide with or without brentuximab is ongoing (NCT04404283).

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2.3. Check-point inhibitors

2.3.1. T-cell checkpoint inhibitors

The immunological interactions between programmed cell death receptor 1 (PD-1) and its ligands (PD-L1 and PD-L2) has shown to prevent T-cell activation and proliferation, weakening immune response. Overexpression of other checkpoint receptors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) has been also proved to lessen immune surveillance in tumors. Antibodies targeting PD-1 and CTLA-4 have been developed with the aim of restoring T-cell function and eventually halting tumor proliferation.

Several T-cell checkpoint inhibitors have been studied in R/R DLBCL. The phase 2 KEYNOTE-170 study demonstrated effective antitumor activity and acceptable safety of pembrolizumab given every 3 weeks for up to 35 cycles (~2 years) in 53 patients with R/R primary mediastinal B-cell lymphoma (PMBCL) whose disease progressed after or who were ineligible for ASCT. In the final analysis, with a median follow-up of 48.7 months, ORR was 41.5% (CR, 21%), 4-year PFS was 33.0% and 4-year OS was 45%. The most common adverse events were neutropenia, asthenia, and hypothyroidism [29]. Several clinical trials are ongoing, with the combination of T-cell checkpoint inhibitors with other drugs, as brentuximab or acalabrutinib [30,31].

2.3.2. Macrophage checkpoint inhibitors

CD47, which is found on both healthy and malignant cells, regulates macrophage-mediated phagocytosis by sending a "don't eat me" signal to the signal regulatory protein alpha (SIRPα) receptor. Blocking CD47 interaction with SIRPα could enhance lymphoma cells killingc by macrophages. Several “macrophage checkpoint” agents are in development including magrolimab, lemzoparlimab, and evorpacept. In a phase 1b trial, a total of 22 patients (15 with DLBCL and 7 with follicular lymphoma) were treated with magrolimab and rituximab. Patients had received a median of 4 previous therapies, and 95% were refractory to rituximab. Among patients with DLBCL, the ORR and CR rate were 40% and 33%, respectively. The most frequent grade 3/4 adverse event was transient anemia [32]. In a phase 2 trial 33 patients with R/R DLBCL, with a median of 2 prior therapies, were treated with magrolimab combined with R-GemOx. After a median follow-up of 11.3 months, the ORR and CR rate were 51.5% and 39.4%, respectively. Median DOR was 18.0 months. The most common grade 3/4 toxicities were hematological [33]. Several trials in R/R DLBCL with other CD47 blockers are ongoing (as examples, NCT03934814, NCT03013218).

2.4. Bispecific antibodies

Bispecific antibodies (BsAbs) have emerged as a novel class of off-the-shelf immunotherapies with clear efficacy in R/R aggressive B-cell lymphomas, including for those patients relapsing after CAR T-cell therapy. BsAbs combine two different monospecific antigen-binding regions from different antibodies to achieve a single antibody-derived molecule with bispecific antigen binding.

2.4.1. T-cell engagers.

Currently, the majority of BsAb under development are T-cell engagers. They target CD20 on B-cells and engage CD3 on T-cells. Those with more advanced development in DLBCL are glofitamab and epcoritamab, whose use has recently been approved by FDA and EMA in adult patients with R/R DLBCL following 2 or more lines of systemic therapy.

Glofitamab is a BsAb with a 2:1 configuration with bivalency for CD20 on B cells and monovalency for CD3 on T cells. In the pivotal phase 2 trial (34), 154 patients with R/R DLBCL were treated with fixed-duration intravenous glofitamab monotherapy (12 cycles total). The median previous lines of therapy of these patients were 3, 90 (58%) were primary refractory and 46 (30%) had failed CAR T-cell therapy. At a median follow-up of 12.6 months, ORR was 52%, and 39% achieved CR. Results were consistent among the 52 patients who had previously received CAR T-cell therapy (35% of whom achieved CR). The 12-month PFS was 37%. Discontinuation of glofitamab due to

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adverse events occurred in 9% of the patients. The most common adverse event was cytokine release syndrome (CRS) in 63% of the patients (grade 3 or higher CRS in 4%). Grade 3 or higher neurologic events appeared in 3% of patients [34].

Epcoritamab is a IgG1 BsAb targeting CD3 and CD20 which is administered subcutaneously in 28-day cycles until disease progression or unacceptable toxicity. In the pivotal phase 2 trial, 157 patients were included [35]. The median prior lines of therapy was 3, 96 (61%) had primary refractory disease, and 61 (39%) had failed to prior CAR T-cell therapy. At a median follow-up of 10.7 months, ORR was 63.1% and CR was 38.9%. Response rates were similar across key pre-specified subgroups. The median duration of response was 12.0 months. The most common adverse events were CRS in 50% (grade 3 in 2.5%), pyrexia in 24%, and fatigue in 23%. Immune effector cell-associated neurotoxicity syndrome occurred in 6.4%.

Another BsAb in development for R/R DLBCL is odronextamab, a fully human IgG4-based BsAb targeting CD20 and CD3. In the phase 1 trial [36], 145 patients with R/R NHL were enrolled (94 to the dose-escalation and 51 to the dose-expansion). The median previous therapies was 3, 42 (29%) patients had received previous CAR-T cell therapy and 119 (82%) were refractory to the last line of therapy. The recommended dose for expansion in patients with DLBCL was 160 mg. The most common grade 3 or worse adverse events were anemia (25%), lymphopenia (19%), neutropenia (19%), and thrombocytopenia (14%). CRS occurred in 41 (28%) patients. In 15 patients with DLBCL without previous CAR T-cell therapy who received doses of 80 mg or higher, the ORR was 53% (all CR), and among the 30 patients with previous CAR T-cell therapy who had received doses of 80 mg or higher, ORR was 33% and CR was 27%.

There are some data that confirm that BsAb can be combined with other therapies safely and effectively, and many clinical trials are now recruiting patients. As some examples, there is a phase 3 trial comparing rituximab, gemcitabine and oxaliplatin (R-GemOx) with glofitamab in combination with R-GemOx in R/R DLBCL patients not eligible for ASCT (NCT04408638). Glofitamab has been also combined with R-CHOP in first-line and compared with polatuzumab R-CHP (NCT03467373). There is also a trial of epcoritamab in combination with different chemotherapies for patients with R/R DLBCL: with rituximab, cytarabine, dexamethasone, and oxaliplatin/ carboplatin (R-DHAX/C) for patients eligible for ASCT, with GemOx for patients not eligible for ASCT, and with other regimens (NCT04663347). Another phase 3 trial is ongoing with the combination in first line of epcoritamab with R-CHOP compared to R-CHOP (NCT05578976).

2.4.2. Natural Killer (NK) cell engagers

There are under investigation a new category of BsAbs targeting NK-cells. NK-cell engagers are not subject to major histocompatibility complex (MHC) restriction and have the potential for less toxicity. CD16 is the most common NK target, but only the CD16A isoform is able to activate tumor cell destruction. On the other hand, CD16A is easily lost due to cleavage by ADAM17. Different strategies have been developed to avoid this. One option could be the addition of an ADAM17 inhibitor in combination with CD16. Other option is to target multiple NK receptors, as NKp30, NKp46, NKG2D and DNAM1. There have already been some preclinical results targeting CD16 and CDp46 on NK cells and CD19 on tumor cells [37].

2.4.3. Other types of BsAbs

Other types of BsAbs are in early development. These are primarily BsAbs targeting multiple immune checkpoint receptors, as PDL1 and 41BB, or PDL1 and CTLA4, or BsAbs targeting multiple antigens on the tumor cell as CD47 x CD19, or CD19 x CD22. They are being studied as monotherapy or in combination with other therapies.

2.5. New CAR strategies

The high rate of relapse in up to 60% of DLBCL patients after CAR T-cell therapy represents a major challenge. On the other hand, the safety of CAR T-cell treatment, with the risk of CRS and / or

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the immune effector cell-associated neurotoxicity syndrome (ICANs), is still a concern. Therefore, there is currently extensive research to improve efficacy and decrease toxicity of these products. Much of this research is still in pre-clinical development.

2.5.1. Bispecific / trispecific / universal CAR T-cells.

One of the mechanisms for relapse after CAR T-cell treatment is tumor cell antigen escape. This can occur through the downregulation of the target antigen by the malignant cells or due to tumor heterogeneity in antigen expression. One of the proposed solutions is the use of dual or triple target CAR T-cells, or even the development of universal CAR T-cells, which would allow a single line of CAR T-cells to bind to several antigens by giving different adaptor molecules as ligands [38].

Data with a CD19-CD20 bispecific CAR T-cell construct in a dose escalation and expansion study have been published. Twenty-two patients (11 with R/R DLBCL) with a median of 4 previous lines of therapy were infused. Grade 3/4 CRS occurred in 1 (5%) patient, and grade 3/4 neurotoxicity in 3 (14%) patients. The ORR to the dose of 2.5×10^6 cells per kg (n= 12) was 100% (CR, 92%). They noted that loss of CD19 was not seen in relapsed patients or treatment failures [39]. Other similar trials for bispecific CAR T-cell products are underway (NCT04007029, NCT04215016).

2.5.2. ON-switch and OFF-switch CARs

CAR T-cells, once infused into patients, start a chain of immunological reactions in an uncontrolled way, leading to the kill of the lymphoma cells, but also to immunological toxicities. The ON-switch CAR is a design that separates the signal domain from the costimulatory domain. The T-cell activation can occur by adding heterodimerizing small molecules that promote the assembly of two fragmented CARs, and the extent of cell activation can be modified by the dosage of the molecules. The OFF-switch CAR, also known as the small molecule-assisted shutoff (SMASh)-CAR, includes a degron domain in the CAR structure and enables CAR degradation when protease inhibitors are given, downregulating T-cell activity [40,41].

ON and OFF CAR T-cells using subtherapeutic concentrations of the clinically approved drug lenalidomide have been developed. [42].

2.5.3. Combination of CARs with other immunostimulatory drugs

One of the mechanisms of CAR T-cell failure is the presence of an immunosuppressive tumor microenvironment. This is being addressed by combining CAR T-cell therapy with other drugs.

One strategy has been the combination with immune checkpoint drugs. A study looked at pembrolizumab administration in R/R patients after treatment with CD19 CAR T-cell therapy. Twelve patients were included in the study, 11 with R/R DLBCL. The median number of prior therapies was 4, median PFS after CAR T-cell infusion was 2.2 months and median time to first pembrolizumab dose was 3.3 months. The most relevant adverse events grade 3/4 after pembolizumab were neutropenia in 3 patients and CRS in 1. Other grade 1/2 toxicities included infusion reaction in 1 patient and fever in 2. Eleven patients were evaluable for response, ORR after pembrolizumab was 27% (1 CR, 2 PR), 9/12 patients showed a re-expansion peak in peripheral blood CAR T- cells [43]. After these results, some of the new CAR constructs are looking at creating a similar effect by including a PD1 blocking molecule in the construct. In the ongoing trial ZUMA-6, R/R DLBCL patients are treated with an anti-CD19 CAR T-cell followed by 4 doses of atezolizumab (NCT02926833).

2.5.4. Off-the-shelf CARs: CAR NK-cells

The high cost, complex process, and long waiting time needed for manufacturing personalized CAR T-cells are factors that hinder patients' access to treatment. Consequently, to overcome these obstacles, the development of universal allogeneic CAR T-cells and other CARs using alternative effector cells are underway ("off-the-shelf" CARs).

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As mentioned before, NKs can directly identify target cells without MHC restrictions, and do not cause graft versus host disease (GVHD). Therefore, they are possible options for producing off-the-shelf CARs. NK cells can be extracted from various allogeneic sources, such as pluripotent stem cells or umbilical cord blood.

In a phase 1/2 trial, HLA-mismatched anti-CD19 CAR NK-cells derived from cord blood were administered to 11 patients with relapsed or refractory CD19-positive lymphoid malignancies. The administration of CAR NK-cells was not associated with the development of CRS, ICANs or GVHD. The maximum tolerated dose was not reached. Eight (73%) patients responded, 7 (64%) achieved CR. Responses were rapid, within 30 days after infusion, and the infused CAR NK-cells expanded and persisted at low levels for at least 12 months [44]. Several CAR NK-based phase 1 clinical trials are now recruiting patients with different lymphomas (NCT05487651, NCT05336409).

3. Discussion

Fortunately, we have a much larger armamentarium than we did a few years ago to treat DLBCL patients. Among all these new therapies, the most mature data reported are with the BsAb glofitamab and epcoritamab, and with the conjugated anti CD19 monoclonal antibody loncastuximab. In the pivotal trials of the BsAb, more than 150 extremely high-risk patients were included, many of them in progression after CAR T-cell therapy, and achieved CR rates of around 40%. Although these results are excellent, it should not be forgotten that follow-up is still very short, nevertheless, the PFS at 1 year with glofitamab is 37% and PFS at 6 months with epcoritamab is 44% [34,35]. Regarding loncastuximab, 145 very high risk R/R DLBCL patients were treated in the pivotal trial, the ORR was close to 50% and the CR rate was around 25%. Again this trial has a short follow-up, PFS at 6 months was around 45% [22]. However, due to these results, these compounds have recently been approved by the FDA and by the EMA to treat R/R DLBCL after two or more lines of systemic therapy.

Among the other compounds discussed, those that seem most promising are the CELMoD iberdomide combined with rituximab [19], and the CD47 inhibitors as magrolimab [32]. Few patients have been treated with these drugs, but the high ORR preludes further development. On the other hand, drugs already approved in other indications, such as the conjugated antiCD30 antibody brentuximab [27,28], and the T-cell check-point inhibitor pembrolizumab [29], appear to be very effective in certain subtypes of DLBCL.

Immunotherapy with CAR T-cells has emerged as a very effective therapy for DLBCL, but not all patients respond and many of them progress. Different strategies are under investigation to improve the efficacy and to reduce the toxicity of these products. One of the strategies is the use of dual target CAR T-cells that could reduce the risk of tumor cell antigen escape. In a small group of patients treated with the CD19-CD20 bispecific CAR T-cell product, the ORR was 100%, and toxicity was lower than with other CARs [39]. As a result of these preliminary results, trials are currently being carried out that will include a larger number of patients. Another important problem of CARs is that they have to be engineered for each individual patient, and the manufacturing process is long and expensive. The manufacturing of universal CARs using allogeneic NK-cells as effector cells is ongoing. In a preliminary trial the ORR was very high without CRS or ICANs toxicity [44]. For this reason, there are different phase 1 trials underway.

In summary, new therapies have been recently approved and will be available for our DLBCL patients briefly, and there are many others in development. Nevertheless, there are still many questions to be answered. As we have more therapeutic options, we have to assess how we will sequence them. Comparison among different strategies is difficult, as there are not trials that compare them directly, and characteristics of the patients differ among the different trials. Therefore, the optimal setting and sequencing of the therapies is unknown. Another important point is how these new therapies can be combined to improve efficacy without increasing toxicity. It is also important the selection of the best treatment for each individual patient. One of the options to select the best treatment modality is to identify predictive biomarkers of treatment responses and toxicities. Hopefully, the results of the ongoing trials will help us to answer some of these questions.

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