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Review

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Harnessing the Immune System: An Effective Way to Manage Diffuse Large B-Cell Lymphoma

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Abstract

Diffuse large B-cell lymphoma (DLBCL) is a heterogenous hematological disorder with malignant potential controlled by immunological characteristics of the tumor microenvironment. Rapid breakthrough in the molecular pathways has made immunological approaches the main anchor in the management of DLBCL, with or without chemotherapeutic agents. Rituximab was the first monoclonal antibody approved for the treatment of DLBCL. Following rituximab that transformed the therapeutic landscape, other novel immunological agents including chimeric antigen T-cell therapy have reshaped the management of relapsed/refractory DLBCL. However, resistance and refractory state remain a challenge in the management of DLBCL. For this literature review, we screened articles from Medline, Embase, Cochrane databases and the European/North American guidelines from March 2010 through October 2022 for DLBCL. Here we discuss immunological agents that will significantly affect future treatment of this aggressive type of lymphoma.

Keywords: Diffuse large B-cell lymphoma; Immunotherapy; Immunomodulatory therapy; Bispecific T-cell engager antibody; Antibody drug conjugates; Checkpoint inhibitors; Chimeric antigen receptor T-cell therapy

Introduction

Immunological interventions are used to target specific antigen of the malignant clone with the least lethal effect on the normal host tissue. However, the immune system also needs pro-effector environmental signals to unleash its lethal effect. Extensive efforts have been made to define antigenic targets differentiating "self" from "non-self", but there appears to be no antigen unique to diffuse large B-cell lymphoma (DLBCL). With the monoclonal antibody rituximab, there was an improvement of nearly 15% 10-year overall survival (OS) when added to CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone) regimen [1]. After the initial breakthrough with rituximab, there has been no improvement in treatment of DLBCL as other novel CD20 antibodies including obinutuzumab or intensifying R-CHOP with 15-day regimen have not improved upon an every 21-day R-CHOP regimen, which remains the standard of care (SOC) for DLBCL treatment [2]. The long-term survival of DLBCL is 40-50%, and for the rest, there is an unmet need for improvement of quality of life and survival. This may be because of the substantial heterogeneity in the biology of DLBCL. Here, we discuss the role of immune-mediated treatment options, including immunomodulatory agents and cellular therapies in the management of DLBCL.

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Overview of Immunological Interventions in the Management of DLBCL

Immunological interventions include immunomodulatory therapy, monoclonal antibodies, bispecific T-cell engager antibody, antibody drug conjugates (ADCs), checkpoint inhibitor therapy, and chimeric antigen receptor T cells (CARs) therapy (Fig. 1, Table 1 [3-25]).

Mechanism of action of the immunomodulatory agents

The immunomodulatory agents, lenalidomide and pomilidomide enhance the activity of B, T, NK, and dendritic cells and enhance antibody-dependent cellular cytotoxicity. Cereblon is identfied as a molecular target that may underlie the effects of lenalidomide on tumor cells, as well as on cells in the tumor microenvironment. Lenalidomide downregulates interferon regulatory factor 4 (the cell survival factor) and the gene SPIB that encodes SPI-B, a transcription factor which is upregulated in activated B cell (ABC)-DLBCL inducing cell death in ABC-DLBCL. Rituximab, the humanized chimeric anti-CD20 monoclonal antibody, induces killing of CD20+ cells via the direct effects of complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity, and the indi-

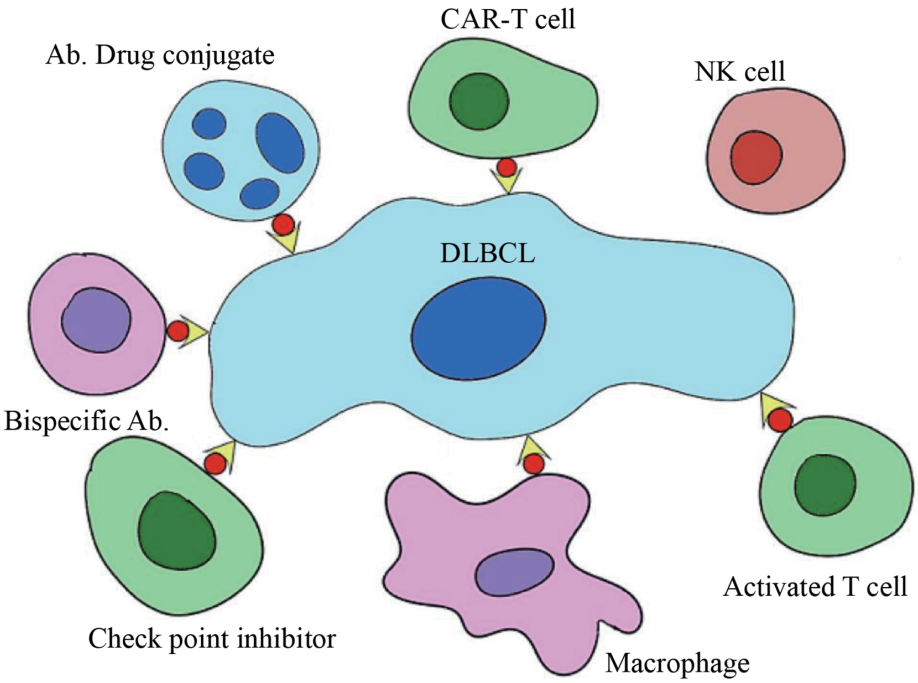

Figure 1. Immunological targets in DLBCL. DLBCL: diffuse large B-cell lymphoma.

rect effects include structural changes, apoptosis, and sensitization of cancer cells to chemotherapy. Obinutuzumab, a type II anti-CD20, works primarily by inducing direct cell death by antibody-dependent cell-mediated cytotoxicity. Ofatumumab is a human monoclonal antibody against CD20 that mainly induces complement dependent cytotoxicity. Tafasitamab is a Fc-enhanced humanized CD19 antibody that induces NK cell-mediated lysis of B cells. Magrolimab, is a humanized, IgG4 isotype, CD47-blocking monoclonal antibody (CD47 antigen is a signal "do not eat me" for the macrophages), inducing phagocytosis of tumor cells by the blockade of CD47 and its ligand SIRPα. An antibody drug conjugate is a monoclonal antibody conjugated to the cytotoxic payload (usually a microtubule-disrupting agent) via a chemical linker that is directed toward a target antigen expressed on the lymphoma cell surface, reducing systemic exposure and toxicity. Bispecific antibodies, target two different antigens (CD19 or CD20 of the lymphoma cells and CD3 of the T-cell), to redirect an immune response to the tumor site, bypassing Fc-mediated or major histocompatibility complex (MHC)-restricted activation of effector cells. Bispecific antibody constructs are available off the shelf. Cancer cells escape immune recognition by exploiting the programmed cell death-1 (PD-1)/PD-1 ligands (PD-L1) immune checkpoint axis, and PD-1 blocking agents have changed the treatment landscape of classical HL and primary mediastinal B-cell lymphoma and the role of these agents in DLBCL is being evaluated. Chimeric antigen receptor redirected T cells (CARs) are autologous T cells genetically engineered to express CARs that can recognize a variety of tumor- associated antigens. The antigen-binding domain of B cell receptor is transfected to the intracellular domain of a CD3 TCR (CD3-zeta) via a viral vector. The CARs are engineered to target CD19/CD22 antigen of lymphoma cells and activate T cells, independently of MHC recognition.

Immunomodulatory agents

Immunomodulatory agents have become an important drug category in the treatment of DLBCL. These agents have a complex mechanism of action (Fig. 2).

Lenalidomide

Lenalidomide is an orally active immunomodulatory drug that enhances the activity of B, T, natural killer (NK), and dendritic cells and enhances antibody-dependent cellular cytotoxicity. Cereblon, the molecular target is needed for the effects of lenalidomide on tumor cells, as well as on cells in the tumor microenvironment. Decreases in cereblon attenuate these effects and confer resistance to lenalidomide and antibody-dependent cellular cytotoxicity. These effects are secondary to cytokine production from T cells. Lenalidomide downregulates the cell survival factor, interferon regulatory factor 4, a transcription factor overexpressed in DLBCL providing its antitumor effects. Treatment with lenalidomide of activated B-cell DLBCL (ABC-DLBCL) resulted in downregulation of SPIB, the gene *SPIB* encodes SPI-B, a transcription factor upregulated in DLBCL. Treatment of ABC-DLBCL cells with lenalidomide induces rapid downregulation of *SPIB* mRNA transcripts and protein causing cell death [26]. Lenalidomide has been shown

Table 1. Immune-Mediated Interventions in the Management of DLBCL

Therapeutic agent	Target	Functional characteristics	Therapeutic role in DLBCL
Lenalidomide [3], pomalidomide [4]	Cereblon	LEN/POM increase NK cell function and IL2 production and decrease angiogenesis	Tafasitamab + lenalidomide in NGC DLBCL - CR 43%, PR 18%; pomalidomide and pembrolizumab in DLBCL - RR 50%, OS 14.7 months
Axicabtagene ciloleucel [4], tisagenlecleucel [7], lisocabtagene maraleucel [8] CAR therapy loncatuximab tesirine (ADC) [9], tafasitamab [10] (monoclonal Ab.)	CD19	Is present during all phases of B cell development until terminal differentiation is needed for signal transduction	Tafasitamab in combination with lenalidomide is approved for treatment of R/R DLBCL patients ineligible for ASCT. Loncastuximab tesirine is approved as a third line treatment in patients with R/R DLBCL - ORR 45.6%, CR 26.7%. Axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel - axi-cel 4-year OS 43%; tisa-cel 1-year OS 55.1%; liso-cel 57.9% - there is no evidence suggestive of difference in survival between these agents.
Blinatumumab (BiTE) [11]	CD19, CD3	Bispecific antibody links CD3 of effector and CD19 of tumor cells	Phase II trial in R/R DLBCL: ORR of 43%
Rituximab [5], ofatumumab [12], obinatuzumab [6]	CD20	Needed for maturation and activation of B cells	Rituximab is approved for treatment of R/R DLBCL in various settings. Ofatumumab and obinutuzumab (ORR 37%) are not FDA approved.
Mosenutuzumab [13], glofitamab [14], plomatamab [15], epcoritamab [16], odonextamab [17] (BiTE)	CD20, CD3	Bispecific T cell engager Ab.	Phase I trials in R/R DLBCL mosunetuzumab: ORR 87%; CR 71%
Inotuzumab ozogamycin [18] (ADC)	CD22	Needed for B-cell receptor downstream signaling	Inotuzumab ozogamicin in R/R DLBCL: OS 9.5 months, PFS 3.7 months
Brentuximabvedotin [19] (ADC)	CD30	"co-stimulatory receptor" for T cells - cytolytic effect	Is in phase I/II for R/R DLBCL with R/CHOP: ORR 44%; CR 17%
Polatuzumab vedotin [20] (ADC)	CD79b	ADC-designed to selectively payload	FDA approved. Based on phase II trial (in combination deliver an ultra-toxic rituximab/bendamustine in R/R DLBCL: ORR 41.5%; CR 38.7%
Magrolimab [21] (monoclonal Ab.)	CD47	Cancer cells overexpress CD47 mechanism to evade phagocytosis	TTI-622-01 (NCT03530683) is a multi-center phase 1a/1b study ongoing with R/R DLBCL. Phase 2 study: ORR 40%; CR 33%
Check point inhibitors [22-25]	9p24	Increased PDL1 expression from mutant 9p24 locus	Nivolumab - phase II study in R/R DLBCL not eligible for ABMT (ORR 10%). Pembrolizumab in phase III trial in untreated DLBCL with R-CHOP (ORR 25%). Pembrolizumab in phase Ib in R/R primary med. B cell lymphoma

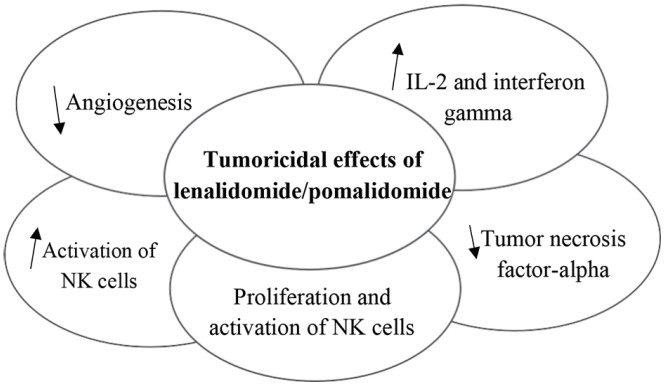

Figure 2. Effects of immunomodulatory agents.

to produce synergistic effects in experimental models when evaluated in combination with rituximab, dexamethasone, bortezomib, and B-cell receptor signaling inhibitors, consistent with mechanisms complementary to these agents [27]. However, in ROBUST trial, patients with ABC-DLBCL who received lenalidomide plus standard R-CHOP21 (R2COP) versus placebo/R-CHOP21 for six cycles did not meet the primary end point of progression-free survival (PFS) (PFS for 2 years was 67% for R2COP and 64% for placebo/R2COP; hazard ratio (HR), 0.85; 95% confidence interval (CI): 0.63 - 1.14; P = 0.29) [28].

In an open-label, multicenter, phase 1b/2 study, 45 patients with relapsed/refractory (R/R) non-germinal DLBCL received ibrutinib plus lenalidomide and rituximab. The overall response rate (ORR) was 44% and complete response (CR)

was 28% [29]. In a phase II study (L-MIND), 81 enrolled patients received tafasitamab + lenalidomide for R/R DLBCL. The ORR was 57.5% (n = 46/80), including CR in 40% of patients (n = 32/80) and partial response (PR) in 17.5% of patients (n = 14/80). The median duration of response (DoR) was 43.9 months (95% CI: 26.1 - not reached (NR), and NR in patients who achieved a CR (95% CI: 43.9 - NR); median PFS was 11.6 months (95% CI: 6.3 - 45.7), with median follow-up of 33.9 months; median OS was 33.5 months (95% CI: 18.3 - NR), with median follow-up of 42.7 months. There were no unexpected toxicities [3]. In a single-arm phase II trial of non-germinal center B-cell-like (GCB) DLBCL, 60 patients received rituximab, lenalidomide and ibrutinib. The ORR after two cycles was 86.2%, and the CR rate was 94.5%. The median PFS and OS were 91.3% and 96.6% at 2 years, respectively [30]. Lenalidomide was used in a phase Ib trial for refractory/recurrent central nervous system lymphoma with ibrutinib, and rituximab was evaluated for response with 13/15 (73%) showing a response: four CR, seven PR, and two stable disease (SD), one progression development (PD). Median PFS was 3.03 months [31]. Lenalidomide associated B-cell acute lymphoblastic leukemia (B-ALL) with high rates of TP53 mutation and hypodiploidy have been reported in myeloma but so far not reported in R/R DLBCL [32].

Pomalidomide (POM)

Pomilidomide is a second-generation immunomodulatory agent that induces cell cycle arrest and apoptosis of cells in neoplastic tissue. It has been used to treat relapsed and/or primary refractory human immunodeficiency virus (HIV)-associated DLBCL. In stage IV R/R DLBCL, 10 patients received pembrolizumab, an immune checkpoint inhibitor, with or without POM. The PFS was 4.1 months (95% CI: 1.3 - 12.4) and OS was 14.7 months (95% CI: 2.96 - NR) [4]. Thirty-three patients in a phase Ia/Ib study enrolled with R/R DLBCL (n = 8), chronic lymphatic leukemia/small lymphocytic lymphoma (CLL/SLL) (n = 5), Richter's transformation (RT) (n = 6), follicular lymphoma (FL) (n = 5), mantle cell lymphoma (MCL) (n = 4), marginal zone lymphoma/lymphoplasmacytic lymphoma (MZL/LPL) (n = 3), and Hodgkin's lymphoma (HL) (n = 2) received an optimized oral triplet combination of a novel BTK inhibitor DTRMWXHS-12 (DTRM-12) with everolimus and POM. About 48% of all patients had a ≥ 50% reduction in sum of the products of lymph node diameter [33].

Monoclonal antibodies

As part of the induction regimen for DLBCL, monoclonal antibodies provide additional benefit (Fig. 3).

Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody that decreases B-cell levels in peripheral lymph nodes and bone marrow (as 95% depletion of B cells in peripheral lymph nodes and bone marrow requiring 60 to 90 days to attain normal levels and improves survival in DLBCL [34]. The addition of rituximab to the CHOP regimen increases the CR rate and prolongs OS in elderly patients with DLBCL, without a clinically significant increase in toxicity [5]. The ORR of rituximab when added to CHOP was 94% [35]. Rituximab to CHOP chemotherapy has resulted in improvement in outcome for DLBCL irrespective of age with the event-free survival (EFS), PFS and OS not different between six versus eight cycles of R-CHOP-14 for DLBCL and it added to the toxicity [36, 37]. Rituximab maintenance therapy improves survival which was not statistically significant in patients with DLBCL [38].

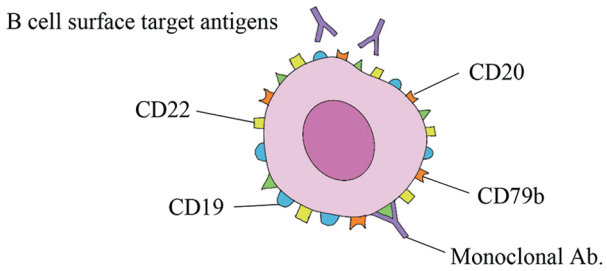

Figure 3. Monoclonal antibodies.

Obinutuzumab

Obinutuzumab is a type II anti-CD20 monoclonal antibody that induces direct cell death and has antibody-dependent cellular cytotoxicity than rituximab that is used in combination with other investigational agents in first-line FL and DLBCL. A flat dose of 1,000 mg for obinutuzumab rather than conventional body surface area-based dosing is advised [6]. A trial with 25 DLBCL and 15 MCL R/R showed response to obinutuzumab monotherapy. Among 40 patients, 21 patients were in the 400/400 mg treatment arm (DLBCL, n = 10; MCL, n = 11) and 19 patients were in the 1,600/800 mg arm (DLBCL, n = 15; MCL, n = 4). The ORR was 37% in the 1,600/800 mg arm and 24% in the 400/400 mg study arm [39]. There are various open-label, multicenter phase Ib/II studies with other investigational agents including atezolizumab plus obinutuzumab and CHOP or bendamustine in first-line FL and DLBCL [40]. Obinutuzumab-CHOP (G-CHOP) did not significantly improve PFS compared with R-CHOP in previously untreated patients with DLBCL and serious adverse events (43% versus 38%) were also more common in the G-CHOP than in the R-CHOP arm [41].

Ofatumumab

Ofatumumab is a human monoclonal antibody against CD20 that induces complement dependent cytotoxicity. In a phase II trial of elderly patients with newly diagnosed DLBCL the ORR was 90.5% and the CRR was 33.3%. Median PFS and OS were 8.6 and 12.0 months, respectively [42]. A phase II study of 85 patients with R/R DLBCL patients eligible/transplant ineligible

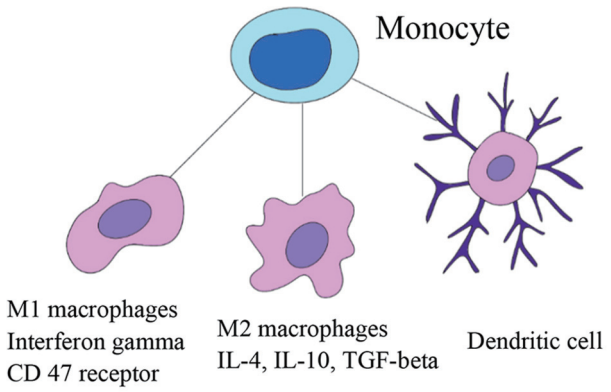

Figure 4. Targeting macrophages with anti-CD47 antibody (magrolimab).

(TI) for autologous stem cell transplantation (ASCT) received ofatumumab 300 mg followed by seven weekly IV infusions of 1,000 mg. The ORR was 13% for the TI group (seven PRs) and 8% for the relapse/progression after transplantation (PT) group (two CRs) [12]. Patients with R/R $CD20^+$ DLBCL were assigned to three cycles of rituximab-dexamethasone, cytarabine, cisplatin (DHAP) or ofatumumab-DHAP. Either ofatumumab 1,000 mg or rituximab 375 mg/m^2 was administered for a total of four infusions (days 1 and 8 of cycle 1; day 1 of cycles 2 and 3 of DHAP). PFS at 2 years was 24% versus 26% and there was no difference in efficacy between these two groups [43].

Targeting NK cells with Fc-enhanced CD19 antibody (tafasitamab)

The CD19 antigen is expressed on DLBCL cells, and the Fc-enhanced, humanized, anti-CD19 monoclonal antibody tafasitamab induces NK cell-mediated lysis of B cells in lymphoma and leukemia. This agent showed promising clinical activity in patients with R/R DLBCL [44]. In a phase II study tafasitamab showed clinical activity in patients with R/R DLBCL with responses in five out of nine patients lasting for more than 12 months, including in patients with rituximab refractory lymphoma [10]. In a phase II study, tafasitamab with lenalidomide was well tolerated and resulted in a high proportion of patients with R/R DLBCL ineligible for ASCT having a CR, and might represent a new therapeutic option in this setting [3].

Targeting macrophages with anti-CD47 antibody (magrolimab)

The M1 macrophages are immunosuppressive and aid tumor growth (Fig. 4). The antigen CD47 is an antiphagocytic signal that is overexpressed on circulating hematopoietic stem cells, lymphoma and leukemia cells to avoid phagocytosis [45]. Magrolimab, a humanized, IgG4 isotype, CD47-blocking monoclonal antibody, induces phagocytosis of tumor cells by the blockade of CD47 and its ligand SIRPα [46]. The anti-CD47-induced phagocytosis by M1 was more prominent than that for M2 [47]. The combination of magrolimab and rituximab demonstrated safety and efficacy in a cohort of patients with R/R DLBCL. Among patients with DLBCL, the CD47 expression is consistently high with the objective response and CR rates of 40% and 33%, respectively with magrolimab. At a median follow-up of 6.2 months among patients with DLBCL, 91% of the responses were ongoing [21].

Bispecific antibodies

Bispecific antibodies, consisting of two different antigens, are used in treatment of R/R DLBCL to redirect an immune response to the tumor site, bypassing Fc-mediated or MHC-restricted activation of effector cells. The initial clinical studies were disappointing due to low efficacy and severe adverse effects in DLBCL. The retargeting is achieved by simultaneous binding of the bispecific molecule to a tumor antigen on the target cell (CD19) and a trigger molecule on the effector cell (CD3), leading to tumor cell destruction [48]. With recombinant antibody technology the current bispecific antibodies consist of several smaller formats where the antibody is essentially reduced to the domains involved directly in the antigen binding [49]. Thus, the redirection of an immune response to the tumor site, bypassing Fc-mediated or MHC-restricted activation of effector cells, is achieved. In this context, CD3 has become widely accepted as the appropriate trigger molecule [48].

Blinatumomab

Blinatumomab, a bispecific T cell engaging antibody (CD19 and CD3), directed against the B cell differentiation antigen showed remarkable single-agent activity in patients with R/R DLBCL and R/R B-cell precursor ALL [11]. Cytokine release syndrome and neurological side effects were dose-limiting. Adverse effects were manageable and transient in nature. Based on the results of an international phase II trial, blinatumomab received FDA approval for the treatment of R/R B-precursor ALL in December 2014 [11]. In a phase III trial of adults with heavily pretreated B-cell precursor ALL, of the 37 patients with minimal residual disease (MRD) positivity, 27 patients (73%) achieved MRD-negative remission with blinatumomab. With a median follow-up of 31 months (range, 5 - 70 months), the 3-year OS rate was 67% (95% CI: 46-81) [50]. Consolidation with blinatumomab in patients with newly diagnosed, high-risk DLBCL who did not progress under R-CHOP was better tolerated than in previous studies in patients with high-risk lymphoma [51]. Richter's syndrome is an aggressive transformation of CLL, clonally related to DLBCL. In a phase II study of blinatumomab four out of nine patients had reduction in nodal disease, including one CR lasting > 1 year [52].

Mosunetuzumab

Mosunetuzumab, a fully humanized immunoglobulin G1 (IgG1) bispecific antibody targeting both CD3 and CD20, induces complete remissions in poor prognosis DLBCL, includ-

ing those who are resistant to or relapse after CARs therapy. In a phase I/II, open-label, multicenter study, 19 patients with DLBCL who were unable to tolerate full-dose chemotherapy received single-agent mosunetuzumab, the ORR was 58% (11/19) and CR rate was 42% (8/19) [53]. A total of 43 patients with R/R DLBCL and newly diagnosed DLBCL received mosunetuzumab-CHOP (M-CHOP), seven patients with R/R DLBCL, and 36 patients with newly diagnosed DLBCL. In R/R non-Hodgkin lymphoma (NHL) treated with M-CHOP (n = 7), the ORR was 86%, with 71% of patients achieving a CR [54]. In a phase I/Ib, dose escalation study of mosunetuzumab in R/R B-cell NHL, the ORR and CR rates were 43.8% (7/16) and 25.0% (4/16, 2 DLBCL and 2 FL), respectively [13].

Plamotamab

Plamotamab is a humanized bispecific antibody that binds both CD20 and CD3 to recruit cytotoxic T cells to kill CD20 expressing malignant cells. In this phase I study of 80 patients with R/R NHL, there were 23 objective responses (43.4% OR) [55]. A randomized, multicenter, open-label, two-part study is in progress comparing the safety and efficacy of plamotamab, tafasitamab, lenolidamide vs. tafasitamab, lenolidamide in adult subjects with DLBCL who have relapsed or are refractory to ≥ 1 prior line of therapy and are ineligible for or refuse autologous stem cell therapy [15].

Epcoritamab

Epcoritamab is a novel bispecific IgG1 antibody redirecting T-cells toward $CD20^+$ tumor cells, expressed on all mature B-cells, but absent on hematopoietic stem cells, pro-B-cells, and plasma cells. In a phase I trial adults with previously untreated DLBCL and an R-IPI score ≥ 3 received flat-dose epcoritamab in combination with standard R-CHOP for six cycles followed by epcoritamab monotherapy. Of the nine patients (four patients with epcoritamab 24 mg; five patients with epcoritamab 48 mg) with median age of 66 (range, 56 - 78), four patients had response assessment, with three patients achieving complete metabolic response. No grade 3 CRS events or cases of febrile neutropenia were reported [56]. In a phase I/II trial including 73 patients with R/R DLBCL, 68 patients received escalating full doses (0.0128 - 60 mg) of subcutaneous epcoritamab, the ORR in patients with R/R DLBCL was 68% (95% CI: 45-86), with 45% achieving a CR at full doses of 12 - 60 mg [16].

Odronextamab

Odronextamab is a hinge-stabilized, fully human IgG4-based CD3 × CD20 bispecific antibody that has demonstrated encouraging safety, and efficacy in patients with R/R DLBCL. In a phase I study, 127 patients with R/R DLBCL were treated at doses ranging from 0.03 to 320 mg. The study included 71 patients with DLBCL, who had not received prior CARs therapy, treated at doses ≥ 80 mg (n = 10); ORR and CR rates were 60%; median observed DoR was 10.3 months (range, 2.9 - 18.6+), with four of six CRs ongoing at last tumor assessment. The median duration of clinical remission was 9.5 months (range, 2.9 - 18.6+) and follow-up is ongoing. In DLBCL patients who were refractory to prior CARs therapy, treated at doses ≥ 80 mg (n = 21), ORR was 33.3%, and CR rate was 23.8%; median observed DoR was 2.8 months (range, 0+ to 18.9) [57]. Odronextamab monotherapy showed a manageable safety profile and encouraging preliminary activity, including durable responses in heavily pretreated patients with R/R DLBCL. In a phase I study of 145 patients with R/R DLBCL with single agent odronextamab without previous CARs therapy who received doses of 80 mg or higher, the objective response rate was 53% (8/15) and all responses were CRs. In patients with R/R DLBCL who had previous CARs therapy and received doses of 80 mg or higher, the objective response rate was 33% (10/30) and CR rate was 27% (8/30) [17].

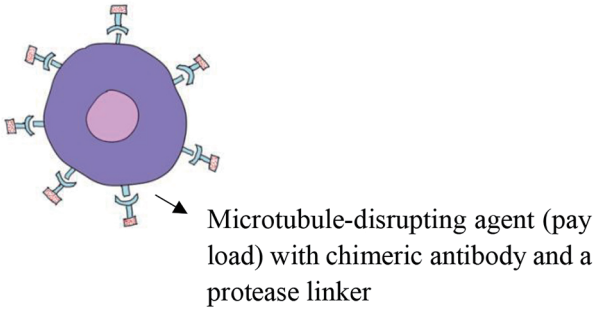

Figure 5. Antibody-drug conjugate.

Glofitamab

Glofitamab is a T-cell-engaging bispecific antibody possessing a novel 2:1 structure with bivalency for CD20 on B cells and monovalency for CD3 on T cells. In a phase I study evaluating glofitamab in 127 patients with RR/ DLBCL, the ORR was 53.8% (CR, 36.8%) among all doses and 65.7% (CR, 57.1%) in those dosed at the recommended phase II dose. Of 63 patients with CR, 53 (84.1%) patients have ongoing CR with a maximum of 27.4 months observation [58]. In a phase II expansion study, 107 patients with R/R DLBCL (35% had received prior CAR-T cell therapy) were given single agent glofitamab. After a median follow-up of 9 months (0.1 - 16), ORR and CR rates by IRC were 50.0% and 35.2%, respectively. CR rates were consistent in patients with and without prior CAR-T cell therapy (32% versus 37%). The median time to CR was 42 days (95% CI: 41 - 48). The majority of CRs (33/38; 87%) were ongoing at data cut. An estimated 84% of complete responders and 61% of responders remained in response at 9 months [14].

Antibody drug conjugate (ADC)

An ADC is a monoclonal antibody attached to a cytotoxic agent via a chemical linker (Fig. 5). The ADCs are used to

treat R/R DLBCL by selectively ablating tumor cells and ameliorating the therapeutic index of cytotoxic drugs. The target, the cytotoxic agent, and the way the agent is attached to the antibody determine the pharmacokinetics, clinical effect, and tolerability [59]. ADCs are a promising class of drugs with the potential to specifically target tumor cells and ameliorate the therapeutic index of cytotoxic drugs. In recent years, three ADCs, brentuximab vedotin (BV), polatuzumab vedotin, and loncastuximab tesirine, are approved for treatment of DLBCL. The ADCs can also diffuse into adjacent cells even if the cells are target-negative, resulting in cell death [60]. There was no statistical correlation between response and level of antigen expression; however, all responding patients had quantifiable CD30 by computer-assisted assessment of immunohistochemistry. It was thought that the bystander killing mechanism of an ADC involved surface antigen targeting, internalization, intracellular linker cleavage, drug release, and diffusion of drug away from the targeted cell. However, other mechanisms may be involved [61]. ADCs are cleaved extracellularly by other mechanisms than direct antigen-internalization by cathepsin. Increased levels of cathepsin B secretion are seen in tumor cells and high expression of cathepsin is also seen in macrophages and stromal fibroblasts [62, 63].

Brentuximab Vedotin (BV)

Brentuximab Vedotin is a CD30-directed monoclonal antibody conjugated to the potent inhibitor of microtubule polymerization monomethyl auristatin E (MMAE) - effective in targeting and killing CD30-expressing lymphoma for patients with relapsed HL and relapsed systemic anaplastic large-cell lymphoma [19]. In a phase II study of R/R high-CD30 expressing high grade lymphoma (anaplastic large cell lymphoma), BV produced disease control rate of 48.5% (16/33) including six CR and six PR; six patients (four CR, two PR) maintained over 16 completed cycles. Response to BV and survival were not associated with CD30 expression levels. Over a median follow-up of 29.2 months, the median PFS and OS rates were 1.9 months and 6.1 months, respectively [64]. A phase II clinical trial evaluated the efficacy and safety of BV in patients with R/R CD30+ primary mediastinal B cell lymphoma. The ORR was 13.3% (2/15), two patients achieved PR, one patient had SD, and the remaining 12 patients had PD. It was decided that BV had very low antitumor activity in this setting [65]. A phase II study evaluated BV monotherapy in 52 patients with CD30-expressing DLBCL. 16 of 52 patients with undetectable CD30 had an objective response, and the median OS was 7.5 months. Correlative analyses of CD30-undetected and CD30-expressing DLBCL combined demonstrated that ≥ 1% CD30 expression by conventional immunohistochemistry (cIHC) resulted in a trend toward a higher response rate and significantly longer median PFS and OS [66]. In a phase II study of R/R DLBCL with variable CD30 expression, 49 patients with DLBCL were treated with BV, and the objective response rate was 44% for DLBCL, including eight (17%) CRs with a median DoR of 16.6 months thus far (range, 2.7 - 22.7+ months) [19]. In a phase 1 trial in which 37 patients with R/R DLBCL were treated with BV, lenalidomide and rituximab, the ORR was 56.7%. The PFS and median OS were 11.2 months and 14.3 months, respectively and results were similar in the $CD30^+$ and CD30 < 1% [67, 68]. In a phase II study, 30 patients with primary mediastinal large B-cell lymphoma (PMBCL) were treated with checkpoint inhibitor nivolumab and BV. At a median follow-up of 11.1 months, the ORR was 70% (51% to 85%), with a 43% complete metabolic response [69].

Inotuzumab ozogamicin (InO)

Inotuzumab Ozogamicn is an anti-CD22 monoclonal antibody-calicheamicin conjugate that binds to CD22-expressing tumor cells with cytotoxic calicheamicin derivative inducing double-strand DNA breakage and subsequent cell death. It was shown to be effective in treating aggressive histology lymphoma and DCBCL [18]. In a phase I study of InO, rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP), in patients with R/R $CD22^+$ B-cell NHL, the ORR was 57% for those with DLBCL [70]. In a randomized trial of InO plus rituximab (166 patients) versus chemotherapy plus rituximab (172 patients) for R/R DLBCL, the median OS and PFS with R-InO were 9.5 (95% CI: 7.0 - 14.5) and 3.7 (2.9 - 5.0) months, respectively [71]. In a phase 1 study, InO combined with rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP) in 21 patients with R/R $CD22^+$ DLBCL B-cell NHL, the overall (objective) response rate was 33% [72]. In a phase I trial of relapsed R/R DLBCL treated with InO, the objective response rate at the end of treatment was 15% for all patients with DLBCL, and the median PFS was 49 days [73]. In a phase II study of InO and rituximab, followed by ASCT in patients with R/R DLBCL, 18 patients underwent HDT-ASCT; 2-year PFS for these patients was 61.1% [74].

Polatuzumab vedotin (Pola)

Polatuzumab vedotin is an ADC that delivers MMAE, a microtubule inhibitor, approved for the treatment of R/R DLBCL transplant ineligible patients [75]. Polatuzumab vedotin plus bendamustine and rituximab (pola + BR) received regulatory approvals for R/R DLBCL based on primary results from the randomized arms of the study [76]. In a phase 1b/2 study, 106 patients with R/R DLBCL were treated with polatuzumab, bendamustine and rituximab. The objective response rate was 41.5% and the CR rate was 38.7%. The PFS and OS were 6.6 and 12.5 months, respectively [76]. In a multicenter, open-label study of polatuzumab combined with bendamustine and rituximab or _obinatzumab_ in patients with R/R DLBCL the ORR was 68% versus 50%, CR of 36% versus 33% and PR of 32% versus 17% [77]. Polatuzumab vedotin plus bendamustine and rituximab was effective for patients with R/R DLBCL, with a median OS of 8.7 months and PFS of 3.8 months [78]. In 14 Israeli centers of the 47 patients (31 patients with *de-novo* DLBCL and 16 patients with transformed lymphoma) treated with polatuzumab-based regimen, the ORR was 61% (29), including 40% (19) CR and 21% (10) PR. The median OS and PFS were 8.3 and 5.6 months, respectively [79]. In a study of

51 patients with R/R DLBCL, treated with polatuzumab, bendamustine and rituximab to bridge to CARs therapy, 6-month PFS and OS were 27.7% and 49.6%, respectively. In the CARs cohort, OS at 6 months was 77.9% [80]. Polatuzumab-based therapy at multiple centers for its efficacy analyzed in USA in patients with R/R DLBCL revealed that the response rate was 50%, including 24% CR. Median DoR was 5.1 months, PFS was 2.0 months, and OS was 5.3 months [81]. In a multicenter retrospective study of polatuzumab for patients with DLBCL who relapsed after SOC CARs therapy, a response was achieved in 45% patients, including CR in 14% patients and PR in 30% with a median OS of 16 weeks [82]. In the United Kingdom, patients with DLBCL (133 patients) ineligible for stem cell transplantation who received polatuzumab vedotin with bendamustine and rituximab, had an ORR of 57.0% (32.8% CR) [20].

Loncastuximab tesirine

Loncastuximab tesirine is an ADC approved for the treatment of B-cell lymphoma. Loncastuximab tesirine consists of a pyrrolobenzodiazepine DNA-alkylating warhead covalently attached via a cleavable linker to an anti-CD19 antibody that binds to B cells [83]. In a study, 183 patients received loncastuximab tesirine, with 3 + 3 dose escalation at 15 to 200 g/kg and dose expansion at 120 and 150 g/kg. The ORR was 45.6%, including 26.7% CRs. The ORR in patients with DLBCL, MCL, and FL were 42.3%, 46.7%, and 78.6%, respectively. Median DoR in all patients was 5.4 months and not reached in patients with DLBCL (doses ≥ 120 μg/kg) who achieved a CR [84]. In response assessment low albumin, bulky disease, and mild/moderate hepatic impairment had a negative effect on OS [85]. In a phase 2 study, loncastuximab tesirine plus ibrutinib improved the survival of patients with DLBCL (35, 22, and 13 patients with DLBCL overall, non- GCB DLBCL, and GCB DLBCL), the ORR (CR + PR) was 57.1% (20/35; 95% CI: 39.4-73.7) in the overall DLBCL cohort, and 45.5% (10/22; 95% CI: 24.4-67.8) and 76.9% (10/13; 95% CI: 46.2-95.0) in the non-GCB DLBCL and GCB DLBCL cohorts, respectively [9].

Checkpoint inhibitor therapy

Cancer cells escape immune recognition by exploiting the programmed cell death-1 (PD-1)/PD-1 ligands (PD-L1) immune checkpoint axis, and PD-1 blocking agents have changed the treatment landscape of classical HL and primary mediastinal B-cell lymphoma and the role of these agents in DLBCL is being evaluated [86]. In the treatment of primary mediastinal B-cell lymphoma with genetic aberrations at 9p24 and upregulation of PD-L1, FDA approved PD-1 blocking agents.. However, unlike HL which is characterized by universal genetic alterations in 9p24.1, resulting in constitutive expression of PD-1 ligands, non-HL does not display a high frequency of 9p24.1 alterations which upregulates PD-L1 ligand, hence most of the patients with DLBCL do not respond to PD-1 blockade [87].

Pembrolizumab

Pembrolizumab, a selective humanized monoclonal antibody blocks the interaction between PD-1 expressed by tumor-associated T-cells and its ligand PD-L1 present on tumor and stromal cells. Therapy with combined pembrolizumab with R-CHOP in 30 previously untreated DLBCL patients at median follow-up of 36 months, the estimated PFS is 83% and OS is 86% [88]. In a phase I/II study, pembrolizumab was given every three weeks to eight patients with progressive DLBCL after anti-CD19 directed therapy. The ORR was 25%, with one patient having continued CR at 280 days [89]. Pembrolizumab was found to be very useful in the management of R/R PMBCL. RT of chronic lymphatic leukemia to DLBCL may be either *de novo* or a therapy-related process, with fludarabine possibly playing a role in reactivating Epstein-Barr virus [90]. In a phase 2 study, pembrolizumab, at a dose of 200 mg every 3 weeks, was given in relapsed and transformed CLL (16 relapsed and nine RT). Objective responses were observed in four out of nine RT patients (44%) and in zero out of 16 CLL patients (0%). All responses were observed in RT patients who had progression after prior therapy with ibrutinib. After a median follow-up of 11 months, the median OS in the RT cohort was 10.7 months but was not reached in RT patients who progressed after prior ibrutinib [91].

Nivolumab

In a phase I, open-label, dose-escalation, cohort-expansion study of 11 patients with R/R DLBCL, nivolumab (humanized monoclonal antibody against PD1) achieved an objective response rate of 36% and the DoR ranged from 6.0 to 81.6 weeks [23]. In a phase II study of 121 patients, nivolumab achieved an objective response rate of 10% and a DoR of 11 months [92]. In a trial with combined checkpoint inhibition with ipilimumab and nivolumab as consolidation following ASCT of seven patients with R/R DLBCL (43% of which were not in CR at time of ASCT), patients had a PFS at 18 months of 83% with checkpoint inhibitor therapy, while the historical reported PFS at 18 months with ASCT alone is 50% [93].

Avelumab

Avelumab is a monoclonal antibody targeting PD-1 ligand. In a phase II study, 28 patients with R/R DLBCL were given avelumab/_zacyti induction for two cycles q2-weekly (Av 10 mg/kg IV + R 375 mg/m^2 IV), followed by R-CHOP21 for six cycles then avelumab 10 mg/kg for six cycles q2-weekly if in complete metabolic response post R-CHOP. ORR post R-CHOP was 89% (all CR). With a median follow-up of 16 months, 1-year PFS was 76% and OS 89% [94]. In a multicenter, randomized, open-label, parallel-arm Ib study 29 adult patients with R/R DLBCL were randomized 1:1:1 to receive avelumab in combination with utomilumab (an immunoglobulin G2 4-1BB agonist) and rituximab (arm A), avelumab in combination with utomilumab and _zacytidine (arm B), or

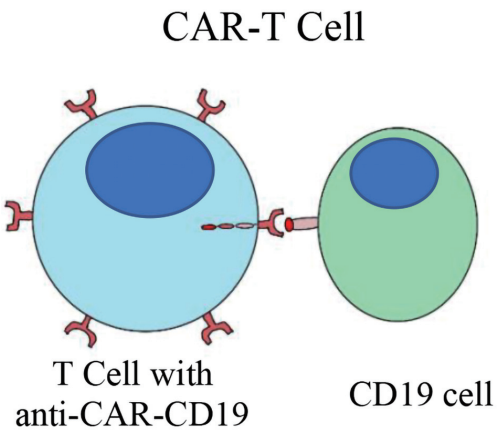

Figure 6. CARs and tumor cell interaction. CARs: chimeric antigen receptor T cells.

avelumab in combination with bendamustine and rituximab (arm C). As the antitumor activity in arms A and B was minimal (one PR in arm A, no responses in arm B and three CRs in arm C) the study was discontinued [24].

Durvalumab

In a phase II open-label trial, 46 patients received durvalumab (a programmed death-ligand 1 inhibitor), combined with R-CHOP or lenalidomide + R-CHOP (R2-CHOP) - 43 received R-CHOP and three R2-CHOP. In this study 54.1% patients receiving durvalumab + R-CHOP achieved CR, 18.9% PR; 67.6% (25 patients) continued to consolidation and were progression-free at 12 months [95]. Durvalumab was evaluated with either tremelimumab (an immune checkpoint blocker) or danvatirsen (a 16-nucleotide antisense oligonucleotide) in a phase Ib dose escalation and dose expansion study. In this study, 32 patients were enrolled with overall objective response rate of 6.3%, with two PRs. Median time to response was 11.0 weeks with median PFS of 7.4 weeks and median OS of 28.0 weeks [25].

Chimeric antigen receptor redirected T cells (CARs)

Chimeric antigen receptor redirected T cells are autologous T cells genetically engineered to express CARs that can recognize a variety of tumor-associated antigens (Fig. 6). They have shown remarkable success in treating patients with R/R DLBCL who have failed to respond to standard chemotherapy or relapsed after ASCT [96]. The antigen-binding domain of B cell receptor is transfected to the intracellular domain of a CD3 TCR (CD3-zeta) via a viral vector (Fig. 6). The CARs are engineered to target a specific cell surface antigen and activate T cells independently of MHC recognition (Fig. 6). Various modifications can enhance CAR effector function, such as co-expression of intracellular costimulatory domains such as CD28 or 4-1BB (CD137) [97]. They have shown remarkable success in treating patients with R/R DLBCL who have failed to respond to standard chemotherapy or relapsed after ASCT. The primary side effects of CARs include cytokine release syndrome with fever, hypotension, altered mental status, and seizures, with some patients requiring intensive care [98]. In DLBCL unresponsiveness to standard chemotherapy and relapse after ASCT are indicators of poor prognosis and the CARs are emerging as a salvage treatment for these patients [99]. Anti-CD19 CARs have activity against chemotherapy-refractory lymphoma with durable complete remissions lasting > 2 years in about 50% of patients with R/R DLBCL, whereas historically the median OS of R/R DLBCL is between 7 and 8 months. Currently, axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are approved in the third line for patients with R/R DLBCL.

Axicabtagene ciloleucel

Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 CARs therapy, showed efficacy in patients with R/R DLBCL. In an international phase III trial, 180 patients with large B-cell lymphoma were randomly assigned to receive axi-cel or standard care. A response occurred in 83% of patients receiving axi-cel and 50% of patients receiving standard care, with a CR in 65% of patients receiving axi-cel. Patients were randomly assigned to receive axi-cel or standard care (two or three cycles of investigator-selected, protocol-defined chemoimmunotherapy, followed by high-dose chemotherapy with ASCT in patients with a response to the chemoimmunotherapy). The median EFS was 8.3 months in the axi-cel group and 2.0 months in the standard-care group, and the 24-month EFS was 41% and 16%, respectively. In an interim analysis, the estimated OS at 2 years was 61% in the axi-cel group and 52% in the standard-care group. No deaths related to cytokine release syndrome or neurologic events occurred [100].

Tisagenlecleucel

Tisagenlecleucel (tisa-cel) was the first approved CARs therapy for childhood and adult relapsed or refractory B-ALL and later for adult R/R DLBCL. In an international phase III trial, 95.7% of 322 patients who received tisa-cel had a response, compared to 32.5% of patients who received salvage chemotherapy and autologous hematopoietic stem-cell transplantation. Ten patients in the tisa-cel group and 13 in the standard-care group died from adverse events. The median EFS in both groups was 3.0 months (HR for event or death in the tisa-cel group, 1.07; 95% CI: 0.82 - 1.40; P = 0.61). It was not superior to standard salvage therapy in this phase III trial [7].

Lisocabtagene maraleucel

Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, chimeric antigen receptor product that was studied in patients with R/R large B-cell lymphoma. It is an effective second-line treatment for patients with R/R DLBCL. In a global,

phase III study with liso-cel versus SOC with salvage chemotherapy followed by ASCT as second-line treatment in patients with R/R DLBCL 232 patients were screened and 184 were assigned to the liso-cel (n = 92) or SOC (n = 92) groups. The median EFS was significantly improved in the liso-cel group (10.1 months, 95% CI: 6.1 - NR) compared with the SOC group (2.3 months) with P < 0.0001. There were no treatment-related deaths in the liso-cel group and one treatment-related death due to sepsis in the SOC group. The authors concluded liso-cel as an effective new second-line treatment in patients with early R/R DLBCL [8].

In an indirect comparison of tisa-cel and liso-cel R/R DLBCL the OS, PFS, CRR, and ORR were similar. The estimated adjusted 2-year OS, 2-year PFS, ORR, and CRR were 45.6%, 38.2%, 62.9%, and 47.7%, respectively, for tisa-cel versus 43.8%, 42.1%, 72.7%, and 53.1% for liso-cel. No significant differences in CR rate were observed [101]. The clinical outcome of 25% in R/R DLBCL who achieved remission at 3 and 6 months with CARs (73.8% and 86.5%, respectively) was maintained on long-term follow-up at 40.3-month period [102].

As second-line therapy for transplant-eligible R/R DLBCL within 12 months of completing chemo-immunotherapy with SOC, phase III clinical trials comparing axi-cel, tisa-cel, and liso-cel may change the treatment algorithm for DLBCL. A total of 437 patients were screened and 359 were randomized to axi-cel and 179 to SOC in the axi-cel (ZUMA-7) study. With a median follow-up of 24.9 months, the ZUMA-7 trial met its primary end point with a median EFS of 8.3 months (95% CI: 4.5 - 15.8) for axi-cel and 2 months (95% CI: 1.6 - 2.8) for SOC, with an HR of 0.40 (95% CI: 0.31 - 0.51; P < 0.001) [100]. There were 322 patients in the tisa-cel versus SOC (BELINDA) trial, with 162 randomized to tisa-cel and 160 randomized to SOC. After a median follow-up of 10 months, the BELINDA trial failed to meet its primary end point, with a median EFS of 3 months in both groups (HR, 1.07; 95% CI: 0.82 - 1.4; P = 0.61) [7]. In the liso-cel versus SOC (TRANSFORM) trial, 92 received liso-cel and 92 received SOC. After a median follow-up of 6.2 months, the TRANSFORM trial met its primary end point, with a median EFS of 10.1 months for liso-cel and 2.3 months for SOC (HR, 0.35) and a 65% risk reduction (P < 0.001) [8].

For patients who are ineligible for CARs therapy because of the urgent need for treatment (the median time between leukapheresis and delivery for axi-cel was 17 days and for tisa-cel 54 days) or failure to collect enough T cells to manufacture of CARs, bispecific antibodies may be an option, as these are readily available. Following bispecific antibodies, T cells can be collected effectively, CARs can be synthesized and expanded for successful CARs therapy [103].

Safety and efficacy of CARs therapy and checkpoint inhibitor therapy

A combination therapy with CD19 CARs and an anti-PD-1 antibody nivolumab was evaluated in patients with R/R DLBCL. The ORR and CR rate were 81.81% (9/11) and 45.45% (5/11), respectively. The median follow-up time was 6 months [104]. In the case of a PMBCL who experienced relapse 3.5 months after axi-cel, the patient received pembrolizumab (after four cycles) and complete metabolic response was confirmed [105]. In a study, 14 patients with heavily pretreated, relapsed B-ALL or B lymphoblastic lymphoma were treated with CD19-directed CARs in combination with pembrolizumab or nivolumab. In this study promising responses were seen in those with early B-cell recovery and bulky extramedullary disease. In contrast, PD-1 inhibition had partial, but no durable, effect in the four B-ALL patients with poor initial marrow response to CARs alone, suggesting a different mechanism may be responsible for poor initial responses [106]. In a study of 12 patients who received CART19 for R/R DLBCL enrolled with progressive disease (n = 8) or relapse (n = 4) following CART19, 11 patients had DLBCL (four germinal center (three "double/triple hit"), four non-germinal center, one T-cell rich DLBCL, one transformed FL, one primary mediastinal B-cell lymphoma) and one patient with FL were sequentially given CARs followed by pembrolizumab. The best ORR was 27% after pembrolizumab, with one patient having a CR, two PRs, and seven patients having progressive disease [107]. In a study assessing the efficacy and toxicity of CAR-T in combination with durvalumab, 12 of 13 patients with R/R DLBCL who received the combination therapy were evaluable for response. The ORR was 50% (five CR, 42%; one PR, 8%). Of the five patients who achieved CR, three patients were in CR at the first restaging after JCAR014 and two patients subsequently converted to CR after the first post-JCAR014 durvalumab infusion. Only one patient who achieved CR has relapsed (median follow-up of 10.6 months, range 3.7 - 11.8). Continued stable disease or evidence of regression was seen in four of six (67%) [108].

Chimeric antigen receptor failure

Immune escape is the primary mechanism from loss or down-regulation of the target antigen. If CD19 CARs fail because of loss of CD19, the immune reconstitution can be restored by CD22 CARs [109]. However, if CARs still express CD19, then the immune response can be restored by taking advantage of checkpoint inhibitor therapy from PD1-PDL1 pathway interaction [110]. It has been documented that the checkpoint proteins PD1 and PD-L1 expressed on CARs and in the tumor microenvironment is up-regulated after infusion of the CAR product [111].

Conclusion

Beneficial immunological effect of "graft-versus-lymphoma" following allogeneic bone marrow transplantation is well established and led to other immunological interventions in DLBCL. The graft-versus-lymphoma was later taken advantage of by the "donor lymphocyte infusion", albeit with limited success. The immune system can now be manipulated in other ways to alter the course of DLBCL. In the last decade, with immune-based therapies we have made rapid advances in the

management of DLBCL. Ever since the advent of rituximab, incremental increases have been made in the management of DLBCL, leading to improved OS. We need standard guidelines to optimize and best utilize these agents in the management of R/R DLBCL

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Conflict of Interest

NV has been on the advisory board of Biogen Idec. Other authors declare there is no conflict of interest in writing this manuscript.

Author Contributions

NV did the literature search and RK wrote the initial version of the article. JR reviewed the article and AM revised the last version of the manuscript. All the authors approved the manuscript for submission.

Data Availability

The authors declare that the data supporting the findings of this study are available within the article.

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