Diffuse Large B-Cell Lymphoma

Subjects: Oncology

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The most common type of non-Hodgkin lymphoma in adults is diffuse large B-cell (DLBCL). There is a historical unmet need for more effective therapies in the 2nd and 3rd line setting. Emerging immunochemotherapies have shown activity in small studies of heavily pre-treated patients with prolonged remissions achieved in some patients. Anti-CD19 CAR (chimeric antigen receptor) T cells are potentially curative in the 3rd line and beyond setting and are under investigation in earlier lines of therapy. Antibody-drug conjugates (ADC's) such as polatuzumab vedotin targeting the pan-B-cell marker CD79b has proven effectiveness in multiply-relapsed DLBCL patients. Tafasitamab (MOR208) is an anti-CD19 monoclonal antibody producing prolonged remissions when combined with Lenalidomide (LEN) in patients who were not candidates for salvage chemotherapy or autologous stem cell transplant. Selinexor, an oral, small-molecule selective inhibitor of XPO1-mediated nuclear export (SINE), demonstrated prolonged activity against heavily-pretreated DLBCL without cumulative toxicity and is being investigated as part of an oral, chemotherapy-free regimen for relapsed aggressive lymphoma. This article reviews current strategies and novel therapies for relapsed/refractory DLBCL.

Keywords: Relapsed Refractory DLBCL ; Immunotherapy

1. Introduction

Diffuse large B-Cell Lymphoma (DLBCL) is an aggressive subtype accounting for 25–30% of Non-Hodgkin lymphoma (NHL) with an incidence of 5.6 per 100,000 persons per year [1][2]. DLBCL is usually symptomatic at presentation with either nodal or extranodal disease. Diagnosis is made when large, transformed B cells (CD19+, CD20+, CD79+) with prominent nucleoli, diffuse growth pattern, and a high proliferation fraction are seen on tissue biopsy [1]. The World Health Organization (WHO) schema classifies by cell of origin (COO) classification including germinal B-cell (GCB) subtype or activated B cell (ABC) subtype, but more recent transcriptome sequencing techniques have identified five distinct subtypes that improve the differentiation among prognostic groups in DLBCL [3][4]. Genomic instability is demonstrated by a median of 17 (range: 0–48) genetic drivers that were clustered into these 5 distinct genetic signatures. In the 2017 revision of WHO classifications, DLBCL with translocations of MYC and BCL2 and/or BCL6—double-hit (DHL) or triple-hit (THL)—are reclassified as Diffuse Aggressive B-Cell Lymphomas, with more intense therapeutic regimens such as DA-EPOCH-R with CNS prophylaxis in the first line setting having a 4 year overall survival of 72.2% [5]. Despite multiple studies attempting to improve upon the outcomes, R-CHOP remains the first line treatment for DLBCL regardless of IPI score, COO, or gene expression profile except for DHL.

DLBCL cases that do not fit a specific subtype have an overall survival rate of 65% when treated with standard R-CHOP (Rituximab, Cyclosporine, Vincristine, Prednisone) therapy [1]. The Standard International Prognostic Index (IPI) is widely used for risk stratification with aggressive B-cell lymphoma, and has been validated with continued prediction of risk in the Rituximab era [6]. Patients with a high IPI score have poor prognosis with an OS as low as 20–25%. Certain mutations and pathways are common in the GCB subtype such as EZH2, BCL2 and PI3K. In the ABC subtype, NF-KB activation, MYD88 mutations and JAK-STAT pathways are more common [7].

While most patients respond, 30–40% of patients with DLBCL relapse or are unable to achieve remission with first-line treatment. In these cases, the prognosis is poor [8]. Approximately 50% of patients with relapsed or refractory (R/R) DLBCL have a response to second-line chemotherapy; up to 50% of these patients proceed to undergo autologous hematopoietic stem-cell transplantation in some settings, and of these, approximately 30 to 40% remain progression-free 3 years after transplantation [8][9][10][11][12]. Median survival for primary and secondary refractory DLBCL is 5–7 months [8].

Patients who progress after receiving R-CHOP receive combination salvage chemotherapy. Commonly used regimens, including R-ICE, R-DHAP, R-GDP, R-GemOx, O-DHAP, O-ICE, and DR-ICE, have similar treatment effects [13][14]. However, analysis of real-world data from 126 community-based hematology/oncology practices in the US between 2010–2016 demonstrated that only 13% of patients who received salvage regimens intended for ASCT eventually underwent ASCT [15].

The unmet need for more effective regimens is highlighted by the wide heterogeneity in regimens used in clinical practice with consistently poor outcomes [13]. Pts that are not candidates for ASCT and those who never make it or have failed CAR-T therapy have poor outcomes with salvage chemotherapy regimens. Response rate comparisons between studies are unreliable due different rates of enrollment of primary refractory disease. In the phase III CORAL trial (*n* = 396) comparing R-ICE and R-DHAP followed by autologous hematopoietic cell transplant (HCT) for chemosensitive patients, the overall response was 63%, and the three year overall survival was 47%. Median overall survival of R/R DLBCL who failed second-line regimens in CORAL was 4.4 months [8]. The LY.12 trial (*n* = 619) compared the platinum-containing regimens R-GDP and R-DHAP followed by autologous HCT and had response rate 45% [12]. SCHOLAR-1 is the most comprehensive analysis of pooled outcomes from several large studies of relapsed and refractory DLBCL (*n* = 636) treated with various standard of care chemotherapy regimens, and the ORR was 26%, CR rate of 7%, and median overall survival was 6.2 months [16][17].

A cost-effectiveness analysis of DLBCL regimens from the Truven database with claims data from US government and private payers highlighted the direct costs associated with the 2/3 of patients with DLBCL who received subsequent 2nd-line regimen after completing R-CHOP [18]. More effective treatment options for this resource intensive condition has the potential to both decrease mortality and reduce the costs of subsequent lines of therapy including ASCT [18][19]. Several innovative treatment modalities are already receiving regulatory approvals (Table 1).

Table 1. Novel Regimens with FDA Approval.

Agent	Year of FDA Approval	Regimen	Population	Relapse < 1 year of DLBCL Diagnosis	Refractory to Last Regimen	DHL/THL	Efficacy Outcomes
Axicabtagene ciloleucel (axi-cel)	**2017**	**Flu/Cy LD**	**R/R DLBCL refractory to 2 lines of therapy**	**30%**	**77%**	**NR**	**ORR 83% CR 58% mOS 24 mos**
Lisocabtagene maraleucel		**Flu/Cy LD**	**R/R DLBCL refractory to 2 lines of therapy**	**NR**	**44%**	**13%**	**ORR 73% CR 53% mOS >12 mos**
Tisagenlecleucel [a]	**2018**	**Flu/Cy LD or Benda-Flu LD**	**R/R DLBCL refractory to 2 lines of therapy**	**NR**	**40%**	**27%**	**ORR 52 CR 40% mOS 12 mos**
Polatuzumab vedotin [20]	**2019**	**Pola + BR**	**R/R DLBCL Ineligible for ASCT**	**53%**	**75%**	**0%**	**CMR 40% mOS 12.4 mos**
Selinexor [21]	**2020**	**Selinexor 60 mg po on days 1 and 3 of each week**	**R/R DLBCL**	**33% §§**	**72%**	**4%**	**ORR 28% CR 12% mOS 9.1 mos**
Tafasitamab [22]	**2020**	**Tafa + LEN 25 mg**	**R/R DLBCL Ineligible for ASCT**	**19% §**	**44%**	**0%**	**ORR 58% CR 33% mOS 22 mos**

FDA: United States Food and Drug Administration; Flu/Cy: Fludarabine/Cyclophosphamide; LD: lymphodepletion; Benda/Flu: Bendamustin/Cyclophosphamide; Pola: Polatuzumab vedotin; BR: Bendamustin and Rituximab; Ritux: Rituximab; LEN: Lenalidomide; Tafa: Tafasitamab; dx: diagnosis; DHL: Double Hit Lymphoma; THL: Triple Hit Lymphoma; R/R DLBCL: Relapsed or Refractory Diffuse Large B Cell Lymphoma; ORR: Overall Response Rate; CR: Complete Response; mOS: Median Overall Survival; mos: months; CMR: Complete Metabolic Response; po: by mouth; NR: Not Reported. [a]: investigational agent with pending Food and Drug Administration approval. § Excluded if received anti-CD20 therapy within 6 months. §§ Excluded if not in PR or CR and received therapy within 14 weeks.

2. Sequencing Therapy

With recent new drug approvals, treatment options for patients with R/R DLBCL have expanded. However, this poses a challenge in sequencing and treatment selection for patients. At this time, the sequencing of therapy is individualized based on the efficacy and side effect profile of treatment. In patients with R/R DLBCL, the treatment should be divided

among transplant eligible and ineligible patients. If they are transplant ineligible or progress after ASCT, they have all the above approved regimens available as option. ASCT ineligible patients should be evaluated for CAR-T therapy as it offers the best ORR among therapies mentioned in Table 1. However, CAR-T can be challenging in terms of accessibility, the patient's functional status, disease burden and other factors. Polatuxumab Vedotin in combination with bendamustine and rituximab is another option and can be used as a bridge to CAR-T as well. Polatuzumab Veodtin in combination with BR had 40% of CRR and manageable toxicities [20]. If patients respond well, Bendamustine can be dropped to allow cell collection for CAR-T. However, it is a three drug regimen and it carries risk of grade 3 or 4 cytopenias and peripheral neuropathy. In patients that are not candidates for CAR-T and goal is palliation, Tafasitamab with lenalidomide is a great option with limited toxicities. Based on the L-Mind study, Tafasitamab + Len had ORR of 60% and CRR of 42.5% and main side effects were cytopenias managed by dose adjustment of lenalidomide [22]. Tafasitamab prior to CAR-T may alter efficacy of CAR-T therapy since they both are CD-19 targeted therapy; however, more data are needed to support this. Selinexor is another option for ASCT ineligible patients with ORR of 28%; relatively lower than other agents. Selinexor also has a significant side effect profile for GI toxicity, hyponatremia and cytopenia, hence would reserve this as a last option.

3. Future of DLBCL and Immunotherapy

MT-3724 is a novel Engineered Toxic Body (ETB) comprised of a proprietarily engineered form of Shiga-like Toxin A subunit (SLT-A) genetically fused to an antibody-like binding domain that binds CD20. ETBs work though a novel mechanism of action whereby the internalization of the fragment when bound to CD20 delivers the toxin intracellularly where ribosomal inactivation leads to targeted cell death [23][24]. MT-3724 is currently being studied in three ongoing Phase 2 studies for relapsed and refractory DLBCL. Loncastuximab tesirine, ADCT-402 is an antibody-drug conjugate composed of a humanized monoclonal antibody against CD19 and conjugated to a pyrrolobenzodiazepine dimer cytotoxin. In phase 2 trials, ADCT-402, 145 pts with relapsed or refractory DLBCL were enrolled and ORR was 45%. The common side effects were cytopenias requiring dose adjustments, which were otherwise well tolerated. Hu5F9-G4, a humanized monoclonal antibody is a macrophage immune checkpoint inhibitor blocking CD47 that induces tumor-cell phagocytosis. A phase 1B study, 22 pts with relapsed NHL were treated with Hu5F9-G4 in combination with rituximab. The ORR in DLBCL subset was 40% with CR of 33%. The most common AEs were infusion reaction, fever and chills. Immune checkpoint inhibitors have gained recognition in multiple solid tumors and demonstrated durable responses. PD-1 and PDL-1 are expressed in many hematologic malignancies and have recently been approved for second line HL. In a phase 1 trial of relapsed DLBCL patients, nivolumab showed an ORR of 36%, but these responses were not durable. There are a few trials in DLBCL being completed with immune checkpoint inhibitors in combination with anti-CD-20 antibodies (NCT03401853) and immunomodulators and targeted agents such as LEN (NCT03015896) and Copanlisib (NCT03484819). Table 1 includes a list early clinical trials involving immunotherapy for treatment of relapsed/refractory DLBCL.

Table 2 - Novel Regimens Under Investigation for Relapsed or Refractory Diffuse Large B Cell Lymphoma

Bispecific Abs				
Epcoritamab (CD3/CD20) Flat dose Subcutaneous weekly Escalation study	Hutchings, et al[41] NCT03625037	Phase 1/2 R/R DLBCL	N= 41	Enrolling Median f/u 4.7 mo ORR 56% CR 44% No dose limiting toxicities

Odronextamab REGN1979 (CD3/CD20) 18 -320mg doses	Bannerji, et al[42] NCT03888105	Phase 1 R/R DLBCL	N=19	Enrolling phase 2 ORR 58% CR 37%
Monsenetuzumab (CD3/CD20)	Schuster, et al[43] NCT03677154	Phase 1/2 R/R DLBCL including p CAR-T	N=119	Enrolling phase 3 ORR 34.7% CR 18.6%
Glofitamab RG6026 (CD3/CD20	Morschhauser, et al[44] NCT03075696	Phase 1/Ib R/R aggressive NHL +/- Obinituzumab	N=21	Enrolling Phase 1 ORR 38% CR 31%
Monoclonal Abs				
Tafasitamab (anti-CD19) (Fc-enhanced, humanized) + Lenolidomide	Nowakowski, et al[25] Maddocks, et al[45] NCT02399085	Phase 1/2 R/R DLBCL Ineligible for ASCT Excluded double-hit	N=81	Enrolling phase 3 ORR 58% CR 33% Median OS 22 mos (95% CI: 18.6 – NR)
Magrolimab (5F9) (anti-CD47, promote phagocytosis) +Rituximab	Advani, et al[46] NCT02953509	Phase 1b/2 R/R DLBCL	N=15	Enrolling, Preliminary results ORR 40% CR 27% On-target anemia primarily 1st dose
Anti-PD-L1 Containing Regimens				
Atezolizumab (anti-PDL1) +Obinituzumab (anti-CD20) +Venetoclax (BCL2 inhibitor)	Herbaux, et al[47] NCT03276468	Phase 2 R/R DLBCL	N=58	Interim Results ORR 23.6% CMR 18%

Mogamulizumab (anti-CCR4) + Pembrolizumab	Joffe, et al NCT03309878	Phase 1b/2 R/R DLBCL Ineligible for ASCT		Enrolling
Avelumab (anti-PD-L1) +/- Utomilumab (4-1BB agonist) +/- Rituximab +/- Bendamustine or Azacitidine	Chen, et al[48] NCT02951156	Phase 1b/3 R/R DLBCL Ineligible for ASCT ECOG≤1		Enrolling
Bispecific CAR T Cell Therapies				
AUTO3 (CD19/CD22) Dual targeted + Pembrolizumab	Osborne, et al NCT03287817	Phase 1/2 R/R DLBCL	N=11	ORR 64% CRR 55%
LV20.19CAR (CD19/CD20) Dual targeted Lentiviral	Shah, et al[49] NCT03019055	Phase 1 R/R NHL 45% DLBCL		Enrolling in expansion phase ORR 82% CR 54.5% No grade 3-4 CRS or NTX in first 11 pts.
Antibody-Drug Conjugates				
Polatuzumab vedotin (anti-CD79b/MMAE) added to BR	Sehn et al[20] Lu et al[28] NCT02257567	Phase 2 R/R DLBCL Ineligible for ASCT	N=80	CMR 40% Median OS 12.4 mos
Polatuzumab vedotin (anti-CD79b/MMAE) added to GemOx	Haioun, et al[31] NCT04182204	Phase 3 R/R DLBCL		Enrolling
Engineered Toxin Bodies				

MT-3724 (CD20 / SLT-I A1)	Fanale, et al[50] Duque, et al[51] NCT02361346	Phase 1 Relapsed B-NHL after anti-CD20 and CT	N=100	Safety and efficacy assessment of 50 mcg/kg/dose ongoing.
PI3K Inhibitor				
Parsaclisib 20 mg po daily	Coleman, et al[52, 53] NCT02998476	Phase 2 R/R DLBCL	N=60	Interim Results ORR 25% CMR 12.5%
Buparlisib 80 mg po daily + Ibrutinib	Batlevi, et al[54] NCT02756247	Phase 1/2 R/R DLBCL, Mantle Cell, Follicular	N=37	Interim Results ORR 31% CMR 23%
BTK Inhibitors				
Acalabrutinib 100mg po BID +Pembrolizumab	Witzig, et al[55] NCT02362035	Phase 1/2 R/R DLBCL	N=61	ORR 26% CR 7%
Zanubrutinib 160mg po BID	Yang, et al[56] NCT03145064	Phase 2 R/R Non-GBC DLBCL Ineligible for ASCT	N=41	ORR 29.3% CR 17.1% Median OS 8.4 mos
Immunomodulators				
R2-GDP Lenalidomide 10mg po d1-14 + R-GDP	Merino, et al[57] EudraCT 2014-001620-29	Phase 2 R/R DLBCL Ineligible for ASCT	N=79	Enrolling ORR 59% CR 32% Median OS 12 mos
R2-ICE Lenalidomide 20mg po d1-14 + RICE	Guerra-Bauman, et al[58] NCT02628405	Phase 1/2 R/R DLBCL Candidates for ASCT		Enrolling

mAb = Monoclonal Antibody; PO = by mouth; BID = twice daily; Mo(s) = month(s); ORR = Overall Response Rate; CR=Complete Response; CMR=Complete Metabolic Response by Positron Emission Testing (PET); Dur.= Duration; CT = Chemotherapy; ATE+OBI+VEN (Atezulizumab+Obinituzumab+Venetoclax); BR = Bendamustin/Rituximab; Gem-Ox = Gemcitabine/Oxaliplatin; AE Trmt DC Ac/Pem =Adverse Events causing Treatment Discontinuation due to Acalabrutinib/Pembrolizumab; SLT-I A1=Shiga-like toxin-I A1; R2-GDP (Lenalidomide, Rituximab, Gemcitabine, Dexamethasone, Cisplatin); R2-IMED (Lenalidomide, Rituximab, Methotrexate, Etoposide, and Dexamethasone); R2-ICE (Lenalidomide, Rituximab, Ifosfamide, Carboplatin, Etoposide)

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