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EMERGING THERAPEUTIC AGENTS IN THE TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Diffuse large B cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma (NHL). The median age at diagnosis of DLBCL is 65, and about one-third of patients are older than age 75 at diagnosis.[1,2] The standard of care for frontline treatment is chemoimmunotherapy, consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). Approximately 60% of patients are cured with standard treatment, but it is inaccessible for up to 25% of patients due to advanced age and underlying comorbidities, including cardiac dysfunction.[2,3] Several biologic factors confer risk of treatment failure, including activated B cell (ABC) cell of origin[4-6] and double expressor phenotype (i.e. and overexpression of c-MYC and BCL2[7,8]).

Patients with DLBCL who relapse or are refractory to RCHOP have a poor prognosis. Currently, the standard approach is platinum-based salvage chemotherapy, such as rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP), to which approximately half of patients will respond, followed by consolidation with autologous stem cell transplant (ASCT). However this aggressive approach, which yields an overall cure rate of 25 to 35%[2,9], is restricted to younger patients without concurrent medical conditions, leaving a paucity of treatment options for patients ineligible for ASCT. Outcomes for those refractory to frontline or subsequent chemotherapy are particularly poor, with overall response rates (ORR) to salvage treatment of 26% and a median overall survival (OS) of 6 months.[10] Without a curative standard, lower intensity treatment options cited for patients ineligible for ASCT include rituximab, gemcitabine and oxaliplatin (R-GemOx) and bendamustine and rituximab (BR)[1] or lenalidomide[11], but access to these therapeutic agents is not consistent across Canadian treatment centres.

Adoptive cellular therapy using CAR-T cells has recently emerged as a potentially curative option for R/R DLBCL, and it may even supplant ASCT as the preferred second line option for R/R DLBCL. The phase 3 randomized controlled trial (RCT) ZUMA-7 reported superior response rates and event-free survival (EFS) with axicabtagene ciloecel (axi-cel) compared to standard of care (two or three cycles of platinum-based chemoimmunotherapy followed by high-dose chemotherapy with ASCT) in patients who were refractory to or had relapsed no more than 12 months after first-line

chemoimmunotherapy.[12] Both axi-cel and tisagenlecleucel have obtained Health Canada approval for R/R DLBCL after two or more lines of systemic therapy.[13] While eligibility for CAR-T is more inclusive than ASCT, Canadian patients have limited access to CAR-T therapies due to a lack of qualified centres, the limitations of CAR-T product supply and prohibitive cost. Toxicity is also a concern, with a significant incidence of cytokine release syndrome (CRS) and neurologic adverse events (AEs).[14] Therefore R/R DLBCL continues to be an area of unmet therapeutic need with no standard of care, particularly for those patients ineligible for ASCT or CAR-T.

Recently there has been unprecedented development of novel agents for patients with R/R DLBCL who are ineligible for ASCT.[2,14] Select agents are discussed in this article (summarized in **Table 1**), with particular attention to the Canadian regulatory landscape.

Monoclonal Antibodies:
Tafasitamab (MOR208) is an Fc-enhanced, humanized monoclonal antibody directed against CD19 approved by Health Canada in 2021.[15] In a phase II open label trial, adults (n=80) with R/R DLBCL who had received no more than three prior lines of therapy and were transplant-ineligible were treated with tafasitamab and lenalidomide (25 mg daily) for up to 12 cycles (28 days each) followed by tafasitamab monotherapy until disease progression.[15] Primary refractory patients were excluded. The initially reported overall response rate (ORR) was impressive at 60% with 43% complete response (CR) (**Figure 1**). The median duration of response (DoR) of 43.9 months was reported in the long term follow up in subjects with at least 35-months of data.[16], and median PFS and OS were 11.6 and 33.5 months respectively. Toxicity was mild with the most common grade 3 or higher AE being neutropenia (48%). After discontinuation of lenalidomide Grade 3 or higher AEs dropped to 29% (from 70%) in the study population.

Antibody-drug conjugates:
Polatuzumab vedotin (pola), an antibody-drug conjugate that delivers microtubule inhibitor monomethyl auristatin E (MMAE) directly to mature B cells with its target CD79b was approved by Health Canada

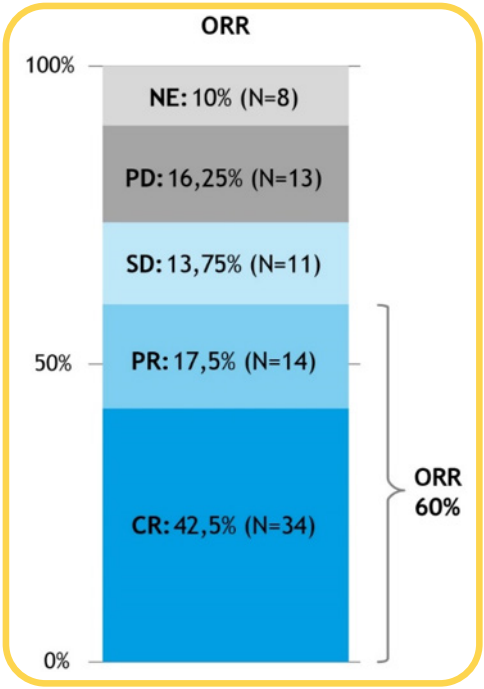

Figure 1. *Response rates with tafasitamab, lenalidomide, and rituximab from L-MIND; Salles et al., 2020.*
CR, complete response; NE, not evaluable; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.

in 2020.[17] The efficacy of pola was established in a phase II trial that randomized patients with R/R DLBCL who were ASCT-ineligible or had prior ASCT to receive pola in combination with BR versus BR alone[17]. Patients in the pola-BR arm had superior ORR (45% vs. 17.5%) and CR rates (40% vs. 17.5%). The addition of pola to BR also improved both PFS (median 9.5 vs. 3.7 months) and OS (median, 12.4 vs. 4.7 months). There was a higher rate of grade 3-4 AEs in the group that received pola-BR, with the most common being neutropenia (46% vs. 33%) followed by anemia (28.2% v 17.9%), and thrombocytopenia (41% v 23.1%), but a similar rate of grade 3-4 infections (23% vs. 22%). Peripheral neuropathy, a known side effect of MMAE-based drug conjugates, was common (44% pola-BR vs. 8% BR), but all were classified as grade 1-2 and resolved in most patients. The addition of Pola to standard chemoimmunotherapy also enhances response rates and PFS in previously untreated DLBCL.[18] It is also being studied in combination with R-GemOx for R/R.[19]

Another antibody-drug conjugate is loncastuximab tesirine (lonca), a humanized anti-CD19 antibody conjugated to SG3199, a pyrrolobenzodiazepine dimer cytotoxin that causes intrastrand DNA crosslinks.[20] A phase II single-arm open label clinical trial enrolled adults with R/R DLBCL, high grade lymphoma with BCL2+/- BCL6 rearrangements or primary mediastinal BCL; the study population was heavily pretreated with 32% having received more than 3 prior lines of systemic therapy. After receiving lonca as a single agent once every 3 weeks for 1 year or until disease progression, an ORR of 48.3% with a 24.1% CR rate was observed. In this study, patients were allowed to continue their use of lonca beyond the one year timepoint. Median PFS was 4.9 months and median OS was 9.9 months. The most common grade 3 or higher AE was neutropenia (26%) followed by thrombocytopenia (18%), and increased gamma-glutamyltransferase (17%). Eight patients (6%) died while on treatment, but none of the fatalities were deemed to have been drug-related. Lonca tesirine is approved in the U.S. for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. It is not yet approved by Health Canada.

Despite CD30 not being universally expressed on B-cell lymphomas, brentuximab vedotin (BV), a

monoclonal antibody against CD30 with MMAE drug conjugate, does produce objective responses in R/R DLBCL. In a phase 2 study that enrolled R/R B-cell non-Hodgkin lymphoma patients, 44% of subjects with DLBCL responded and 17% had CR. The median DoR was 5.6 months (16.6 months for complete responders).[21] Neutropenia (37%) was the most common grade 3 and higher AE followed by peripheral neuropathy (28%). BV has also been studied in combination with lenalidomide in a phase 1 dose expansion trial[22], showing an ORR of 57%, a CR rate of 35%, median PFS of 10.2 months and median OS of 14.3 months. Responses were higher in CD30+ DLBCLs (73%) in this study but in the previous study there was no statistical correlation between response and level of CD30 expression.[21] The toxicities observed were consistent with those seen with single agent use, but most patients required G-CSF support. These promising results have led to the current ECHELON3 trial, a phase 3 RCT studying lenalidomide plus rituximab with or without BV.[23]

Novel Agent	Ab Target or Drug Class	Regimen (comparator)	Phase	ORR % (CRR %)	Median PFS (months)	Median OS (months)
Tafasitamab[15]	CD19	Tafasitamab + Lenalidomide*	2 open label	58 (40)	11.6	33.5
Loncastuximab tesirine[20]	CD19	Loncastuximab tesirine	2	48 (24)	4.9	9.9
Brentuximab vedotin[21]	CD30	Brentuximab vedotin	2	44 (17; not reported for PFS and OS)		
Brentuximab vedotin[22]	CD30	Brentuximab vedotin + Lenalidomide	1/ dose expansion trial	57 (35)	10.2	14.3
Polatuzumab vedotin[31]	CD79b	Polatuzumab vedotin + R	2 (randomized)	54 (21)	5.6	20.1
Polatuzumab vedotin[17]	CD79b	Polatuzumab vedotin + BR* vs. BR	2 (randomized)	45 (40)	9.5	12.4
Blinatumomab[24]	CD19-CD3	Blinatumomab	2	35 (17)	3.7	5.0
Mosunetuzumab[25]	CD20-CD3	Mosunetuzumab	1/1b	45 (25)	Not reported	Not reported
Selinexor[26]	XPO1	Selinexor	2b	28 (12)	2.6	9.1
Venetoclax[29]	BCL2	Venetoclax	1	18 (12)	1	32 at 12 months
Lenalidomide[32]		Lenalidomide	2/3	27.5	13.6	31.0
Umbralisib[30]	PI3K	umbra; U2; U2 + benda-mustine	2	Umbra 13 (3); U2 32 (11); 43 (17)	Not reported	Not reported
Ibrutinib[28]	Bruton's Tyrosine Kinase	Ibrutinib + Lenalidomide + R	1b/2	44 (28)	5.5	9.5

Table 1. *Select Agents for Treatment of Relapsed/Refractory DLBCL; courtesy of Anthea Peters, MD*

BR, bendamustine + rituximab; C, cycle; D, day; NR, not reached; R, rituximab; umbra, umbralisib; U2, umbralisib + ublituximab
**indicates Health Canada approval*

Bispecific antibodies:
Bispecific antibodies, or bispecific T-cell engagers (BiTEs), target B (CD19 or CD20) cells and T (CD3) cells, thereby redirecting T cells to engage with and eliminate malignant B cells. The agent in this class furthest in development is blinatumomab, which targets CD19 and CD3. Blinatumomab has received regulatory approval for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and an approval with conditions for pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. In a phase 2 trial of R/R DLBCL, blinatumomab produced a moderate response rate but relatively short survival.[24] There was a high rate of neurologic AEs, including grade 3 encephalopathy and aphasia. Another consideration for the use of this agent is its requirement to be dosed as a continuous intravenous infusion.

Mosenetuzumab is a bispecific antibody with a much longer half-life allowing dosing every three weeks. Durable responses in aggressive and indolent B-cell NHLs in a phase 1 dose escalation study have been recently reported.[25] Despite a heavily pretreated aggressive NHL population in the study, with 34% of subjects having had prior ASCT and 12% having received prior CAR-T, 35% of subjects responded with 20% CRs, and DoR in those with CR was a median of 23 months. Cytokine release syndrome occurred in 27% of all patients but only 1% were classified as grade 3 or higher.

Other mechanisms:
Selinexor is an oral selective inhibitor of nuclear export of oncoproteins mediated by XPO1.[26] This agent is already approved in the U.S. for use in multiple myeloma, and was evaluated in patients with R/R DLBCL in the phase 2b SADAL trial in which heavily pretreated patients (n=127) were given selinexor 60 mg taken on days 1 and 3 weekly until disease progression or unacceptable toxicity. Responses with this single oral drug were promising, with an ORR of 28% (36/127) and a CR rate of 12% (15/127). The most common grade 3-4 adverse events were hematologic in nature. The median PFS reported in the SADAL trial was 2.6 months. Selinexor shows promise and is being combined with other agents in further studies, such as a phase 2/3 study in progress using R-GDP with or without selinexor.[27]

Ibrutinib, best-known for its use in chronic lymphocytic leukemia (CLL), does have activity in DLBCL, as shown in a phase 1b/2 trial in combination with lenalidomide and rituximab. The ORR in this study was higher in non-germinal center B-cell-like (non-GCB)DLBCL at 65% vs. 44% in the entire cohort.[28] Another drug typically used for CLL, BCL-2 inhibitor venetoclax, has minimal single agent activity in DLBCL.[29] Umbralisib, a PI3K-inhibitor, has objective activity alone and in combination with ublituximab with or without bendamustine, but results using this agent are preliminary and currently only available in abstract form.[30]

Conclusions:
Options for tolerable treatment are needed in R/R DLBCL in patients who are ineligible for ASCT or unable to access CAR-T cell therapy. Herein, several emerging novel agents with promise for further development as single agents or in combination regimens were reviewed. Many of these are monoclonal antibody-based and have a toxicity profile that makes them desirable particularly for the elderly and comorbid patient. The sequencing of agents that target CD19 with regards to CAR-T will be a question of interest.

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