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The Evolving Landscape of DLBCL Treatment Beyond the First Line in 2024

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Introduction

The landscape for treating relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in 2024 is rapidly evolving, with various treatment options emerging. Traditionally, salvage chemotherapy followed by autologous stem cell transplant (ASCT) has been the primary treatment for young, fit patients with R/R DLBCL, and only limited options exist for those ineligible for transplant. However, recent research and regulatory approvals, such as chimeric antigen receptor (CAR) T-cell and bispecific antibody therapies, have significantly improved our ability to treat patients previously considered palliative for R/R DLBCL.

Moreover, further research has demonstrated that these advanced technologies are not only effective in the transplant setting but also in individuals who are not traditionally eligible for ASCT and those with comorbid conditions. One anticipated development has been the provincial approvals of bispecific T-cell engagers (BiTEs), such as epcoritamab and glofitamab, which target CD20 and CD3. BiTE therapy holds promise as an off-the-shelf treatment option, potentially offering wider availability to patients compared to CAR T-celll therapy or even post-CAR T-cell failure.[1,2]

With advancements in treatments, physicians may be unfamiliar with the safety profiles and potential toxicities. Concerns about CAR T-cell and BiTE treatments have been raised, particularly regarding the risk of cytokine release syndrome (CRS) and/or immune effector cell-associated neurotoxicity syndrome (ICANS). Despite these concerns, the ability to manage CRS and ICANS improves with increasing experience and advancements in treatment algorithms.[3,4]

In addition to CAR T-cell therapy and BiTEs, targeted approaches for R/R DLBCL have seen recent approvals for patients who are not ideal candidates for ASCT or CAR T-cell therapy. These include combinations, such as

tafasitamab (an anti-CD19 monoclonal antibody) and lenalidomide, or polatuzumab vedotin (an anti-CD79b-conjugated monoclonal antibody) with bendamustine, rituximab, and selinexor, an oral inhibitor of exportin 1. Unfortunately, there are disparities in drug access in different provinces in Canada. For example, institut national d'excellence en santé et services sociaux (INESSS) in Quebec has approved the funding of tafasitamab, while Canada's Drug Agency (CDA) did not recommend reimbursement, and therefore, the rest of the country does not have access. The reverse is true for polatuzumab-rituximab-bendamustine. Selinexor is not Health Canada approved or funded for this indication.

Table 1 outlines many of the latest advancements for R/R DLBCL. It is essential to highlight that three major CAR T-cell-producing companies currently treat patients with regulatory approval in the third-line setting, which may provide a potential cure. These products include Tisa-Cel, Axi-Cel, and Liso-Cel, each with the potential to significantly impact the future of DLBCL treatment. In Canada, Tisa-Cel, Axi-Cel, and Liso-Cel are approved for third-line therapy, while only Axi-Cel and Liso-Cel are available for second-line therapy, as Tisa-Cel did not demonstrate benefits in the second-line setting.

Regarding safety, it is unclear whether the differences in toxicity are related to the design of the CAR T-cell construct, as none of the constructs have been compared in clinical trials. The understanding of CRS diagnosis and management was still evolving during the studies. Despite this limitation, a retrospective study from the French real-life registry DESCAR-T compared Axi-Cel with Tisa-Cel using a propensity score-matched comparison. This study showed that Axi-Cel may demonstrate higher efficacy but more toxicity than Tisa-Cel, regarding the incidence and severity of CRS, ICANS, and prolonged cytopenias. As a result, some centres may prefer Tisa-Cel for less fit patients in third-line.[5]

BiTE therapy is also rapidly advancing, yet a comprehensive understanding of its therapeutic potential remains to be discovered. The current data does not decisively indicate curative capabilities comparable to CAR T-cell therapy. Future research should explore the potential of BiTE therapy to deliver curative benefits and ascertain the parameters for treatment cessation. Additionally, investigating the necessity of a fixed duration strategy (glofitamab)[2] versus a continuation strategy (epcoritamab)[6] will provide valuable insights for clinical practice and patient care.

In the context of second-line relapse treatment, the data indicate that Axi-Cel[7] and Liso-Cel[8] are excellent options and show superiority over ASCT. However, Tisa-Cel[9] did not demonstrate statistically significant improvement in the second-line setting and thus is not expected to be marketed in Canada in the second-line-setting.

Understanding when and to whom to provide these new therapies is rapidly evolving. In the early stages, CAR T-cell therapy clinical trials had strict criteria and were only offered to fit individuals with Eastern Cooperative Oncology Group (ECOG) performance score (PS) 0–1 and clearly defined normal organ function.[10,11] As these therapies became more common in clinical practice, many of these restrictions were lifted, and most centres now consider adequate organ function to allow more patients to benefit from the therapy. Real-world data analysis using Center for International Blood and Marrow Transplant Research (CIBMTR) data has shown that Axi-Cel is effective for those over 65 years. However, those with ECOG PS ≥2 had inferior outcomes and a higher incidence of ICANS.[12]

In the transplant-ineligible population, CAR T-cell therapy has been studied in two other clinical trials: the Pilot[13] (Liso-Cel) and Alycante[14] (Axi-Cel) trials, which specifically examined the use of CAR T-cell therapy in older and historically transplant-ineligible populations in the second-line setting. In the Alycante study with Axi-Cel, a phase II trial, patients were eligible if they had an ECOG PS of 0–2 and were considered ineligible for transplant based on age ≥65 years, Hematopoietic Cell Transplantation (HCT)-specific Comorbidity Index (HCT-CI) ≥3, or prior ACST. In the Pilot study using Liso-Cel, patients only required adequate vascular access and one of the following criteria to be considered transplant ineligible: age ≥70 years, ECOG PS of 2, diffusion capacity of the lung for carbon monoxide (DLCO) <60%, left ventricular ejection fraction (LVEF) ≤40%, creatine clearance (CrCL) between 30–60, and liver function tests showing aspartate transaminase (AST) and alanine aminotransferase (ALT) >2 and ≤5 times the upper limit of normal. Despite the increase in age and comorbidities, both toxicity and outcomes were comparable to data obtained from studies in younger and healthier patients.

When determining the best treatment options for patients with R/R lymphoma, the practitioner must consider the availability and

Drug	Study *(n)*	Administration	ORR	mPFS or mEFS *(months)*	Toxicity Grade ≥3 of Special Interest
2L					
Axi-cel[7]	Zuma-7 (359)	IV - Fixed	ORR 83%, CR 65%	8.3 EFS	CRS: 6%, ICANS 21%
Axi-cel[14]	ALYCANTE (62)	IV - Fixed	ORR 76%, CR 60%	12.3 EFS	CRS: 8%, ICANS 15%
Liso-cel[8]	Transform (184)	IV - Fixed	ORR 87%, CR 74%	10.1 EFS	CRS: 1%, ICANS 4%
Liso-cel[13]	Pilot (74)	IV - Fixed	ORR 80%, CR 54%	9.03 PFS	CRS: 1%, ICANS 4%
Tisa-cel[9]	Belinda (322)	IV - Fixed	ORR 46%, CR 28%	3.0 EFS	CRS: 5%, ICANS 2%
≥ 2L					
Pola-BR[16]	NCT02257567 (152)	IV - Fixed	ORR 42%, CR 39%	6.6 PFS	NA
Tafa-Len[17]	L-MIND (81)	IV- Continuous	ORR 58%, CR 40%	11.6 PFS	NA
≥ 3L					
Tisa-cel[10]	Juliet (165)	IV - Fixed	ORR 52%, CR 40%	3.5 PFS	CRS: 22%, ICANS 12%
Axi-cel[18]	Zuma-1 (111)	IV - Fixed	ORR 82%, CR 54%	5.8 PFS	CRS: 13%, ICANS 28%
Liso-cel[5]	Transcend (269)	IV - Fixed	ORR 73%, CR 53%	6.8 PFS	CRS 2%, ICAN 10%
Glofitamab[2]	NP30179 (154)	IV - Fixed	ORR 52%, CR 39%	4.9 PFS	CRS: 4%, ICANS 3%
Epicoritamab[6]	EPCORE (157)	SC-Continuous	ORR 63%, CR 39%	4.4 PFS	CRS: 2.5%, ICANS 0.6%
Selinexor[19]	SADAL (127)	PO	ORR 28%, CR 12%	3.5 PFS	NA

Table 1. Therapeutic advancements for R/R DLBCL; *courtesy of Mark Bosch, MD.*

Abbreviations: CR: complete response, **CRS:** cytokine release syndrome, **DLBCL:** diffuse large B-cell lymphoma, **EFS:** event-free survival, **ICANS:** immune effector cell-associated neurotoxicity syndrome, **IV:** intravenous; **NA:** not applicable, **ORR:** overall response rate, **PFS:** progression-free survival, **R/R:** relapsed/refractory, **2L:** second line, **3L:** third line

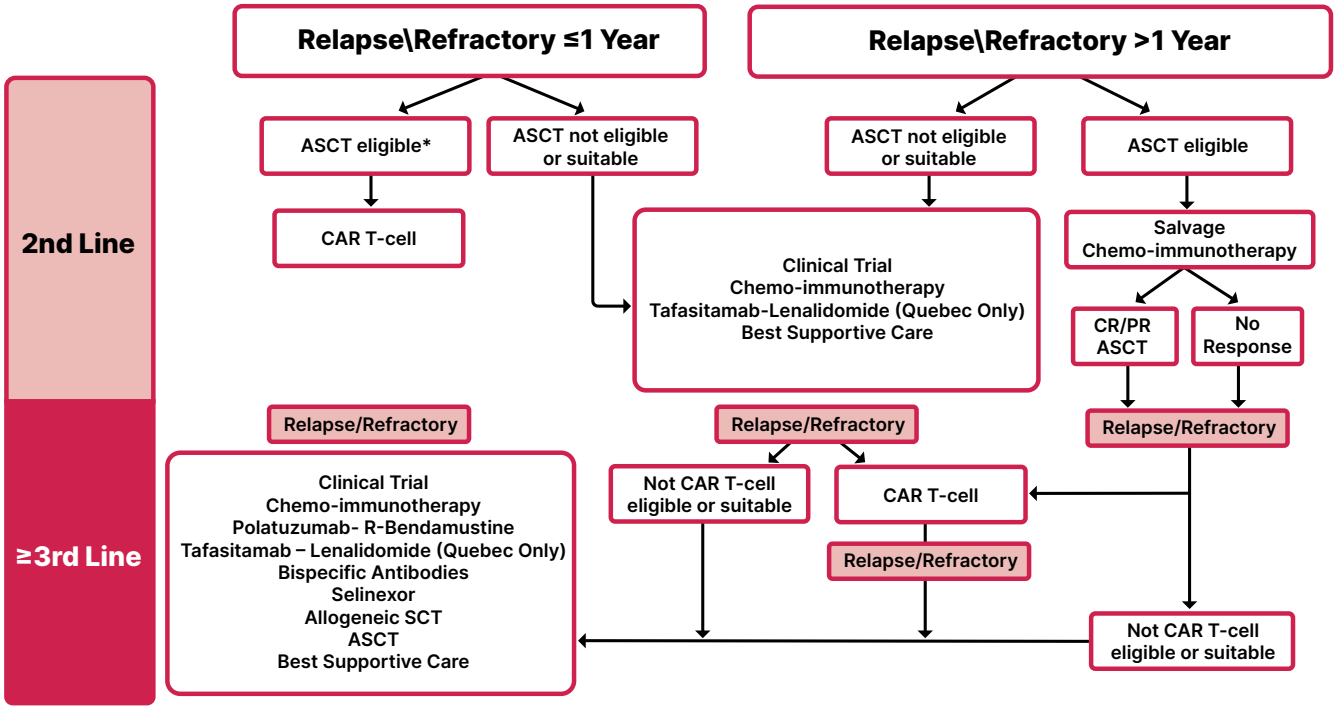

Figure 1. Algorithm for the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma; *adapted from Barca*[20].

*Access to second-line CAR T therapy in Canada is currently limited to patients deemed "transplant-eligible," as per Health Canada's approval and provincial funding. The definition of what constitutes transplant eligibility for patients is recognized as a complex issue.

Abbreviations: ASCT: autologous stem cell transplant, **BiTE:** bispecific T cell engager, **CAR:** chimeric antigen receptor, **CR:** complete response, **PR:** partial response.

funding of the latest treatments. CAR T-cell therapy is approved for second-line treatment and is currently funded in British Columbia, Alberta, Saskatchewan, Ontario, and Quebec, with additional provinces expected to follow in the future.

In addition, further clarity will need to be sought on whether we will have the same access to CAR T-cell therapy in all large B-cell lymphomas (LBCL). For example, LBCL, like Richter's transformation and primary central nervous system (CNS) lymphoma, still does not have the data to support provincial funding. In addition, not all second-line relapses were eligible for CAR T-cell therapy based on trials in the second-line. For instance, the original trials only included those who relapsed within one year from treatment. Whether this strict definition will be adhered to by the provinces and if this will change over time will need to be seen.

Above is an example of an algorithm that could guide treatment (**Figure 1**).

Factors Affecting Treatment Choice:

Various factors must be considered when determining the optimal treatment approach for patients with R/R DLBCL to achieve the best possible outcomes. These factors encompass the specifics of the disease, the patient's health status, and practical considerations that influence the choice between CAR T-cell therapy, bispecific antibodies, and other therapies.

Disease Characteristics:

The specific characteristics of the disease significantly influence treatment choice. Factors such as the stage of the disease, genetic mutations, tumour burden, and the

aggressiveness of the lymphoma play a crucial role in determining the most appropriate treatment strategy. For instance, patients with high tumour burden or aggressive disease may benefit more from the potent and rapid response offered by off-the-shelf products like BiTEs instead of waiting for the lengthy CAR T-cell assessment, collection, manufacture, and infusion process.

When treating this disease, it is essential to consider the speed and timing of therapy. For example, initiating CAR T-cell therapy earlier, such as in the second line instead of waiting until the third line, may expand the number of patients benefitting from this curative technology. Treating patients before their disease becomes more aggressive can also be crucial, as aggressive disease may cause patients to lose eligibility to receive their CAR T-cell infusion.

Treatment Characteristics:

Apart from disease characteristics, changes in how patients have been treated in the past are increasingly showing significant impacts on outcomes, especially in the context of immunotherapies. Previously, the number of cycles and lines of chemotherapy used could affect the patient's ability to gather stem cells. In current practice, there is much greater concern about the specific type of chemotherapy that patients may have been exposed to before cellular therapy. Current literature indicates that bendamustine impacts the quality of the cell manufacturing.[15] These data also suggest that using bendamustine up to nine months before collection produces a lower overall response rate ([ORR], 53% vs. 72%; P <0.01) and overall survival ([OS], 10.3 vs. 23.5 months; P = 0.01) in comparison with the bendamustine-naïve group.[15]

Patient-Specific Factors:

Considering the patient's characteristics and health status is crucial when selecting the proper treatment. Factors such as biological age, performance status, presence of comorbidities, and overall health condition play a significant role in determining the suitability of CAR T-cell or BiTE therapy. Younger patients with good performance status and fewer comorbidities may be better candidates for the potentially more intensive and personalized approach of CAR T-cell therapy. In contrast, older patients or those with significant comorbidities may benefit more from the targeted and potentially less toxic nature of off-the-shelf bispecific antibodies. Further data will be needed to delineate this. Our ability to manage side effects of interest, such as CRS and ICANS, will play a significant role in determining who are considered to qualify for these therapies. The exact specifics remain unknown; however, this will evolve with time.

Prioritizing Treatment Goals and Preferences:

When deciding between CAR T-cell therapy, BiTEs, or other therapies, it is crucial to grasp the patient's treatment goals, preferences, and expectations. Some patients may prioritize achieving a swift and profound response to treatment, even if it entails a higher risk of side effects, favouring CAR T-cell therapy. Others may prioritize a more targeted and potentially less toxic approach, favouring bispecific antibodies. Additionally, in a large geographic area, some patients may prefer to stay in their home setting and opt for treatments that may not be considered the standard of care, presenting unique challenges. Engaging patients in shared decision-making and considering their preferences can assist in customizing the treatment approach to align with their objectives and values.

Availability and Cost Considerations:

Practical and financial considerations, such as the availability of CAR T-cell or BiTE therapy in a given healthcare setting, can impact treatment choice. For example, CAR T-cell therapy may have limited availability in certain regions or healthcare facilities, making it necessary to explore alternative options like BiTEs. Additionally, the cost of treatment, including the price of the therapy itself, supportive care, and monitoring, can influence decision-making, especially in settings where cost-effectiveness is a significant concern.

It is also essential to consider the cost of these therapies in a clinical context. For instance, CDA has determined the incremental cost-effectiveness ratio (ICER) for Axi-Cel, a CAR T-cell therapy in the second line, is $404,418 per quality-adjusted life year (QALY) compared with the standard of care. At the same time, the ICER for the BiTE glofitamab is $230,682 per QALY gained compared to salvage chemotherapy. Clearly, these new therapies come with substantial costs.

Conclusion

In conclusion, the decision-making process regarding choosing CAR T-cell or BiTE therapy involves a comprehensive assessment that considers disease characteristics, patient-specific factors, treatment goals and preferences, and availability and cost considerations. This multifaceted approach aims to provide patients with the most suitable and effective treatment while considering their circumstances. With more significant data, regulatory approvals, and experience, a new paradigm will be unlocked for relapsed patients who were once difficult to treat and cure.

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Financial Disclosures

None declared.

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