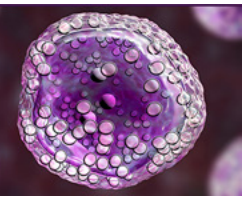
MANAGEMENT OF LARGE B-CELL LYMPHOMAS:
A CRITICAL UPDATE ON RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA AND CAR T-CELL THERAPY



Clinical Insight

INTRODUCTION

B-cell lymphomas are the predominant subtype of non-Hodgkin lymphoma (NHL), a heterogeneous group of lymphoproliferative neoplasms accounting for the seventh leading site of new cancer cases and 3% to 4% of cancer-related deaths in the United States.[1] Among NHL, diffuse large B-cell lymphoma (DLBCL) is the most common subtype, accounting for 30%–40% of all B-cell NHL cases diagnosed annually.[1–3] DLBCL is an aggressive neoplasm, with patients typically presenting with rapidly enlarging lymphadenopathy, high frequency of extranodal disease, and constitutional symptoms, necessitating prompt treatment.[4] While the remission rate with first-line chemoimmunotherapy such as R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) for patients with DLBCL is approximately 70%,[5] relapse occurs in 30%–40% of patients, with an additional 10% developing refractory disease after initial treatment (primary refractory disease).[4,6,7] Refractory DLBCL (disease not adequately responsive to treatment) or relapsed DLBCL (disease that recurs even after achieving a complete response to the initial regimen) are persistent challenges in managing patients with DLBCL.[8] Currently, there is no standard of care for managing disease that has relapsed following transplant or is multiply relapsed/refractory disease, with palliative approaches being employed predominantly.[8]

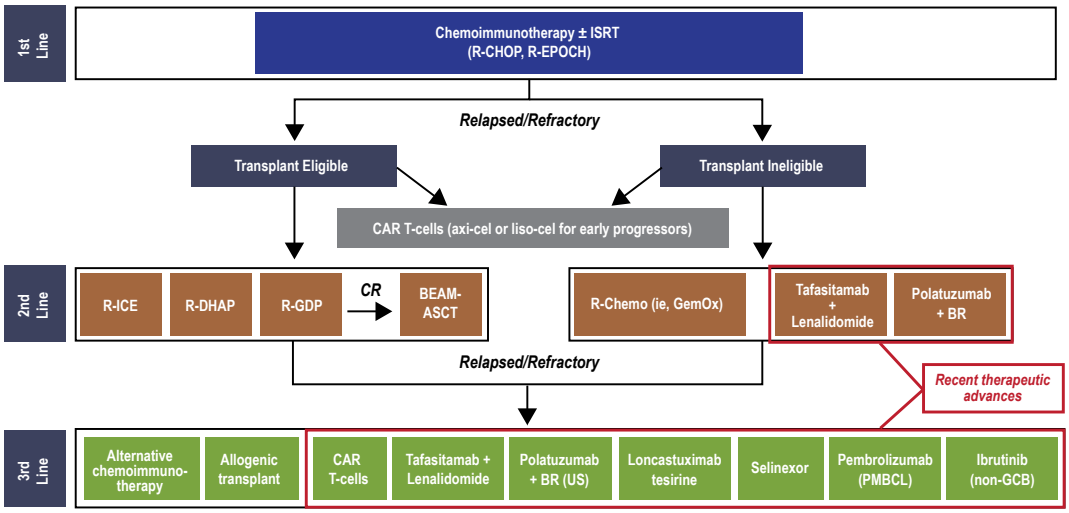
RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA TREATMENT OPTIONS

Historically, patients who are considered sufficiently young and fit to undergo high-dose chemotherapy received a platinum-based, second-line regimen followed by autologous stem cell transplant for chemotherapy sensitive disease, whereas transplant-ineligible patients were treated with a palliative-intent regimen without the goal of cure.[1]

Two trials recently compared treatment with chimeric antigen receptor (CAR) T-cells to a salvage chemotherapy and transplant-based approach in patients with early relapsed or primary refractory DLBCL. Axicabtagene ciloleucel (axi-cel) or lisocabtagene maraleucel (liso-cel) showed significant superiority of CAR T-cells in the second-line setting for high-risk patients.[9,10]

For patients who are transplant-eligible and relapse beyond 1 year from their initial chemoimmunotherapy, standard salvage chemotherapy and transplant can still be considered.[1] Transplant-ineligible or CAR T-cell-ineligible patients can be considered for palliative-based approaches which include multiple novel therapy options, including tafasitamab-lenalidomide and polatuzumab combined with bendamustine and rituximab (BR). In the third-line setting, even more options are available. CAR T-cells are available in the third-line or later setting for patients who did not receive them in second-line. Tafasitamab/lenalidomide and polatuzumab BR are available for patients who did not receive them in second-line. Additional newer agents include the anti-CD19-directed antibody drug conjugate loncastuximab tesirine, exportin 1 gene (XPO1) inhibitor selinexor, or the immune checkpoint inhibitor pembrolizumab in primary mediastinal B-cell lymphoma or the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib in nongerminal-center activated B-cell type diffuse large B-cell lymphoma.

Summary of the Current DLBCL Treatment Landscape



CAR T-CELL THERAPY PATIENT SELECTION

Many patients who were not eligible for clinical trials of CAR T-cells are appropriate to receive CAR T-cells in the real-world setting.[11] Real-world studies with either axi-cel or even tisa-cel have shown a significant proportion of patients would not have qualified to enroll in the clinical CAR T-cell trials.[12-14] It is critically important for patients to be referred early to a CAR T-cell center in order to be evaluated for their candidacy for a CAR T-cell treatment.[15] Ideally, at the time of first relapse, patients should be referred for consideration of second-line CAR T-cell therapy. If they are not eligible for second-line CAR T-cell therapy, referral ensures that the patient is known to the CAR T-cell center so they can receive CAR T-cells as a third-line treatment option if second-line treatment fails.

TOXICITY MANAGEMENT

The 2 main toxicities associated with CAR T-cell therapy are cytokine release syndrome (CRS) and neurologic toxicity, referred to as immune effector cell-associated neurologic syndrome (ICANS).[16] There are well-defined algorithms for the management of CRS neurotoxicity. Supportive care and tocilizumab are the mainstay of CRS management, whereas corticosteroids are the key treatment for mitigating neurologic toxicities. Other novel therapy toxicities and management strategies are provided in the table below.[17-19]

Agent	Toxicity	Any	≥ Gr 3	Management
Polatuzumab vedotin CD79b antibody drug conjugate (MMAE payload)	**Peripheral neuropathy**	40%	0%	• Premedicate with APAP/ diphenhydramine • ***PJP* and HSV prophylaxis required when combined with bendamustine**
	GI toxicities	56%	6.6%	
	Infusion reactions	18%	2.2%	
	Myelosuppression	49%	42%	
	Infections (pneumonia/URTI)	35%	16%	
Loncastuximab tesirine CD19 antibody drug conjugate (PBD payload)	**Fluid retention/edema**	28%	3%	**• Corticosteroid prophylaxis w/dexamethasone x 3 days (start day before therapy)**
	AST elevation	41%	<1%	
	Dermatological toxicities	52%	4%	
Selinexor Oral nuclear export inhibitor	Myelosuppression	58%	31%	• Suppoortive care management • Early intervention • Use of Neurokinin-1 antagonists and/or olanzapine for additional N/V prevention
	GI toxicities (Nausea/ diarrhea)	94%	9%	

AST, aspartate transferase; URTI, upper respiratory tract infection; *PJP, pneumocystis iiroveci* pneumonia; HSV, herpes simplex virus