DLBCL Relapse: EHA 2026 Addresses Gaps in Treatment Strategy

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> Managing relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) remains a significant clinical challenge, with a substantial proportion of patients experiencing treatment failure after initial therapy. The EHA 2026 congress provided a platform to address current therapeutic gaps, review daily practice, and outline future directions for improving outcomes in this high-risk population.1

KEY TAKEAWAYS

- The Pivot: The focus is shifting from single-agent efficacy to optimal sequencing and combination strategies for R/R DLBCL.
- The Data: While CAR T-cell therapy offers durable responses in some, a significant proportion of patients still fail, necessitating further therapeutic innovation.
- The Action: Clinicians should consider early integration of novel agents and carefully evaluate patient-specific factors for treatment escalation or de-escalation.

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma. Approximately 30-40% of patients with DLBCL will experience relapse or become refractory to initial chemoimmunotherapy, typically R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).1 For these patients, outcomes are historically poor, with a median overall survival (OS) of less than 6 months in the pre-CAR T-cell era for those refractory to second-line therapy.2 The advent of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) improved outcomes for chemosensitive relapses, but a substantial unmet need persists for patients who are refractory to salvage chemotherapy or ineligible for ASCT.3

Current daily practice for R/R DLBCL typically involves salvage chemotherapy regimens such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), or R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin).4 These regimens aim to reduce tumor burden and achieve chemosensitivity. Patients achieving a complete or partial response to salvage therapy are often considered for ASCT. However, a significant proportion of patients do not achieve chemosensitivity or relapse post-ASCT, leading to a need for further therapeutic options.5 The decision to proceed with ASCT is also influenced by patient fitness, comorbidities, and age, further limiting its applicability in a broad patient population.

Addressing Gaps and Next Moves

The EHA 2026 discussions highlighted several critical gaps in the current management of R/R DLBCL. One primary concern is the lack of consensus on optimal sequencing of novel agents, particularly in the second-line setting. Chimeric

antigen receptor (CAR) T-cell therapies, such as axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), have demonstrated superior event-free survival (EFS) compared to standard of care in second-line R/R DLBCL, particularly for patients with primary refractory disease or early relapse (within 12 months of initial therapy).6,7 For instance, the ZUMA-7 trial showed a Hazard Ratio (HR) of 0.40 (95% CI, 0.31-0.51; $p < 0.0001$) for EFS with axi-cel versus standard of care.6 Despite these advances, a substantial proportion of patients (approximately 60% in some trials) still do not achieve durable responses with CAR T-cell therapy or experience relapse post-CAR T.8 The complex manufacturing process, potential for severe toxicities like cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS), and the requirement for specialized treatment centers also present practical challenges to widespread adoption.

Another significant gap is the management of patients who are ineligible for or fail CAR T-cell therapy. Bispecific antibodies targeting CD3 and CD20, such as epcoritamab and glofitamab, have shown promising activity in heavily pretreated R/R DLBCL.9,10 These agents work by engaging T-cells and redirecting them to lyse CD20-expressing lymphoma cells. For example, glofitamab, administered as a fixed-duration regimen, achieved a complete response (CR) rate of 39.4% (95% CI, 30.0-49.3) in a pivotal phase 2 study.10 Similarly, polatuzumab vedotin, an antibody-drug conjugate, in combination with bendamustine and rituximab (Pola-BR), demonstrated improved OS compared to BR alone in relapsed/refractory patients ineligible for ASCT, with a HR of 0.42 (95% CI, 0.24-0.73).11 The challenge lies in integrating these agents into existing treatment algorithms, especially in earlier lines of therapy, and identifying patient subsets most likely to benefit.12

Discussions at EHA 2026 also focused on the role of novel combinations and strategies to overcome resistance mechanisms. This includes exploring combinations of CAR T-cells with checkpoint inhibitors or other targeted agents, as well as developing next-generation CAR T-cell constructs.13 Furthermore, the importance of real-world data and biomarker identification to guide treatment selection was emphasized. The heterogeneity of DLBCL, both clinically and molecularly, necessitates a personalized approach, moving beyond a one-size-fits-all strategy.14 The ongoing development of predictive biomarkers for response to CAR T-cell therapy and other novel agents is critical to optimize patient selection and improve resource allocation.15 This includes genetic profiling, protein expression analysis, and liquid biopsy approaches to identify minimal residual disease and predict treatment failure earlier.

CLINICAL IMPLICATIONS

The EHA 2026 discussions underscore a persistent tension in R/R DLBCL management: the undeniable efficacy of CAR T-cell therapy for a subset of patients, juxtaposed with the significant proportion who still fail or are ineligible. Clinicians are now faced with a complex decision tree, where the optimal timing and sequencing of CAR T-cells versus bispecific antibodies or antibody-drug conjugates are not yet definitively established. The current landscape demands a nuanced understanding of each agent's profile and careful patient selection, rather than a simple linear progression of therapies.

The industry's rapid development of novel agents, while beneficial, creates a challenge for guideline bodies like ESMO and NCCN to keep pace with the evolving evidence. The data for bispecific antibodies, for instance, are compelling, but their integration into earlier lines of therapy, particularly for patients who might otherwise proceed to CAR T-cells, requires more head-to-head comparisons or robust real-world evidence. Without clear

guidance, there is a risk of suboptimal sequencing, potentially exhausting effective options prematurely or exposing patients to unnecessary toxicities.

For patients, this evolving landscape offers hope, but also complexity. The promise of durable remission with CAR T-cells is significant, yet the logistical hurdles, potential toxicities, and the reality of treatment failure remain. The availability of multiple effective agents means that even after CAR T-cell failure, there are often further options. However, the financial burden and access issues associated with these advanced therapies continue to be a barrier, highlighting the need for health systems to adapt to these high-cost, high-impact treatments.

Doctors seeking concise guidance on navigating advanced DLBCL relapse options, particularly post-CAR T-cell, will find practical strategies within the Oxford Handbook of Clinical Haematology.

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