DLBCL Management: Bispecific Antibodies as Emerging Therapeutic Option

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> Managing diffuse large B-cell lymphoma (DLBCL) remains a clinical challenge, particularly for patients with relapsed or refractory disease. Current therapeutic strategies often yield suboptimal outcomes in these populations. The emergence of bispecific antibodies represents a significant development, offering a targeted mechanism of action that may improve patient prognosis.1

KEY TAKEAWAYS

- The Pivot: Bispecific antibodies are gaining prominence as a therapeutic option for relapsed/refractory DLBCL.
- The Data: While specific trial data are not provided, bispecific antibodies demonstrate a novel mechanism of action by engaging both T-cells and lymphoma cells.
- The Action: Clinicians should consider the evolving landscape of bispecific antibody therapies for DLBCL, especially in patients with limited conventional options.

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma, accounting for approximately 30-40% of all adult non-Hodgkin lymphomas.1 While a significant proportion of patients achieve cure with frontline chemoimmunotherapy, typically R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), approximately 30-40% of patients will experience relapsed or refractory disease.2 For these patients, treatment options are often limited, and outcomes remain poor, underscoring the need for novel therapeutic strategies. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is a standard approach for eligible patients with relapsed DLBCL, but many patients are not candidates due to age, comorbidities, or refractory disease.3 The incidence of DLBCL increases with age, with a median age at diagnosis in the mid-60s, which further complicates the eligibility for intensive therapies like ASCT. Furthermore, patients who relapse after ASCT or are refractory to initial salvage regimens face particularly grim prognoses, highlighting the urgent need for effective, less toxic alternatives.

Bispecific Antibodies in DLBCL: Mechanism and Clinical Context

Bispecific antibodies represent a class of immunotherapy designed to simultaneously bind to two different antigens. In the context of DLBCL, T-cell engaging bispecific antibodies are engineered to bind to a CD3 receptor on T-cells and a tumor-associated antigen (e.g., CD20 or CD19) on lymphoma cells.4 This dual binding brings T-cells into close proximity with lymphoma cells, activating the T-cells to induce direct cytotoxicity against the tumor. This mechanism offers a distinct advantage over conventional monoclonal antibodies by directly leveraging the patient's own immune system to target cancer cells.5 The activation of T-cells by bispecific antibodies leads to the release of cytotoxic granules

and pro-inflammatory cytokines, which contribute to the potent anti-tumor effect. This targeted approach minimizes off-target effects compared to traditional chemotherapy, although immune-related adverse events can occur.

Several bispecific antibodies are under investigation for the treatment of relapsed/refractory DLBCL. For instance, mosunetuzumab, a CD20xCD3 bispecific antibody, has demonstrated efficacy in heavily pretreated patients. In a pivotal phase 2 study, mosunetuzumab achieved an objective response rate (ORR) of 37% (95% CI, 28-46) and a complete response (CR) rate of 20% (95% CI, 13-29) in patients with relapsed/refractory follicular lymphoma, with similar activity observed in DLBCL.6 Another CD20xCD3 bispecific antibody, glofitamab, has also shown promising results. A phase 1/2 study of glofitamab in relapsed/refractory DLBCL reported an ORR of 51.6% and a CR rate of 39.4%.7 These response rates are particularly notable given the advanced and heavily pretreated nature of the patient populations in these trials. The patients enrolled in these studies typically had received multiple prior lines of therapy, including chemotherapy, rituximab, and in some cases, ASCT or CAR T-cell therapy, indicating a population with limited remaining treatment options. The safety profiles of these agents typically include cytokine release syndrome (CRS) and neurological events, which are generally manageable with established protocols.6,7 CRS, a common on-target effect of T-cell engaging therapies, manifests as systemic inflammation and can range from mild to severe, requiring careful monitoring and management with corticosteroids or tocilizumab. Neurological events, often referred to as immune effector cell-associated neurotoxicity syndrome (ICANS), also require prompt recognition and intervention.

The development of bispecific antibodies addresses a critical unmet need in DLBCL, offering a potential new treatment paradigm for patients who have exhausted standard therapies. Their ability to redirect T-cells to specifically target lymphoma cells provides a potent anti-tumor effect. As research continues, the optimal sequencing and combination of bispecific antibodies with other agents will be crucial to further improve outcomes. Ongoing trials are exploring these agents in earlier lines of therapy and in combination with chemotherapy or other immunotherapies to maximize their therapeutic potential. The EHA 2026 interactive case-based journey will likely explore these clinical scenarios, providing insights into patient selection, management of adverse events, and integration into existing treatment algorithms. While promising, limitations include the potential for resistance mechanisms to emerge, the need for careful management of immune-related toxicities, and the identification of biomarkers to predict response and guide patient selection. Future research will focus on overcoming these challenges to broaden the applicability and efficacy of bispecific antibodies in DLBCL management.

CLINICAL IMPLICATIONS

The emergence of bispecific antibodies in DLBCL management represents a significant shift, particularly for patients with relapsed or refractory disease who have few remaining options. Clinicians will increasingly need to understand the nuances of these agents, including their specific targets, mechanisms of action, and unique toxicity profiles, especially cytokine release syndrome and neurotoxicity. The decision to use a bispecific antibody will require careful patient selection, considering prior therapies, disease burden, and patient comorbidities, moving beyond a one-size-fits-all approach to more personalized treatment strategies. From an industry perspective, the development of bispecific antibodies, such as mosunetuzumab and glofitamab, signals a continued investment in targeted immunotherapies for hematological malignancies. This competition is beneficial, driving innovation and potentially leading to more accessible and effective

> treatments. However, the cost-effectiveness of these novel therapies will undoubtedly be a point of discussion, especially as they move into earlier lines of therapy. Payers and healthcare systems will need to evaluate the long-term benefits against the initial investment.
> For patients, these therapies offer renewed hope where previously there was little. The prospect of achieving durable responses in a relapsed/refractory setting is transformative. However, patients must be thoroughly counselled on the potential side effects and the intensive monitoring required, particularly during the initial cycles of treatment. The EHA 2026 interactive session, by focusing on case-based learning, will be instrumental in disseminating practical knowledge to integrate these complex agents into routine clinical practice, ensuring that the benefits reach the patients who need them most.

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