Update on diffuse large B-cell lymphoma: highlights from the 2022 ASCO Annual Meeting

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) and has high heterogeneity. Approximately 30%–50% of patients develop relapsed/refractory (R/R) disease, which remains a major cause of mortality1-3. In recent years, a variety of novel therapies have emerged, including bispecific T-cell engagers (BiTEs), antibody–drug conjugates (ADCs), chimeric antigen receptor T cells (CAR-T), and selective BTK inhibitors, which have provided effective treatment strategies for patients with DLBCL1,4. Recently, the 58th Annual Meeting of the American Society of Clinical Oncology (ASCO) was held in Chicago, presenting cutting-edge studies in DLBCL. Here, we discuss a selection of interesting data on this topic.

Bispecific antibodies

BiTEs are bispecific antibodies designed to target both CD3 and tumor-specific antigens, which induce T-cell activity and promote tumor cell death5. Bispecific antibodies have the potential to revolutionize DLBCL therapy.

Glofitamab is a novel BiTE that exerts anti-tumor effects by binding both CD20 on B-cells and CD3ε on T-cells in a 2:1 configuration6,7. The results of a pivotal phase II extension study of glofitamab in patients with R/R DLBCL were orally presented by Australian researchers8. At a median follow-up of 12.6 months, 155 patients with DLBCL who had received at least 2 prior lines of therapy were included in the study. The objective response rate (ORR) and complete response rate (CRR) were 51.6% and 39.4%, respectively. The median progression-free survival (PFS) was 4.9 months, and the median duration of response was 18.4 months. Although cytokine release syndrome (CRS) occurred in 63% of patients, only 3.9% experienced grade 3 or higher effects.

Epcoritamab (Epco), another BiTE antibody targeting CD3/CD20, achieved an ORR of 68% and a CRR of 45% for R/R DLBCL in a previous study9. At the ASCO meeting, Falchi et al.10 reported an ORR of 96% and CRR of 68% for Epco + R-CHOP in 33 patients with untreated high-risk DLBCL. Other 2 phase 1/2 studies focused on patients with R/R DLBCL treated with Epco+GemOx and Epco+R-DHAX/C. The ORR values were 92% and 83%, and the CRR values were 60% and 61%, respectively11,12. All studies showed manageable safety. BiTEs showed promising efficacy not only in untreated patients but also in heavily pretreated patients, including those with prior exposure to CAR-T cells and/or with highly refractory DLBCL. Further studies focusing on BiTEs are proceeding in multiple countries, and BiTEs may become a new treatment option for DLBCL patients. Because BCL2 and TP53 mutations have been shown to be associated with poor prognosis in patients with DLBCL with R-CHOP treatment, BiTE therapy has high potential for those patients3.

ADCs

ADCs contain a monoclonal antibody conjugated to a cytotoxic drug via a chemical linker. ADCs can selectively deliver cytotoxic drugs directly to target cancer cells13. Polatuzumab vedotin (Pola) is a CD79b-targeted ADC delivering the microtubule inhibitor monomethyl auristatin E (MMAE). Pola has shown promising efficacy for R/R DLBCL as monotherapy or combined with an anti-CD20 monoclonal
antibody-containing regimen, thus resulting in ORRs of 13%–56%14-16. However, the CRRs have been unsatisfactory (0%–15%), thus prompting combination treatment with additional agents14-16. At the ASCO meeting, Lynch et al.17 presented preliminary results from an investigator-initiated trial for upfront treatment of aggressive B-cell NHLs. In this study, 18 patients received 6 cycles of Pola with dose-adjusted etoposide, cyclophosphamide, doxorubicin, and rituximab (Pola-DA-EPCH-R). The ORR was 88%, and the CRR was 24%17. However, 5 severe adverse events were observed, including one grade 5 sepsis/typhlitis, 3 febrile neutropenia, and one grade 3 perforated colonic diverticula. Other grade 3 adverse events (AEs) included hyperglycemia, oral mucositis, asymptomatic pulmonary embolism, abdominal pain, and hypokalemia17. These findings are similar to those for other Pola combination regimens presented at the annual meeting. Polatuzumab has shown favorable efficacy in patients with primary and R/R DLBCL. However, the increase in treatment-associated AEs may limit its clinical application16,18.

CAR-T therapy

CAR-T therapy has changed the therapeutic landscape for several hematological malignancies with promising efficacy19. Axicabtagene ciloleucel, tisagenlecleucel, and lisocetogene maraleucel are autologous CAR-T-cell products targeting CD19, which have been approved by the U.S. Food & Drug Administration for the treatment of patients with DLBCL who have relapsed or have failed ≥2 line regimens, according to the JULIET, ZUMA-1, and TRANSCEND studies20-23. Patients with heavily pretreated DLBCL receiving CAR-T therapy have a median PFS of 5.9-6.8 months and a median overall survival (OS) of 11.1–21.1 months. The best ORRs of patients in these studies were approximately 52%–74%, and the CRRs were 40%–54%. The incidence of grade 3/4 CRS in the JULIET, ZUMA-1, and TRANSCEND studies was 10%, 22%, and 2%, respectively20-23. The results of these studies suggest the efficacy and safety of CAR-T cells as a therapeutic option for patients with R/R B-cell lymphoma. However, severe life-threatening toxicity, modest antitumor activity, antigen escape, and limited trafficking and tumor infiltration have restricted the clinical use of CAR-T therapy24. In a phase 1 study presented by US researchers at the 2022 ASCO Annual Meeting, Ying et al.27 presented the results of a 2-year follow-up of relma-cel in R/R DLBCL. Among 58 efficacy-evaluable patients, the best ORR and CRR were 77.6% and 53.5%, respectively. The 2-year PFS, duration of response, and OS rates were 38.3%, 38.1%, and 69.0%, respectively. The incidence of grade 3 or higher AEs was 72.9%, and hematological toxicity was the most common AE27.

Monoclonal antibodies

Targeting CD27 with monoclonal antibodies provides co-stimulation of immune cell activity30. Varilulimab is a novel agonist immunoglobulin G1 anti-CD27 antibody that mediates antitumor immunity and targets CD27, which is expressed on nearly all mature B-cell lymphomas31. Varilulimab has been demonstrated to cause T-cell activation and to demonstrate anti-tumor activity in preclinical models30,32. At the 2022
ASCO Annual Meeting, Villasboas presented the results of the DIAL study (NCI 10089), a randomized phase 2 trial of varilumab combined with nivolumab in patients with R/R aggressive B-cell NHL. A total of 53 patients enrolled in the study received nivolumab, either alone (group 1, n = 27) or combined with varilumab (group 2, n = 26). The ORR, median OS, and PFS did not statistically differ between arms. AEs of grade 3 and above were observed in 8 (33.3%) and 7 (30.4%) patients in groups 1 and 2, respectively. Dual immunomodulatory therapy did not enhance anti-tumor activity in patients with aggressive B-NHL over that with nivolumab alone.

**Conclusion**

The treatment modes for lymphoma are changing rapidly. Novel chemotherapy-free approaches, such as targeted therapy and immunotherapy, may lead to improved outcomes for patients with DLBCL and other B-cell lymphoma histologies. The results from the 2022 ASCO Annual Meeting indicated more possibilities for the treatment of lymphoma to provide patients with more therapeutic options.

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**Conflict of interest statement**

No potential conflicts of interest are disclosed.

**References**


