EDITORIAL

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 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%\textsuperscript{14-16}. However, the CRRs have been unsatisfactory (0%–15%), thus prompting combination treatment with additional agents\textsuperscript{14-16}. At the ASCO meeting, Lynch et al.\textsuperscript{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\%\textsuperscript{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 hypokalemia\textsuperscript{17}. 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 application\textsuperscript{16,18}.

**CAR-T therapy**

CAR-T therapy has changed the therapeutic landscape for several hematological malignancies with promising efficacy\textsuperscript{19}. Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene 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 studies\textsuperscript{20-23}. 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%, respectively\textsuperscript{20-23}. 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 therapy\textsuperscript{24}. In a phase 1 study presented by US researchers at the 2022 ASCO Annual Meeting, anti-CD20 CAR-engineered allogeneic gamma delta (\(\gamma\delta\)) T cells (ADI-001) were used to treat patients with R/R B-cell lymphoma\textsuperscript{25}. ADI-001 cells’ expression of histocompatibility complex independent \(\gamma\delta\) T-cell receptors enables them to directly recognize and bind tumor cell surface antigens, thus complementing CAR targeting while decreasing the risk of graft-vs.-host disease and the incidence of other AEs. In the 6 evaluable patients, the ORR was 67\%, and all patients achieved complete remission after 28 days of follow-up. The AEs of special interest (SIAEs) were grade 1/2 CRS in 2 patients and grade 1 immune effector cell-associated neurotoxicity syndrome in 1 patient. Allogeneic CAR-T-cell therapy demonstrated promising efficacy and was well tolerated in patients with R/R DLBCL. Moreover, the development of allogeneic CAR T cells could potentially decrease the cost and increase access to this class of therapeutics\textsuperscript{26}.

The RELIANCE study is a multicenter phase 2 trial of remicabtagene autoleucel (relma-cel), an autologous CAR-T-cell product targeting CD19, in Chinese patients with R/R large B-cell lymphoma. At the 2022 ASCO Annual Meeting, Ying et al.\textsuperscript{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 AE\textsuperscript{27}.

Currently, CAR-T-cell therapy has significantly improved the prognosis of patients with R/R B-cell lymphoma, thus providing a new treatment strategy for patients unable to receive hematopoietic stem cell transplantation and whose disease progresses after multiple lines of therapy. Han et al.\textsuperscript{28} have developed a novel method to generate sufficient CAR-T cells from limited peripheral blood to treat B-cell malignancies, thereby providing an alternative to the traditional CAR-T cell generation method. However, limited sample sizes in clinical studies and severe toxicity remain barriers to developing effective CAR-T-cell therapies. More evidence is needed to evaluate the efficacy and safety of CAR-T-cell therapy\textsuperscript{29}.

**Monoclonal antibodies**

Targeting CD27 with monoclonal antibodies provides co-stimulation of immune cell activity\textsuperscript{30}. Varilumab 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 lymphomas\textsuperscript{31}. Varilumab has been demonstrated to cause T-cell activation and to demonstrate anti-tumor activity in preclinical models\textsuperscript{30,32}. At the 2022
ASCO Annual Meeting, Villasboas presented the results of the DIAL study (NCI 10089), a randomized phase 2 trial of varlilumab 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 varlilumab (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**

1. Cheson BD, Nowakowski G, Salles G. Diffuse large B-cell lymphoma: new targets and novel therapies. Blood Cancer J. 2021; 11: 68.
2. Susanibar-Adaniya S, Barta SK. 2021 Update on diffuse large B cell lymphoma: a review of current data and potential applications on risk stratification and management. Am J Hematol. 2021; 96: 617-29.
3. Qin Y, Chen H, Liu P, Zhang C, Yang J, Gui L, et al. Prognostic value of BCL2 and TP53 genetic alterations for diffuse large B-cell lymphoma patients treated with R-CHOP. Cancer Biol Med. 2021; 19: 893-909.
4. Wang L, Sun Y, Liu X, Li H, Lu C, Yang R, et al. SY-1530, a highly selective BTK inhibitor, effectively treats B-cell malignancies by blocking B-cell activation. Cancer Biol Med. 2021; 19: 995-1007.
5. Kamakura D, Asano R, Yasunaga M. T cell bispecific antibodies: an antibody-based delivery system for inducing antitumor immunity. Pharmaceuticals (Basel). 2021; 14: 1172.
6. Broske AME, Korfi K, Belousov A, Wilson S, Ooi CH, Bolen CR, et al. Pharmacodynamics and molecular correlates of response to glititamab in relapsed/refractory non-Hodgkin lymphoma. Blood Adv. 2022; 6: 1025-37.
7. Bacac M, Colombetti S, Herter S, Sam J, Perro M, Chen S, et al. CD20-TCB with obinutuzumab pretreatment as next-generation treatment of hematologic malignancies. Clin Cancer Res. 2018; 24: 4785-97.
8. Dickinson M, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥ 2 prior therapies: pivotal phase II expansion results. J Clin Oncol. 2022; 40(16 suppl): 7500.
9. Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, et al. Dose escalation of subcutaneous epocitamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021; 398: 1157-69.
10. Falchi L, Offner F, Belada D, Brody J, Linton KM, Karimi Y, et al. First-line treatment (Tx) with subcutaneous (SC) epocitamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): phase 1/2 data update. J Clin Oncol. 2022; 40(16 suppl): 7523.
11. Brody J, Wahlin BE, Phillips TJ, Costello R, Lugtenburg P, Cordoba R, et al. Epocitamab (epco) with gemcitabine + oxaliplatin (GemOx) in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) ineligible for autologous stem cell transplant (ASCT) induces high response rate even in pts failing CAR T therapy. J Clin Oncol. 2022; 40(16 suppl): 7527.
12. Abrisqueta P, Falchi L, Phillips TJ, Yos SD, Nijland M, Offner F, et al. Subcutaneous epocitamab + R-DHAX/C in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) eligible for autologous stem cell transplant (ASCT): preliminary phase I/2 results. J Clin Oncol. 2022; 40(16 suppl): 7528.
13. Chau CH, Steeg PS, Figg WD. Antibody-drug conjugates for cancer. Lancet. 2019; 394: 793-804.
14. Dorman D, Bennett F, Chen Y, Dennis M, Eaton D, Elkins K, et al. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood. 2009; 114: 2721-9.
15. Pfeifer M, Zheng B, Erdmann T, Koeppen H, McCord R, Grau M, et al. Anti-CD22 and anti-CD79b antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia. 2015; 29: 1578-86.
16. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020; 38: 155-65.
17. Lynch RC, Poh C, Uijiani CS, Warren EH, Smith SD, Shadman M, et al. Polatuzumab vedotin with dose-adjusted etoposide,
cyclophosphamide, doxorubicin, and rituximab (Pola-DA-EPCH-R) for upfront treatment of aggressive B-cell non-Hodgkin lymphomas. J Clin Oncol. 2022; 40(16 suppl): 7546.

18. Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trneny M, Sharman JP, et al. Polatuzumab Vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022; 386: 351-63.

19. Larson RC, Maus MV. Recent advances and discoveries in the mechanisms and functions of CAR T cells. Nat Rev Cancer. 2021; 21: 145-61.

20. Westin JR, Kersten MJ, Salles G, Abramson JS, Schuster SJ, Locke FL, et al. Efficacy and safety of CD19-directed CAR-T cell therapies in patients with relapsed/refractory aggressive B-cell lymphomas: observations from the JULIET, ZUMA-1, and TRANSCEND trials. Am J Hematol. 2021; 96: 1295-312.

21. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019; 20: 31-42.

22. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019; 380: 45-56.

23. Abramson JS, Palomba ML, Gordon LJ, Lunning MA, Wang M, Arnason J, et al. Lisoctagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020; 396: 839-52.

24. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J. 2021; 11: 69.

25. Neelapu SS, Hamadani M, Miklos DB, Holmes H, Hinkle J, Kennedy-Wilde J, et al. A phase 1 study of ADI-001: anti-CD27 CAR-engineered allogeneic gamma delta (γδ) T cells in adults with B-cell malignancies. J Clin Oncol. 2022; 40(16_suppl): 7509.

26. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. "Off-the-shelf" allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov. 2020; 19: 185-99.