CAR-T cell therapy: unravelling its potential in extra-nodal diffuse large B cell lymphoma

Salman J. Khan[1,2]^, Muhamad Alhaj Moustafa[1]^

[1]Division of Hematology and Medical Oncology, Mayo Clinic, Jacksonville, FL, USA; [2]Public Health, University of Massachusetts, Amherst, MA, USA

Correspondence to: Muhamad Alhaj Moustafa, MD, MS. Division of Hematology and Medical Oncology, Mayo Clinic, 4500 San Pablo Rd S, Jacksonville, FL 32224, USA. Email: AlhajMoustafa.Muhamad@mayo.edu.

Comment on: Beyar Katz O, Perry C, Grisariu-Greenzaid S, *et al.* Response rates of extra-nodal diffuse large B cell lymphoma to anti-CD19-CAR T cells: A real word retrospective multicenter study. Eur J Haematol 2023;111:63-71.

Keywords: Diffuse large B cell lymphoma (DLBCL); CD19-directed chimeric antigen receptor-T cell therapy (CD19-directed CAR-T cell therapy); extra-diffuse large B cell lymphoma (extra-nodal DLBCL)

Submitted Sep 06, 2023. Accepted for publication Feb 27, 2024. Published online Apr 18, 2024.
doi: 10.21037/cco-23-95
View this article at: https://dx.doi.org/10.21037/cco-23-95

Diffuse large B cell lymphoma (DLBCL) is the most common type of lymphoma (1). It arises from germinal or post-germinal center cells and typically expresses CD19, CD20, and CD79a (2). Although most DLBCLs arise in lymph nodes, 25–40% occur in extra-nodal (EN) sites (3,4). The common EN sites are the gastrointestinal (GI) tract, mediastinum, breast, thyroid, skin, and testis (5). It is established that nodal (N) and EN DLBCLs have different clinical features, prognoses, and outcomes (6). The first-line therapy for DLBCL typically involves treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and its variations. A modified regimen of polatuzumab-R-CHP, in which vincristine was replaced with polatuzumab, is also being considered a new standard treatment for DLBCL after the phase 3 POLARIX trial showed improvement in 2-year progression-free survival (PFS) (7). Chimeric antigen receptor (CAR)-T cell therapy presented a revolutionary treatment with remarkable clinical responses in relapsed/refractory (R/R) DLBCL (8). The Food and Drug Administration (FDA) approved several CAR-T cell products, including axicabtagene ciloleucel, lisocabtagene maraleucel, and tisagenlecleucel for the treatment of R/R DLBCL (9-13). Literature about the efficacy and responses to CAR-T cell therapy among different subgroups of DLBCL is scarce. ZUMA-1, JULIET, TRANSEND, ZUMA-7, and TRANSFORM are the pivotal trials that led to the FDA approval of the available CAR-T products in DLBCL (9-13). The outcomes of EN DLBCL treated with the FDA-approved CD19-directed CAR-T cell therapy products are not well characterized in these pivotal trials. We will give an overview of the efficacy of CD19-directed CAR-T cell therapy in the EN DLBCL based on the available literature (*Table 1*).

Multiple retrospective studies have attempted to evaluate the outcomes of patients with EN-DLBCL who received CD19-directed CAR-T therapy (14-17). However, most of these studies were limited by the small number of patients and the possible biases that can affect the validity and generalizability of their findings, such as selection bias, information bias, and confounding bias, among others.

One of the largest studies comparing EN and N disease outcomes in patients receiving tisagenlecleucel and axicabtagene ciloleucel by Beyar Katz *et al.* included 126 patients (14). At the time of lymphodepletion, 72 patients had EN, 42 had N, and 12 had no disease. Although there was no difference in median PFS and overall survival (OS) when patients with EN disease compared to those with N disease, patients with 3 or more EN sites had a shorter PFS of 4.3 months compared to 12.3 months in patients with less than 3 EN sites. Similarly, OS was shorter, 8.7 months

^ ORCID: Salman J. Khan, 0009-0004-3417-679X; Muhamad Alhaj Moustafa, 0000-0001-8582-1219.

Table 1 Comparison of the studies evaluating extra-nodal and nodal DLBCL

Author	Year	Type	CAR-T product	Number of patients (EN&N)	ORR (EN&N)	PFS (EN&N)	OS (EN&N)
Beyar Katz *et al.* (14)	2023	Retrospective	Tisagenlecleucel (79.4%) and axicabtagene ciloleucel (20.6%)	72&42 (12 no disease)	58.1%&64.3%	4.3&12.3 months	8.7&16.5 months
Voltin *et al.* (15)	2023	Retrospective	Tisagenlecleucel (91%), axicabtagene ciloleucel (9%)	25&22	Not mentioned	8.0%&18.2% (1 year)	38.6%&67.0% (1 year)
Vercellino *et al.* (16)	2020	Multicenter cohort	Tisagenlecleucel or axicabtagene ciloleucel	116 (EN&N)	Not mentioned	Not mentioned	Not mentioned
Song *et al.* (17)	2022	Retrospective	CD19-directed made by Shanghai HuaDao Biopharma Limited Corporation	19&18	73.7%&88.9%	42.1%&83.3% (1 year)	63.2%&94.4% (1 year)
Zhou *et al.* (18)	2020	Retrospective	Not mentioned	32 (EN&N)	Not mentioned	Not mentioned	Not mentioned

DLBCL, diffuse large B cell lymphoma; CAR, chimeric antigen receptor; EN, extra-nodal; N, nodal; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

compared to 16.5 months, respectively (14). This study also showed that patients with certain EN locations had significantly worse outcomes, where all patients with GI tract (n=9), urinary tract (n=9), or pharynx (n=3) progressed on treatment or had an early relapse.

A study from Germany attempted to identify patient and tumor risk factors associated with not responding to CD19-directed CAR-T therapy in 47 patients with R/R aggressive B-cell lymphoma by Voltin *et al.* (15). These patients received either tisagenlecleucel (91%) or axicabtagene ciloleucel (9%) for the treatment of DLBCL (n=33), transformed follicular lymphoma (n=10), primary mediastinal B-cell lymphoma (n=2), and high-grade B-cell lymphoma (n=2) (15). The study evaluated multiple variables including metabolic tumor volume (MTV) or maximum standardized uptake value (SUVmax). Utilizing forward selection method, the study identified EN disease as the most predictive factor for OS with no other patient or tumor characteristic considered of added value in their analysis (15). Similar findings were also described by the French group led by Vercellino *et al.* in their multicenter cohort study of 116 patients with aggressive B cell lymphoma treated with either tisagenlecleucel or axicabtagene ciloleucel (16). The presence of more than 2 EN sites emerged as a strong predictor of early relapse and shorter PFS and OS along with high tumor metabolic volume >80 mL.

Beyond the commercially approved products by the FDA, a study by Song *et al.* compared the outcomes of N and EN DLBCL in patients receiving CD19-directed CAR-T product made by Shanghai HuaDao Biopharma Limited Corporation, including a CD19-specific single-chain variable fragment, hinge domain, transmembrane domain, CART costimulatory domain 4-1BB and T cell activation domain CD3 ζ (17). A total of 37 patients (19 patients with EN disease) were included in this study. More than half of the patients (11 patients with N disease and 10 with EN disease) received combined autologous stem cell transplantation (ASCT) in addition to the CAR-T product. Patients with EN disease had a lower overall response rate (ORR), 73.7%, and complete response rate (CR), 42.1%, compared to 88.9% and 66.7% in N DLBCL, respectively. The median PFS was 5 months for patients with EN disease compared to 15 months in the N disease group. Similarly, median OS was 7 months for the EN group and 16 months for the N group. The addition of ASCT to CAR-T therapy showed no OS benefit. The conclusion of the study was that EN primary disease sites were associated with worse outcomes compared to N primary disease sites.

Another study from China with a small number of patients (n=32) with non-Hodgkin lymphoma by Zhou *et al.* demonstrated a worse prognosis with the presence of soft

tissue EN sites. The hazard ratio for relapse was 13.7 for patients with EN lesions involving soft tissue compared to 0.5 for bone marrow only involvement (18).

The worse prognosis of EN disease might be related to the poor infiltration of CAR-T cells into the affected soft tissues which was described mainly in solid tumor literature. There are multiple proposed causes for the decreased penetration and efficacy of CAR-T products in EN diseases, such as the extracellular matrix, which presents a physical barrier that excludes tumor-infiltrating effector T-cells and CAR-T cells, hostile microenvironment (immunosuppressive cells or cytokines), and aberrant tumor vasculature leading to reduced delivery of the CAR-T cells as well as depletion in nutrition and oxygen (19).

In general, the existence of EN sites resulted in less favorable outcomes with CAR-T therapy. While there is no conclusive evidence pinpointing the specific EN site associated with the worst prognosis, it appears that a greater quantity of EN sites is linked to a poorer prognosis. Finally, the associated poorer prognosis of R/R DLBCL with EN involvement is likely related to the aggressive biology of the disease. A more careful evaluation of these cases and further exploration of the physical, metabolic, and immunological barriers to the CAR-T cell infiltration of EN tissue is warranted.

Furthermore, achieving improved and enduring responses may necessitate more focused and intensified approaches. Enhancing CAR-T products and their delivery methods, extending beyond intravenous administration to infiltrate the tumor microenvironment, and integrating novel agents such as antibodies (naked, with payloads, bispecific, trispecific, etc.), Bruton kinase inhibitors, and others in the pre- or post-CAR-T phases could potentially mitigate the unfavorable prognosis associated with EN disease.

Finally, navigating the complexities of CAR-T therapy in EN DLBCL underscores the inadequacy of a one-size-fits-all approach. The heterogeneity within this subset necessitates a nuanced understanding that considers diverse clinical presentations, microenvironmental factors, and predictive markers. While existing evidence highlights differences in treatment response, it also underscores the need for intensified research efforts to address knowledge gaps. From our perspective, recognizing variations in treatment responses and delving into the underlying mechanisms governing these responses is crucial. Although many studies are retrospective, their collective findings provide a foundation for a more comprehensive approach. Larger multi-center real-world studies are imperative, offering a broader and more representative understanding of EN DLBCL responses to CAR-T therapy. EN DLBCL demands a tailored and personalized approach, and concerted efforts can unlock the full potential of CAR-T therapy in reshaping the landscape of lymphoma treatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Chinese Clinical Oncology*. The article has undergone external peer review.

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-95/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-95/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89:3909-18.
2. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene

expression profiling. Nature 2000;403:503-11.
3. Zucca E, Roggero E, Bertoni F, et al. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol 1997;8:727-37.
4. Zucca E, Roggero E, Bertoni F, et al. Primary extranodal non-Hodgkin's lymphomas. Part 2: Head and neck, central nervous system and other less common sites. Ann Oncol 1999;10:1023-33.
5. El-Galaly TC, Villa D, Alzahrani M, et al. Outcome prediction by extranodal involvement, IPI, R-IPI, and NCCN-IPI in the PET/CT and rituximab era: A Danish-Canadian study of 443 patients with diffuse-large B-cell lymphoma. Am J Hematol 2015;90:1041-6.
6. Bobillo S, Joffe E, Lavery JA, et al. Clinical characteristics and outcomes of extranodal stage I diffuse large B-cell lymphoma in the rituximab era. Blood 2021;137:39-48. Erratum in: Blood 2022;139:1772.
7. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med 2022;386:351-63.
8. Shi Y, Han Y, Yang J, et al. Clinical features and outcomes of diffuse large B-cell lymphoma based on nodal or extranodal primary sites of origin: Analysis of 1,085 WHO classified cases in a single institution in China. Chin J Cancer Res 2019;31:152-61.
9. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.
10. Mohty R, Moustafa MA, Aljurf M, et al. Emerging Role of Autologous CD19 CAR T-Cell Therapies in the Second-Line Setting for Large B-cell Lymphoma: A Game Changer? Hematol Oncol Stem Cell Ther 2022;15:73-80.
11. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2021;22:1403-15.
12. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med 2022;386:640-54.
13. Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. Lancet Oncol 2022;23:1066-77.
14. Beyar Katz O, Perry C, Grisariu-Greenzaid S, et al. Response rates of extra-nodal diffuse large B cell lymphoma to anti-CD19-CAR T cells: A real word retrospective multicenter study. Eur J Haematol 2023;111:63-71.
15. Voltin CA, Gödel P, Beckmann L, et al. Outcome Prediction in Patients With Large B-cell Lymphoma Undergoing Chimeric Antigen Receptor T-cell Therapy. Hemasphere 2023;7:e817.
16. Vercellino L, Di Blasi R, Kanoun S, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. Blood Adv 2020;4:5607-15.
17. Song Z, Xu L, Tang G, et al. Prognostic differences of refractory/relapsed nodal and extranodal diffuse large B-cell lymphoma in the chimeric antigen receptor T cell therapy era. Clin Chim Acta 2022;532:72-8.
18. Zhou L, Li P, Ye S, et al. Different sites of extranodal involvement may affect the survival of patients with relapsed or refractory non-Hodgkin lymphoma after chimeric antigen receptor T cell therapy. Front Med 2020;14:786-91.
19. Kankeu Fonkoua LA, Sirpilla O, Sakemura R, et al. CAR T cell therapy and the tumor microenvironment: Current challenges and opportunities. Mol Ther Oncolytics 2022;25:69-77.

Cite this article as: Khan SJ, Alhaj Moustafa M. CAR-T cell therapy: unravelling its potential in extra-nodal diffuse large B cell lymphoma. Chin Clin Oncol 2024;13(2):31. doi: 10.21037/cco-23-95