Real-world CAR-T findings for large B-cell lymphoma from a single institution experience

Forat Lutfi, Aung M. Tun, Marc Hoffmann, Nausheen Ahmed

Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Westwood, Kansas, USA

Correspondence to: Forat Lutfi, MD; Marc Hoffmann, MD; Aung M. Tun, MD; Nausheen Ahmed, MD. Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, 2650 Shawnee Mission Pkwy, Westwood, KS 66205, USA. Email: flutfi@kumc.edu; mhoffmann@kumc.edu; atun@kumc.edu; nahmed5@kumc.edu.

Comment on: Benoit A, B Boies MH, Déry N, *et al.* CAR T-Cells for the Treatment of Refractory or Relapsed Large B-Cell Lymphoma: A Single-Center Retrospective Canadian Study. Clin Lymphoma Myeloma Leuk 2023;23:203-10.

Keywords: B-cell lymphoma; cytokine release syndrome (CRS); chimeric antigen receptor T-cell (CAR-T); immune effector cell therapy; immune effector cell associated neurotoxicity (ICANS)

Submitted Sep 17, 2023. Accepted for publication Jan 23, 2024. Published online Apr 17, 2024.
doi: 10.21037/apm-23-545
View this article at: https://dx.doi.org/10.21037/apm-23-545

The single-center retrospective study by Benoit *et al.* on early outcomes following standard of care (SOC) third line or greater chimeric antigen receptor T-cell (CAR-T) therapy for relapsed/refractory (r/r) large B-cell lymphoma (LBCL) with axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) provides interesting and relevant real-world insight (1). In this Canadian study, the patient population and SOC indication mirror that of its initially approved label in third line or greater SOC use in the United States.

The patient population in this study had a 100% success rate of apheresis to CAR-T infusion, which is higher than that in registrational trials, and may be reflective of the timing of decision to pursue CAR-T therapy and appropriate use of bridging therapies. While similar to the registrational trials and real-world studies (RWS) in terms of r/r advanced stage III/IV disease, this study's patient population was likely skewed towards a more chemotherapy refractory population with aggressive disease characteristics as 47% in axi-cel and 40% in tisa-cel recipients had prior consolidative autologous hematopoietic stem cell transplant (autoHCT) and >30% with bulky disease (defined as ≥10 cm) in both axi-cel and tisa-cel recipients. This finding may also be reflective of differences in healthcare utilization in the Canadian healthcare system.

The assessment of initial response was done using positron emission tomography/computed tomography (PET/CT) imaging at one month. The study's practice of obtaining a second post-treatment PET/CT at two months after CAR-T therapy instead of three months in those with a partial response (PR) is not a common practice and was not done in the ZUMA-1 or JULIET registrational trials (2,3). At this time there are no clear guidelines on the workup and evaluation for PR or stable disease (SD) at 1 month. Some have noted that responses may deepen over time, especially with 4-1BB co-stimulatory products where CAR-T cells have longer persistence and time to response may be longer. An American Society of Transplant and Cellular Therapy (ASTCT) Guideline Committee survey of lymphoma and cellular therapy physicians conducted in 2021 demonstrated heterogeneity in time to first scan using PET/CT, as well as frequency of scans in the first-year post CAR-T in LBCL. In this survey, 91% of responders would perform a month 3 scan but only 69% would obtain a scan at month 1. When obtaining a scan at month 1, only 14% would order additional investigations for PR at month 2, while 55% would order additional investigation for PR at month 3 (4). The rationale for ordering more frequent imaging in those with a month 1 PR is due to the high risk for relapse and presents a challenging clinical dilemma (5). Real-world data from the US Lymphoma CAR-T consortium in those receiving axi-cel for r/r LBCL

demonstrated that among 93 patients with a month one PR, a significant minority (32%) achieved a deepened response to CR by month three (6). Obtaining imaging at an earlier timepoint may identify those with progressive disease (PD) at an earlier timepoint and perhaps with less advanced disease, allowing for a more successful and early intervention following post-CAR-T relapse. This is of particular note with the recent availability of CD20×CD3 bispecific antibodies (glofitamab, epcoritamab) which have shown a complete response (CR) rate of >30% in those with relapse after CD19 directed CAR-T therapy (7,8).

The median follow-up of 5.3 months in the axi-cel group is incredibly short, while for the tisa-cel group it was nearly twice as long at 11.2 months. The CR and best overall response rate (ORR) for axi-cel (47% and 87%) and tisa-cel (40% and 90%) is interesting. The CR rate in axi-cel was less than ZUMA-1 but comparable to that in the RWS cohort. The ORR was higher in the study at month 1 but at month three the ORR and CR rate were notably lower in the study than ZUMA-1 or RSW. For tisa-cel the finding in the study was similar. This suggests a better initial response but higher rates of early relapse. While the number of patients in this study is quite small making broad conclusions difficult, it does perhaps give further credence to close follow-up and monitoring for early relapse even in those with an initial response. The inclusion of a detailed analysis of those with a PR at month one and subsequent conversion to a CR or PD would have perhaps provided further understanding of these early relapses. As demonstrated in previous study of those with a month one PR following axi-cel, imaging characteristics of increased disease bulk (total lesion glycolysis and tumor metabolic volume) were predictive of future PD (5). The higher incidence of bulky disease in this study certainly may have accounted for this, where an early PR is likely to ultimately become PD as CAR-T exhaustion and unfavorable CAR-T to tumor ratio may occur (9).

The management of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity (ICANS) in this study utilized a ZUMA-1 cohort 4 strategy for axi-cel and the standard JULIET strategy for tisa-cel (10). This is consistent with the current prevailing wisdom of CRS and ICANS management for these two respective CAR-T therapy products. The incidence of all grades CRS and ICANS was comparable to what would be expected, although no occurrences of high grades CRS and ICANS is quite unexpected, particularly given the high-risk features of those treated in this study. This may be explained by the higher utilization of tocilizumab and dexamethasone compared with ZUMA-1, JULIET, and other RWS. The study authors note the proportion of patients receiving corticosteroids in the tisa-cel cohort was similar in the study (20%), JULIET (10%), and RWS (15%). However, with a P value of 0.05 and a small sample size of 10, this is near statistical significance and importantly this is a clinically meaningful difference in corticosteroid utilization.

Subgroup analysis findings of lower response in those with refractory and bulky disease are expected findings. However, we would not expect CRS to be predictive of lower ORR, in fact this finding is contrary to the traditional thought that CRS is indicative of a CAR-T mediated response. Rather, this again is likely an indirect surrogate to the deleterious impact of corticosteroids given for CRS management on CAR-T cell function, persistence, and ultimately their efficacy. Higher incidence of hematologic toxicity with axi-cel is somewhat unexpected, we typically see similar rates regardless of product, although prolonged cytopenias is more often seen with the longer persisting 4-1BB products like tisa-cel (11). Increased hematologic toxicity in those without bone marrow disease involvement and without stage IV disease is unexpected. We would typically expect a higher incidence of toxicity in those with higher stage disease and in those with bone marrow involvement due to increased inflammation and CAR-T activity in bone marrow causing disruption of bone marrow microenvironment leading to impaired hematopoiesis. The incidence of cytopenias at month 1 was quite common with resolution by month 3 in most cases. We previously published similar findings in a study of bridging therapy prior to CAR-T infusion which included 52 patients receiving bridging therapy and 23 patients without bridging. In that study, over 70% of patients had cytopenias at month 1 with most recovering their counts by month 6. Bridging therapy and in particular bridging with radiation therapy were predictors of prolonged cytopenias after month 1 (12).

The most surprising finding is the rates of early relapse at month 3. While it is certainly the case that most relapses will occur in the first year following CAR-T therapy, many patients are cured and achieve durable responses. The 5-year follow-up of ZUMA-1 demonstrated disease specific survival at 5 years of 51% with 31% continued to be in remission while for JULIET 38% had progression free survival at a median follow-up of 40 months (13,14). The CHU study population certainly had higher risk features of disease, in particular those relapsing after autoHCT and those with bulky disease which may account for the higher

incidence of relapse (15,16). However, an additional and important factor that we all have been griping with for some time is the impact of a ZUMA-1 cohort 4 approach where early intervention with tocilizumab and corticosteroids is followed. In our single-institution experience of over 100 patients, this approach decreased intensive care unit utilization by more than 50%, significantly reduced the incidence of high-grade CRS and ICANS, and did not result in decreased efficacy, although this data has yet to mature with a median follow-up time of only 18 months. While most centers have adopted this early intervention approach, finding decreased toxicities and lower overall cumulative dose of corticosteroids used, there is nonetheless emerging concern that we may be trading short-term decreased toxicity for less long-term durable responses. Only time with further follow-up and larger multi-institution studies will assist us in ultimately determining the correct approach. It is thus our practice to continue the early intervention, ZUMA-1 cohort 4 styled approach until further study demonstrates otherwise. However, while we practice early intervention, as our colleagues at CHU, we also strive to limit the lymphocidal effect of corticosteroids by decreasing total corticosteroid dose with the use of the IL-1 antagonist, anakinra, typically for seven consecutive days at a dose of 100 mg twice daily for those with grade 2 or higher CRS or ICANS (17,18).

The finding of early cytopenias mostly resolving at month three is consistent with our experience as well. Most patients require G-CSF in the first month, often given between days 7 and 30 after CAR-T infusion. For those that have prolonged cytopenias we consider a CD34 selected stem cell boost if cells are available from a previous collection for autoHCT (rare in LBCL, common in multiple myeloma) or a thrombopoietin receptor agonist like eltrombopag or romiplostim. Given the low incidence of prolonged cytopenias in the CHU population, these interventions were unlikely to be necessary and we surmise that the zero incidence of high-grade CRS and only two patients with high-grade ICANS was a factor in explaining the few cytopenias at month 3.

Overall, we commend our colleagues at the CHU de Québec-Université Laval for their detailed findings and analysis of their real-world experience with CD19 directed CAR-T therapy with axi-cel and tisa-cel in the third line and beyond for patients with r/r LBCL. It represents an important contribution to the literature and provides a number of interesting points to guide further study. Although, it must be noted, that given the number of patients in the study is quite small and that it is a single institution experience, caution must be warranted to avoid over interpreting its findings.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*. The article has undergone external peer review.

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-545/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-545/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. Benoit A, B Boies MH, Déry N, et al. CAR T-Cells for the Treatment of Refractory or Relapsed Large B-Cell Lymphoma: A Single-Center Retrospective Canadian Study. Clin Lymphoma Myeloma Leuk 2023;23:203-10.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531-44.
3. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell

Lymphoma. N Engl J Med 2019;380:45-56.
4. Ahmed N, Kumar A, Kharfan-Dabaja MA, et al. ASTCT Committee on Practice Guidelines Survey on Evaluation & Management of Diffuse Large B-cell Lymphoma after Failure of Chimeric Antigen Receptor T Cell Therapy (CAR-T) Therapy. Transplant Cell Ther 2022;28:523-9.
5. Lutfi F, Goloubeva O, Kowatli A, et al. Imaging Biomarkers to Predict Outcomes in Patients With Large B-Cell Lymphoma With a Day 28 Partial Response by (18) F-FDG PET/CT Imaging Following CAR-T Therapy. Clin Lymphoma Myeloma Leuk 2023;23:757-63.
6. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. J Clin Oncol 2020;38:3119-28.
7. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2022;387:2220-31.
8. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol 2023;41:2238-47.
9. Cheng J, Zhao L, Zhang Y, et al. Understanding the Mechanisms of Resistance to CAR T-Cell Therapy in Malignancies. Front Oncol 2019;9:1237.
10. Topp MS, van Meerten T, Houot R, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021;195:388-98.
11. Si X, Gu T, Liu L, et al. Hematologic cytopenia post CAR T cell therapy: Etiology, potential mechanisms and perspective. Cancer Lett 2022;550:215920.
12. Lutfi F, Holtzman NG, Kansagra AJ, et al. The impact of bridging therapy prior to CD19-directed chimeric antigen receptor T-cell therapy in patients with large B-cell lymphoma. Br J Haematol 2021;195:405-12.
13. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood 2023;141:2307-15.
14. 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.
15. Sermer D, Batlevi C, Palomba ML, et al. Outcomes in patients with DLBCL treated with commercial CAR T cells compared with alternate therapies. Blood Adv 2020;4:4669-78.
16. Lyu C, Cui R, Wang J, et al. Intensive Debulking Chemotherapy Improves the Short-Term and Long-Term Efficacy of Anti-CD19-CAR-T in Refractory/Relapsed DLBCL With High Tumor Bulk. Front Oncol 2021;11:706087.
17. Gazeau N, Liang EC, Wu QV, et al. Anakinra for Refractory Cytokine Release Syndrome or Immune Effector Cell-Associated Neurotoxicity Syndrome after Chimeric Antigen Receptor T Cell Therapy. Transplant Cell Ther 2023;29:430-7.
18. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv 2020;4:3123-7.

Cite this article as: Lutfi F, Tun AM, Hoffmann M, Ahmed N. Real-world CAR-T findings for large B-cell lymphoma from a single institution experience. Ann Palliat Med 2024. doi: 10.21037/apm-23-545