blood advances

CAR T-cell reality for R/R LBCL: challenges and challengers

Paolo F. Caimi and Craig S. Sauter

Department of Hematology and Medical Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH

Comment on Riedell et al, page 1232

In this issue of *Blood Advances*, Riedell et al[1] present important "real-world evidence" (RWE) for liso-cabtagene maraleucel (liso-cel) in relapsed or refractory large B-cell lymphoma (R/R LBCL) per standard of care indication with results that essentially mirrored those of the 3 prospective, pivotal clinical trials with this cellular product (TRANSCEND, TRANSFORM, and PILOT). This retrospective, multicenter analysis from 8, mostly large, urban, academic cancer centers reported on 101 adult patients with R/R LBCL who received liso-cel in the first 17 months after US Food and Drug Administration (FDA) approval. The median time from apheresis to infusion (ie, vein to vein) was nearly 6 weeks (39 days).

It is important to highlight that the investigators did not report on the patients intended for liso-cel treatment who did not receive the therapy. With a median follow-up of 15 months, the 1-year progression-free survival (PFS) and overall survival (OS) were an encouraging 55% and 68%, respectively. Although follow-up was somewhat short, these 1-year metrics showed the value of this therapy, delivered with the intent of cure, given the understanding that most progression events occur within 6 to 12 months. The RWE presented can be described as largely validating of clinical trial observations, although limitations in practice equally need to be highlighted.

This study reaffirms that disease burden, as measured by the surrogate of serum lactate dehydrogenase (LDH) level before lymphodepletion (LD), is the most impactful prognostic factor for patients who are proceeding with chimeric antigen receptor (CAR) T-cell therapy, as appropriately highlighted and referenced by the authors. (1) Importantly, the authors reported the administration of liso-cel to a relatively older and comorbid cohort, 33% of whom would have been ineligible for the original TRANSCEND clinical trial. In a manner similar to a previous RWE analysis of the first-to-market axi-cabtagene ciloleucel (axi-cel) for R/R LBCL, including 298 patients, those who would have been ineligible for the pivotal trial experienced inferior PFS.[1,2] This earlier RWE analysis of axi-cel also reported on the value of elevated LDH (vs normal LDH) as a prognostic marker for both progression (hazard ratio [HR] for PFS, 1.9; $P = .001$) and death (HR for OS, 3.0; $P = .0001$).[2] But, in contrast with the current liso-cel RWE study in which most patients (84%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, less than half of the patients in the axi-cel RWE study had an ECOG PS of 0 to 1 and experienced superior PFS ($P = .01$) and OS ($P = .02$) relative to patients with an ECOG PS of ≥ 2.[2] Clearly, these results that show the impact of tumor bulk and PS on outcomes present a story of "good patients doing better." Of interest, with 25% of the patients in this liso-cel RWE study receiving bendamustine LD, likely secondary to a national fludarabine shortage, the investigators observed a reduced incidence of any grade cytokine-release syndrome and severe immune effector cell–associated neurotoxicity with bendamustine LD without observable compromise in efficacy. Similar findings were reported in a single-center retrospective analysis ($n = 59$) of patients treated with axi-cel.[3] These provocative findings need to be validated prospectively but highlight the opportunity for novel research on the impact of LD on CAR T-cell toxicities and efficacy.

Limitations and considerations need to be highlighted in the context of this reported liso-cel RWE analysis. In the liso-cel RWE cohort, only 15% of patients had 1 previous line of therapy. However, because both axi-cel and liso-cel are now approved as second-line therapy for early R/R LBCL in transplant-eligible patients[4,5] and with liso-cel additionally having approval for transplant-ineligible patients,[6] one could conceivably expect that future analyses will show that most patients are prescribed liso-cel upon first relapse. The permanence of CAR T cells as second-line treatments for R/R DLBCL could be challenged given the rapidly evolving landscape and the emergence of exciting novel agents, particularly CD3-CD20 bispecific T-cell engager antibodies (BsAbs), including the FDA-approved agents glofitamab and epcoritamab. Although these agents are currently restricted to

third or greater lines of therapy, recent prospective studies showed high response rates. The randomized trial STARGLO impressively demonstrated that the complete response (CR) rate more than doubled for glofitamab + gemcitabine + oxaliplatin (gem/ox) vs rituximab + gem/ox in transplant-ineligible patients, the majority of whom were enrolled during second-line therapy.[7] A recent phase 1/2 study evaluated glofitamab and rituximab + ifosfamide + carboplatin + etoposide (R-ICE) as second-line therapy for transplant and CAR T-cell eligible patients and achieved an overall response rate of 83%, which compared favorably with the historic rates achieved with R-ICE alone.[8]

Based on these results, and acknowledging the findings of Riedell and others who suggested that lower disease burdens may positively impact CAR T-cell outcomes, one could propose research studies that position BsAbs as a line of therapy that precedes CAR T cells for R/R LBCL with the intention of tumor debulking. A recently published study from the DESCAR-T registry demonstrated, through an elegant propensity score matching analysis, that previous BsAb therapy (predominately directed against CD20) does not seem to "burn a bridge" (no pun intended) for patients eventually destined to proceed to CAR T-cell therapy.[9] If, upon longer follow-up, the BsAb-containing regimens deliver on their early promise of response durability, one could go 1 step further and question whether the TRANSFORM and ZUMA-7 second-line study designs should be reconsidered using novel first-line salvage therapies, such as BsAb + platinum containing combinations. As more patients achieve CR with more effective salvage/bridging therapies, salient questions for researchers include the role of CAR T-cell therapy as consolidation of remission and whether the role of autologous transplantation should be (re-)examined.[10]

Deep examination of the CAR T-cell therapy results, particularly in the context of the emerging R/R LBCL treatment landscape, further highlights the major issue of access to autologous gene engineered therapies given their logistical resource intensity and time to therapy limitations. These well-recognized limitations of CAR T-cell therapy also affect retrospective studies. The enclosed RWE analysis is based on a cohort of patients who were infused with liso-cel and who were thus able to withstand a wait of at least 2 months on average (considering the additional time from diagnosis of relapse to apheresis). Although a third of patients would not have been ineligible for the TRANSCEND trial, the inclusion is inherently biased toward selecting patients with favorable-risk R/R LBCL that can wait for this therapy. This limitation was recently highlighted by investigators at the Levine Cancer Institute with CAR T-cell products that had a median decision-to-vein time that exceeded 2 months.[11] The enclosed liso-cel RWE study from Riedell et al is an important addition to the literature by describing the efficacy and toxicity of liso-cel in patients with R/R LBCL who can overcome all barriers and successfully receive the therapy,[12] but access to autologous CAR T cells, especially for patients with more aggressive disease, continues to be a vital consideration.

Conflict-of-interest disclosure: P.F.C. reports serving on advisory boards for AbbVie, Bristol Myers Squibb (BMS), Genentech, Genmab, Novartis, and Synthekine; and receiving research funding from Genmab, Recordati Rare Diseases, and Luminary Therapeutics. C.S.S reports serving as a paid consultant/adviser for Kite/a Gilead company, Celgene/BMS, Gamida Cell, Karyopharm Therapeutics, Ono Pharmaceuticals, MorphoSys, CSL Behring, Syncopation Life Sciences, CRISPR Therapeutics, and GlaxoSmithKline; and receiving research funding from Juno Therapeutics, Celgene/BMS, BMS, Precision Biosciences, Actinium Pharmaceuticals, Sanofi-Genzyme, Cargo Therapeutics, Affimed, and Nkarta.

References

1. Riedell PA, Grady CB, Nastoupil LJ, et al. Lisocabtagene maraleucel in relapsed/refractory large B-cell lymphoma: a cell therapy consortium real-world analysis. *Blood Adv*. 2025;9(5):1232-1241.
2. 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(27):3119-3128.
3. Ghilardi G, Paruzzo L, Svoboda J, et al. Bendamustine lymphodepletion before axicabtagene ciloleucel is safe and associates with reduced inflammatory cytokines. *Blood Adv*. 2024;8(3):653-666.
4. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852.
5. 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(7):640-654.
6. 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(8):1066-1077.
7. Abramson JS, Ku M, Hertzberg M, et al. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. *Lancet*. 2024;404(10466):1940-1954.
8. Diefenbach CS, Caimi PF, Saba NS, et al. Glofitamab in combination with rituximab plus ifosfamide, carboplatin, and etoposide shows favorable efficacy and manageable safety in patients with relapsed or refractory diffuse large B-cell lymphoma, eligible for stem cell transplant or chimeric antigen receptor T-cell therapy: results from a phase Ib study. *Blood*. 2024;144(suppl 1):987.
9. Crochet G, Iacoboni G, Couturier A, et al. Efficacy of CAR T-cell therapy is not impaired by previous bispecific antibody treatment in large B-cell lymphoma. *Blood*. 2024;144(3):334-338.
10. Shadman M, Ahn KW, Kaur M, et al. Autologous transplant vs. CAR-T therapy in patients with DLBCL treated while in complete remission. *Blood Cancer J*. 2024;14(1):108.
11. Hu B, Vaidya R, Ahmed F, et al. Real-world analysis of barriers to timely administration of chimeric antigen receptor T cell (CAR T) therapy in diffuse large B-cell lymphoma. *Transplant Cell Ther*. 2024;30(11):1082.e1-1082.e10.
12. Hoffmann MS, Hunter BD, Cobb PW, Varela JC, Munoz J. Overcoming barriers to referral for chimeric antigen receptor T cell therapy in patients with relapsed/refractory diffuse large B cell lymphoma. *Transplant Cell Ther*. 2023;29(7):440-444.

https://doi.org/10.1182/bloodadvances.2024015525