blood advances

Comorbidities in DLBCL: too "Severe4" CAR-T therapy?

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Comment on Shouse et al, page 3516

Anti-CD19 chimeric antigen receptor T-cell (CAR-T) therapies have dramatically altered the treatment landscape for relapsed and refractory large B-cell lymphoma (R/R LBCL), with improved outcomes compared with those of conventional chemotherapy-based approaches, and real-world studies reinforce these findings.[1-6] However, the spectrum of outcomes for patients varies significantly: although ~80% to 90% of the patients have an initial response to therapy, the majority eventually experience progression, with only ~40% of patients achieving long-term disease-free survival.[1-6] Although certain clinical factors, including measures of tumor burden, performance status, and comorbidities, have been associated with response to CAR-T therapy, no validated predictors for outcome have been developed to date.[5-7] Shouse et al aimed to address this problem in their recent article, highlighted in this issue of *Blood Advances*.[8]

Shouse et al performed a large, real-world retrospective study of 577 patients with R/R LBCL who underwent leukapheresis for CAR-T therapy at 9 academic centers, developing a model for predicting progression-free survival (PFS) and overall survival (OS) after CAR-T treatment and validating their findings with a second cohort of more than 200 patients. Based on earlier work showing an association with outcome, they evaluated components of the cumulative illness rating score (CIRS), which quantifies the presence and severity of comorbidities across 14 organ systems, along with classic prognostic factors in LBCL.[7,9] Using machine learning and multivariate analysis on a multicenter learning cohort, they identified that the presence of at least 1 severe comorbidity (score $\geq$3) in the respiratory, upper gastrointestinal, hepatic, or renal organ systems (which they defined as "Severe4") was independently prognostic for inferior outcomes (see figure). In the learning cohort, 9% of patients had a Severe4 comorbidity, and these patients had inferior PFSs (hazard ratio [HR] for progression, 2.15; $P < .001$) and OSs (HR 1.94; $P < .001$). The validation cohort recapitulated these findings, with 16% of patients having Severe4 comorbidities and independently inferior PFSs (HR 1.85; $P = .003$) and OSs (HR 1.70; $P = .019$).

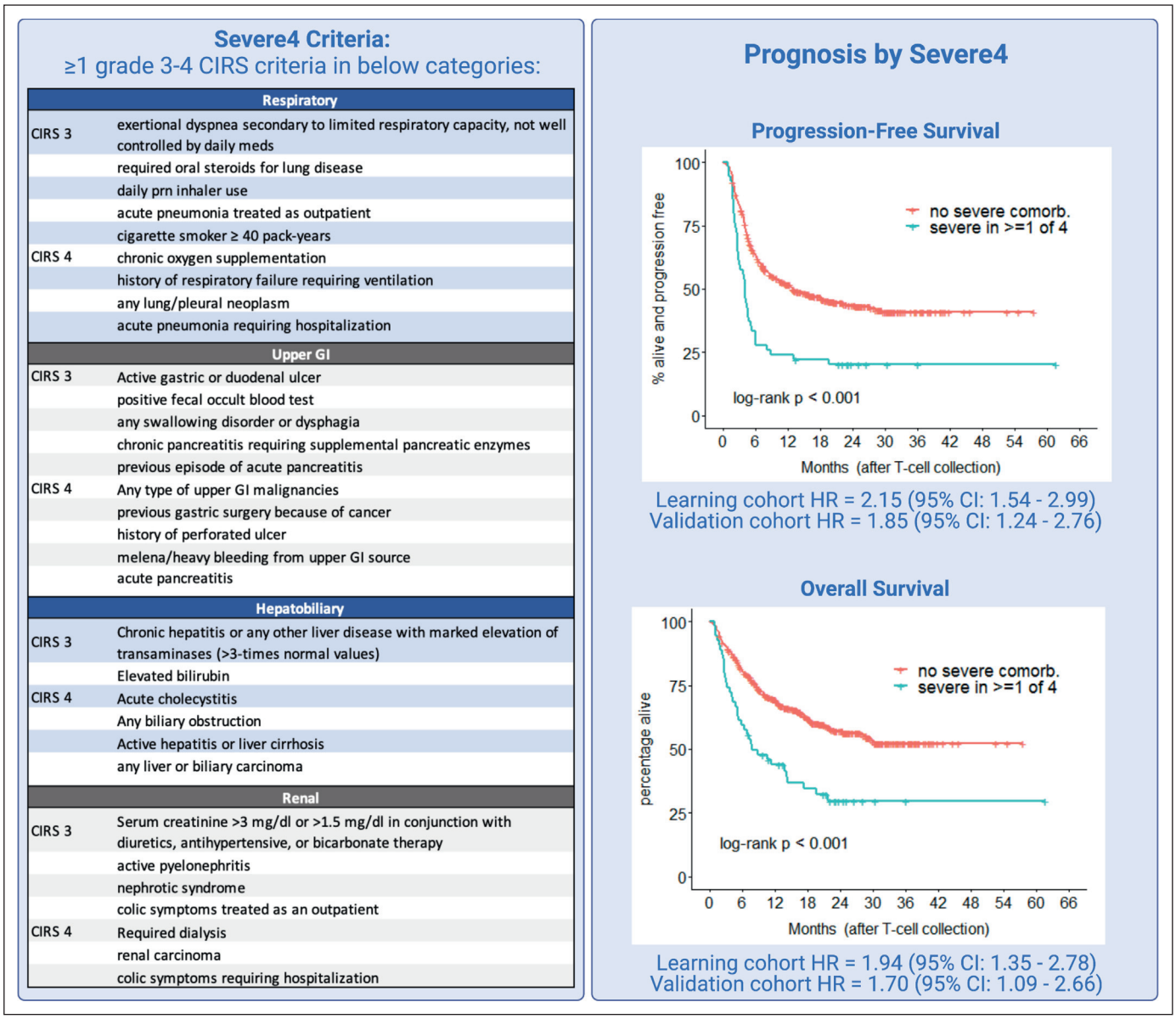
These findings are reinforced by prior work that noted similar associations: investigators on this study previously identified inferior survival based on comorbidities using CIRS, and in another large retrospective study, moderate and severe hepatic and respiratory diseases were associated with inferior response to treatment.[5,7]

This study provides a valuable and convenient tool for assessing the prognosis in candidates for CAR-T therapy. Unlike the hematopoeitic cell transplantation comorbidity index for transplant, only knowledge of patients' medical history is needed, and advanced testing, such as pulmonary function testing or echocardiogram, is not necessary.

Severe4 status is simple to determine: an online CIRS calculator can facilitate rapid assessment of comorbidities for the 4 organ systems.[10]

The next question is this: how can this metric be best used? These findings are certainly helpful in informing discussions with potential CAR-T therapy recipients and defining the expectations for prognosis for them. However, although patients with Severe4 characteristics may have worse outcomes, it is unclear whether alternative therapy would be superior to CAR-T therapy for these patients. Approximately 20% to 25% of the patients with Severe4 still achieved long-term PFS, and there is no clear alternative therapy that would exceed these outcomes. As such, this metric may be prognostic but may not change the treatment patterns at this time. One could imagine future clinical trials aimed at improving therapy, specifically for this high-risk population.

We must also consider the type of patients best represented in this study. All patients received CAR-T therapy in the third or later line. Recently, the ZUMA-7 and TRANSFORM studies showed event-free



Criteria for Severe4 based on CIRS guidelines and Kaplan-Meier curves of outcomes based on presence or absence of Severe4 characteristics. CI, confidence interval; GI, gastrointestinal. Professional illustration created using BioRender.com.

survival benefits over salvage chemotherapy and transplant in patients with refractory disease or early relapse after front-line therapy, and second-line CAR-T therapy is now recommended for these patients.[3,4] Although it seems likely that the Severe4 characteristics would be prognostic in the second-line setting, data to support this are not yet available. In addition, 71% and 97% of patients in the learning and validation cohorts, respectively, received axicabtagene ciloleucel. Further studies evaluating Severe4 in lisocabtagene maraleucel and tisagenlecleucel would be needed to ensure that these findings can be generalized to these therapies.

In addition to PFS and OS, an important area of investigation is the ability to predict CAR-T therapy–related toxicity, particularly cytokine release syndrome (CRS), immune effector cell associated neurotoxicity syndrome (ICANS), and prolonged cytopenias. The Severe4 model developed by Shouse et al was designed and optimized for predicting PFS and OS but not necessarily for toxicity. Severe4 was independently associated with severe (grade ≥3) CRS, but not ICANS, in the learning cohort, and although patients had a higher risk of severe CRS in the validation cohort, this did not achieve statistical significance upon multivariate analysis. A different metric, a cumulative CIRS score of ≥7, did predict for ICANS. CIRS ≥7 uses all 14 organ systems, including neurological, psychiatric, cardiac, and vascular comorbidities, which may be more associated with ICANS or CRS. It is possible that by using similar analytical methods and optimizing the predictors of toxicity, we could use a CIRS-based approach to anticipate toxicity, which may inform prophylactic measures to mitigate toxicity during treatment.

Shouse et al developed a tool that can be conveniently used to identify a subset of recipients who would potentially have significantly worse outcomes after CAR-T therapy. To our knowledge, this metric uses the largest cohort for prognostic outcome investigation in CAR-T to date, with validation of their findings in another large cohort, thus reinforcing the findings. Severe4 can be used to inform prognosis for CAR-T therapy candidates, with only a few highly effective options for R/R LBCL. Although this may not change management at this time, it can enrich our discussions with patients regarding treatment expectations and may serve as an important metric for future clinical trials and investigations by identifying a population with unmet needs.

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References

1. 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(1):31-42.
2. 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.
3. 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.
4. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. 2022;399(10343):2294-2308.
5. Jacobson CA, Locke FL, Ma L, et al. Real-world evidence of axicabtagene ciloleucel for the treatment of large B-cell lymphoma in the United States. *Transplant Cell Ther*. 2022;28(9): 581.e1-581.e8.
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(27): 3119-3128.
7. Kittai AS, Huang Y, Gordon M, et al. Comorbidities predict inferior survival in patients receiving chimeric antigen receptor T cell therapy for diffuse large B cell lymphoma: a multicenter analysis. *Transplant Cell Ther*. 2021;27(1):46-52.
8. Shouse G, Kaempf A, Gordon MJ, et al. A validated composite comorbidity index predicts outcomes of CAR T-cell therapy in patients with diffuse large B cell lymphoma. *Blood Adv*. 2023;7(14):3516-3529.
9. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc*. 2008;56(10): 1926-1931.
10. MD+Calc. Cumulative Illness Rating Scale-Geriatric (CIRS-G). Accessed 20 June 2023. https://www.mdcalc.com/calc/10088/cumulative-illness-rating-scale-geriatric-cirs-g

https://doi.org/10.1182/bloodadvances.2023009834