Editorial Commentary

Can we truly define 'Fitness' for CAR-T therapy in large B cell lymphoma patients?

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Comment on: Kuhnl A, Kirkwood AA, Roddie C, *et al.* CAR T in patients with large B-cell lymphoma not fit for autologous transplant. Br J Haematol 2023;202:65-73.

Keywords: Chimeric antigen receptor T cell (CAR-T); lymphoma; fitness; geriatric oncology

Submitted Jul 30, 2023. Accepted for publication Oct 09, 2023. Published online Oct 24, 2023.
doi: 10.21037/cco-23-78
View this article at: https://dx.doi.org/10.21037/cco-23-78

CD19 directed chimeric antigen receptor T cell (CAR-T) therapy has changed the therapeutic landscape of relapsed/refractory large B cell lymphoma (r/r LBCL). CAR-T with axicabtagene ciloleucel (Axi-cel) and Lisocabtagene maraleucel (Liso-cel) are superior to conventional second line chemotherapy and autologous stem cell transplant (ASCT) in early treatment failure (1,2). Axi-cel, Liso-cel and tisagenlecleucel (Tisa-cel) are all effective as third line or later therapy even after prior ASCT (2-4). Increasingly, patients with r/r LBCL who would not have met clinical trial eligibility criteria are being evaluated for CAR-T (5,6), but criteria for CAR-T fitness remain poorly defined. In this context, Kuhnl *et al.* have described CAR-T outcomes with Axi-cel or Tisa-cel for LBCL in patients deemed 'unfit' for ASCT (7).

In this multi-center analysis from a United Kingdom National Service evaluation, 20% of patients referred for CAR-T were deemed unfit for ASCT based on the treating physician's judgment. All patients had received two or more lines of therapy. Unfit patients were required to have good performance status of Eastern Cooperative Oncology Group (ECOG) 0–1 and to have received full dose R-CHOP. Half of those deemed unfit were due to age alone, and the median age of the unfit group was 71 years (range, 46–78 years). The remainder were deemed unfit predominantly due to frailty, cardiac dysfunction or renal dysfunction; 19% of unfit patients had an ejection fraction <50%, and 26% had a glomerular filtration rate <50 mL/min. The median Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) was 1 with only 18% scoring ≥3. Unfit patients had similar disease burden, response to last treatment, and bridging therapy as compared to fit patients. However, 34% of unfit patients dropped out prior to CAR-T infusion, primarily due to clinical deterioration.

In terms of efficacy, there was no significant difference observed between fit and unfit patients who underwent CAR-T. One year progression free survival (PFS) and overall survival (OS) were the same, and there were no differences in PFS by reason for unfitness (age, frailty, comorbidities) or by age group (<70, 70–74, or ≥75 years). Risk factors for CAR-T failure [performance status, elevated lactate dehydrogenase (LDH), and liver involvement] were similar between fit and unfit patients and consistent with prior analysis by this group (8).

For toxicity, unfit patients were more likely to develop immune effector cell associated neurotoxicity syndrome (ICANS) with odds ratio (OR) 2.1, but there was no increase in high grade ≥3 ICANS (OR 1.0). There was no increase in cytokine release syndrome (CRS) or prolonged cytopenias. Axi-cel and Tisa-cel had similar PFS in unfit patients, but Axi-cel recipients were more likely to develop CRS and ICANS regardless of age or comorbidities. One-year non-relapse mortality (NRM) was 7% for both fit and unfit patients, but NRM was higher at 17% in those with high HCT-CI ≥3.

This analysis by Kuhnl *et al.* adds to the growing

data on application of CAR-T for LBCL in elderly or unfit patients (7). A subgroup analysis of older patients (≥65 years) in the ZUMA-1 Axi-cel study found similar efficacy between older and younger patients with no increase in toxicity (9). In a real-world analysis of Axi-cel from the Center for International Blood & Marrow Transplant Research registry (CIBMTR), 57% of patients would not have met eligibility for ZUMA-1 (5). The most common reasons for ineligibility were due to prior malignancy or comorbidities, such as pulmonary or cardiovascular disease. Disease outcomes were lower in ZUMA-1 ineligible patients but still respectable with 1-year PFS 43% *vs.* 52% and 1-year OS 58% *vs.* 67%. Patients ≥65 years had higher rates of CRS (OR 1.4) and ICANS (OR 1.7) but better response rate (OR 1.3). Notably, significant pulmonary or hepatic comorbidities along with ECOG ≥2 were associated with worse disease outcomes. In a similar real-world analysis of Tisa-cel from the CIBMTR, there was no difference in safety or efficacy in patients ≥65 years (6).

Liso-cel has been shown to be effective in patients considered unfit for ASCT in the phase 2 PILOT study (10). Subjects were deemed ineligible for ASCT based on any one characteristic: age ≥70 years, ECOG 2, or comorbidity (pulmonary, cardiac, renal, hepatic). The primary reasons for ASCT ineligibility in this trial were age (79%), performance status ECOG 2 (26%) and creatinine clearance <60 mL/min (25%). Disease outcomes and rates of ICANS and CRS were comparable to previously reported results with Liso-cel. However, the organ function criteria for ASCT eligibility in PILOT were stricter than those used by many transplant centers, and subjects were not required to be evaluated by a transplant physician for ASCT eligibility.

Data on CAR-T in the very elderly are encouraging. In the Liso-cel PILOT study, 46% of patients were age ≥75 years, and there was not a difference in disease outcomes by age in an exploratory subgroup analysis. More recently, a CIBMTR analysis of age on CAR-T in LBCL found that age did not impact disease outcomes of PFS or OS (11). In this series, 34% of patients were 65–74 years and 10% were very elderly at ≥75 years. Although there was no difference in CRS, there was an increased risk of ICANS in older patients with hazard ratios of 2.0 and 2.5 for ages 65–74 and 75+ respectively, when compared to younger patients. A recent single institution report utilizing comprehensive geriatric assessment in CAR-T patients found that selected older patients had similar disease outcomes as younger recipients, although cognitive impairment was associated with CRS and worse survival (12).

In terms of comorbidities, the data are more mixed. In the Liso-cel PILOT study, 44% of patients had an HCT-CI ≥3 with no observed differences in safety or disease outcomes. However, a multi-center retrospective series has reported worse PFS and OS in patients with high comorbidity as defined by Cumulative Illness Rating Scale (CIRS total score ≥7 or single organ system of ≥3), although high CIRS was not associated with CRS or ICANS (13). Although comorbidity by CIRS and performance status were prognostic, a high HCT-CI was not predictive. Of note, HCT-CI is typically collected as part of patient evaluation in cell therapy/transplant, but CIRS scoring is not in common use. Importantly, neither HCT-CI or CIRS has been prospectively validated in CAR-T. More recently, a severe comorbidity index (SEVERE4) based on respiratory, upper gastrointestinal, hepatic, and renal dysfunction has been proposed, based on a retrospective multi-center series (14). This index predicted inferior PFS and OS after CAR-T and was also tested in a validation cohort of Axi-cel. In addition, it was also predictive of high-grade CRS but not ICANS. For hematologic toxicity post CAR-T, the CAR-HEMATOTOX has been proposed based on markers of hematopoietic reserve and inflammation (15). Preliminary data suggest a trend for disease outcomes with CAR-HEMATOTOX, although it is not associated with CRS or ICANS.

Renal dysfunction is a common complication in lymphoma, and poor renal function can be a contraindication for ASCT. A retrospective series has found that baseline renal insufficiency is not a poor prognostic factor for CAR-T in LBCL, although development of acute kidney injury during CAR-T was associated with worse PFS and OS (16). This series included two patients with end stage renal disease on dialysis at baseline who underwent CAR-T therapy. CAR-T for LBCL has also been safely performed in kidney transplant recipients (17). Similarly, CAR-T in myeloma with renal insufficiency has shown similar efficacy with no increase in CRS or ICANS, although cytopenias were more frequent (18). However, lymphodepletion chemotherapy needs to be dose adjusted for renal dysfunction, and bendamustine may be considered instead of fludarabine/cyclophosphamide, due to its short half-life and minimal renal excretion. Data for CAR-T in severe pulmonary or cardiac disease are sparse, and patients with significantly impaired cardiopulmonary reserve may have difficulty tolerating CRS. Baseline neurologic dysfunction would also be of concern in assessment and management of ICANS.

Given the available data, advanced age alone should no longer be considered a contraindication for CAR-T in an otherwise fit candidate without significant organ comorbidities. The lymphoma outcomes in older patients are similar to those of younger age, although older patients may have greater toxicity risk, particularly ICANS. In terms of comorbidities, CAR-T can also be successfully performed in advanced kidney disease, and other moderate organ comorbidities (e.g., cardiac, pulmonary, hepatic) are also not absolute barriers. Prognostic scores such as CIRS, SEVERE4 and CAR-HEMATOTOX may prove helpful in identifying appropriate candidates for CAR-T but need validation in larger and prospective studies. CAR-T products with a 4-1BB activating domain (Tisa-cel or Liso-cel) are preferable in patients of older age or with significant comorbidities, as they have less risk of CRS and ICANS compared to CD28 constructs. However, the recent development of CD3/CD20 bispecific antibodies such as epcoritamab and glofitamab may change the use of CAR-T in this patient population (19,20). With the inherent difficulties of cross study comparisons, the risks of severe ICANS and CRS may be less with bispecifics, and efficacy data with bispecifics is less mature.

Finally, it is important to recognize that there remains no clear definition of the 'unfit' candidate for CAR-T. Kuhnl *et al.* used relatively strict criteria determine ASCT eligibility, and there is always potential bias regarding transplantation eligibility based on the eye of the beholder. Inevitably, we predict similar bias will emerge regarding CAR-T and bispecific eligibility. Future considerations may also focus on resource utilization given the high cost of CAR-T. We recognize that the older patient may not plan to return to work, but quality of life (QOL) studies have demonstrated that CAR-T responding recipients have a more rapid return to normal QOL compared to ASCT (21,22). Therefore, CAR-T patients will require less on going need for close medical intervention, compared to those undergoing ASCT.

Thus, as a community, we may best be served in focusing on descriptions of trial eligible versus ineligible in our retrospective analyses, rather than placing ourselves at risk for unintended investigator bias using ambiguous terms, such as 'fit' *vs.* 'unfit'. Certainly, we welcome trials such as BMT CTN 1704 which is prospectively designed to identify factors that would predict toxicities and complications in older patients undergoing allogeneic transplantation. Such a study would benefit the CAR-T world, but current CAR-T lymphoma outcomes are more impacted by disease biology rather than by age and comorbidities. Better identification and especially validation of factors that predict for poor disease outcomes after CAR-T are needed. We would caution therefore against limiting potentially life-saving therapies based on age or fitness criteria that have not been validated. The current study by Kuhnl *et al.* supports the practice of many immune effector cell physicians—that restricting CAR-T eligibility based on vague and inexact age and fitness should not occur.

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-23-78/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-78/coif). A.I.C. reports research support from Novartis and Fate Therapeutics and consulting fees from Kite, Intellia Therapeutics, and Elsevier. R.T.M. reports serving as consultant for AlloVir, Kite and Novartis, research support from Gamida, Orca Therapeutics, AlloVir and Novartis, participating in a DSMB for Athersys, Novartis, and VorPharma, and a patent with Athersys. The authors have no other 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.

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Cite this article as: Chen AI, Maziarz RT. Can we truly define 'Fitness' for CAR-T therapy in large B cell lymphoma patients? Chin Clin Oncol 2024;13(1):15. doi: 10.21037/cco-23-78