blood advances

Maybe you can't drive this CAR?

Benjamin A. Derman

Section of Hematology/Oncology, University of Chicago, Chicago, IL

Comment on Haslam et al, page 1032

In this issue of *Blood Advances*, Haslam et al[1] have written a provocative article describing the true reach of chimeric antigen receptor T-cell therapy (CAR T) in lymphoma, acute lymphoblastic leukemia, and multiple myeloma (MM), arriving at the conclusion that only a very small percentage of patients are eligible for and benefit from CAR T in the real world. The authors used cancer-specific death data for respective tumor types as a stand-in for eligibility for CAR T; the theory being that CAR T is only given in later lines before a patient succumbs to their disease. They then multiplied CAR T–eligible patients by the reported response rates for respective CAR T to provide a best-case estimate of the benefit of CAR T. Despite the high rates of response to CAR T across indications in clinical trials, the authors estimated that the percentage of patients in the United States with CAR T–treatable hematologic malignancies who were eligible for CAR T was only 3.9%, thereby resulting in a 3.4% "response rate" using their modified method.

These results are in stark contrast to the enthusiasm around CAR T for hematologic malignancies. There are 3 US Food and Drug Administration (FDA)–approved CAR T for diffuse large B-cell lymphoma (DLBCL) in the third line and beyond (axicabtagene ciloleucel [axi-cel], tisagenlecluecel, and lisocabtagene maraleucel) based on nonrandomized studies that yielded response rates of 52% to 83% and 24-month progression-free survival (PFS) of 33 to 40.6 months, all with notable "tails" at the ends of the Kaplan-Meier curves, suggesting some patients may be cured.[2-4] For MM, 2 CAR Ts (idecabtagene vicleucel [ide-cel] and ciltacabtagene autoleucel [cilta-cel]) gained FDA approval for patients with disease progression after ≥4 prior lines of therapy and exposure to an anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulatory imide. In the single-arm karMMa study, ide-cel generated a response rate of 73% and a median PFS of 8.8 months,[5] and the nonrandomized CARTITUDE-1 study involving cilta-cel led to a response rate of 98% and a median PFS of 34.9 months.[6]

Much of the discrepancy between the calculated "real-world" response rate of 3.4% and the much higher response rates in clinical trials has to do with eligibility. Cancer-specific death was used as a stand-in for eligibility because it was thought to capture patients with the requisite prior lines of therapy; the authors accurately argued that this may even overestimate the eligibility because some patients could have died before meeting the labeled indications for CAR T. However, we now have evidence that CAR T can be used earlier in DLBCL and MM to great effect, long before patients will die from their disease. For example, the ZUMA-7 trial comparing axi-cel with the standard of care in the second line for refractory DLBCL not only identified a PFS advantage in favor of axi-cel over the standard of care but also an overall survival (OS) advantage, leading to its approval for this indication.[7] In the case of MM, 2 randomized phase 3 studies showed a PFS benefit to earlier-line ide-cel and cilta-cel compared with the standards of care in their respective trials, although the FDA has not yet ruled on whether the labeled indications for either product will change as OS data mature.[8,9] If a change in the "lines of therapy designation" occurs for MM as well, there is likely to be a rapid increase in the number of CAR T–eligible patients, which will, in turn, significantly increase the adjusted response rate and overall benefit.

Haslam et al's[1] work highlights the limited overall benefit of CAR T in the current grand scheme of advanced hematologic malignancies. It is a clarion call to investigators and industry partners to continue to generate data that demonstrate the benefit of CAR T in earlier lines of therapy and to regulatory agencies to consider approval for earlier indications without erecting unnecessary barriers. A recent

study in relapsed/refractory MM found that drug-class refractoriness, and not the number of prior lines of therapy, was associated with PFS[10]; this is an increasingly relevant distinction because more drugs are combined earlier. Yet, trial eligibility criteria and FDA approvals have classified patients by prior lines of therapy, which may put some patients at risk of dying from their disease before they can receive CAR T. One way to overcome this is to eschew the lines of therapy as a criterion for CAR T and instead focus on drug-class refractoriness.

Even if all of this is done, there remain issues with maintaining adequate supply of CAR T for patients who need it, owing previously to lentiviral vector shortages and more recently to regulatory agencies throttling production.[11] Moreover, vein-to-vein times (from T-cell collection to infusion) remain unacceptably long in some disease states. This leads to some patients being collected for CAR T but never infused and, therefore, inadvertently encourages clinicians to select patients for CAR T with more indolent disease who can survive the vein-to-vein time. Payors also create barriers by limiting patients in their choices of in-network centers who can administer CAR T and delaying the approval of CAR T through requiring single-case agreements; this adds to the "brain-to-vein" time (the time from making the decision to proceeding with CAR T to the actual infusion). Structural issues that more often afflict marginalized individuals, such as the distance from CAR T centers, underinsurance or uninsurance, lack of social support, and delayed referral, may limit access as well.

The work of Haslam et al[1] casts a pall over the hype of CAR T and demonstrates that the current use of CAR T may not be making as much of an impact on the natural history of advanced hematologic malignancies as hoped. Said more positively, the current situation is the worst it ever will be! Supply will increase, vein-to-vein times will shorten, structural issues will be addressed in a multifaceted fashion, and CAR T will be used earlier in disease states to bring about deeper and more durable responses for more patients. For CAR T, it is time to put patients in the driver's seat and get moving!

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