COMMENTARY

blood advances

TO THE EDITOR:

Navigating the narrow bridge to CAR T-cell therapy

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When the pivotal phase 2 ZUMA-1 trial was first published in the *New England Journal of Medicine* in 2017, chimeric antigen receptor (CAR) T-cell therapy was widely regarded as a major breakthrough for patients with refractory diffuse large B-cell lymphoma. These patients, who historically would have had dismal outcomes, had an objective response rate of 82% and an 18-month overall survival of 52%.[1] The results of ZUMA-1 were subsequently bolstered by the JULIET study, in which patients had an equally impressive 12-month relapse-free survival of 65%.[2] Of course, the patients on the ZUMA-1 and JULIET trials were carefully selected, as is the case in most clinical trials, and likely consisted of a less-sick cohort. In particular, the ZUMA-1 trial notably did not allow for any bridging therapy. In reality, patients who are candidates for CAR T-cell therapy often have progressive symptomatic disease that requires some form of treatment to support them during the period between leukapheresis and CAR T-cell infusion.

In this issue, Pinnix et al compare the outcomes of 81 patients who received any bridging therapy prior to planned treatment with commercially available axicabtagene ciloleucel to 67 patients who did not.[3] Notably, the patients who received bridging therapy had worse 1-year progression-free survival (PFS) and overall survival than patients who did not. Bridging itself is unlikely to have led to worse outcomes; instead, the patients who needed bridging therapy were likely sicker than those who did not. It is also important to note that the entire cohort had worse outcomes than those published in the ZUMA-1 and JULIET trials, likely representing an ambitious attempt to give CAR T-cell therapy to all eligible patients, a de facto "real-world" experience. One in 6 patients in this series did not go on to receive the planned CAR T-cell therapy, most commonly because of disease progression and despite best efforts with bridging therapy. These data suggest that earlier referrals for consideration of CAR T-cell therapy, before the patient is in a dire condition, may be important.

At present, there are more unknowns than knowns about how to best bridge patients to CAR T-cell therapy and about the effect of bridging therapy on outcomes, including toxicity. These are highlighted eloquently in the hypothesis-generating paper by Pinnix et al, which included patients bridged with systemic therapy, radiation therapy (RT), and combined modality therapy. Most importantly, there is the question of how to best bridge these patients. In this paper, there was a suggestion that patients bridged with RT had improved PFS as compared with patients bridged with systemic therapy. Because 69% of patients bridged with systemic therapy received cytotoxic chemotherapy, perhaps this is an indication that this may not be the optimal strategy for patients with chemorefractory disease. All patients in this series who had bridging with RT went on to receive CAR T cells as compared with only 74% of patients who had bridging with systemic therapy. Also of note, patients bridged with RT also had higher response rates than patients bridged with systemic therapy alone, though it is possible that patients selected for RT bridging had more limited disease. This may also partially explain why patients who received RT bridging had better outcomes than patients who received other types of bridging and had a 1-year PFS that was comparable to those select patients who did not require bridging therapy.

For patients who undergo bridging with RT, a second set of questions must be answered regarding the timing, the dose and fractionation, and the field size. At present, the most common practice is for the patient to undergo leukapheresis, followed by RT prior to infusion of the CAR T-cell product. Interestingly, in the MD Anderson series, 2 patients had leukapheresis after the start of RT but still went on to have successful manufacturing and infusion of the CAR T-cell product. The median time from leukapheresis to axicabtagene ciloleucel infusion was 29 days for all patients with no difference between the bridged and nonbridged patients; this was most certainly due to excellent coordination of care, which may not be as readily available at institutions with less CAR T-cell therapy experience.

The second question specific to RT bridging pertains to the optimal dose. Previously published series have used a variety of fractionation schemes including 3 Gy × 10 fractions and 4 Gy × 5 fractions with good tolerance and effect.[4] The benefit of a shorter course is that it facilitates fast treatment in the window between leukapheresis and CAR T-cell infusion. The disadvantage is that these doses may not be optimal to definitively treat aggressive non-Hodgkin lymphomas. This may be particularly relevant for patients who do not get any benefit from CAR T cells, whether from failed manufacturing or lack of antitumor effect. With adequate care coordination, some patients with more limited disease may benefit from comprehensive treatment using smaller fractions to standard doses of 36 to 40 Gy, as was done for many of the patients in the Pinnix et al series.

The last question specific to RT bridging is, How much disease should be treated? Should all of the disease be irradiated using a comprehensive RT field, as was done for 9 patients in this cohort, or should a focal RT field that excludes active disease be used instead? In the Pinnix et al series, 75% of patients treated focally progressed or relapsed, with the majority of these relapses in sites of active lymphoma excluded from the RT field. Although it conceptually makes sense to attempt to debulk disease as much as possible prior to CAR T-cell infusion, there are some potential pitfalls. Practically, the larger the field, the more concern there is for toxicity. Theoretically, there is the potential risk that without adequate antigen, patients may have inadequate T-cell activation, although the patients who were treated comprehensively in this cohort still did well. Additional research is needed to better evaluate how expansion is impacted when patients achieve a complete response prior to CAR T-cell therapy.[5]

Finally, there is the question of whether bridging therapy can decrease toxicity, specifically grade 3 or higher cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome. These toxicities are difficult and expensive to manage as well as potentially fatal. There were no deaths in the group receiving RT bridging although there were 7 deaths in the group receiving systemic therapy bridging, most commonly from septic shock. Notably, all of the patients who died of infectious complications had received cytotoxic chemotherapy bridging, an important observation in this group of heavily pretreated patients. Data are emerging from the University of Pennsylvania that tumor burden may affect the incidence of cytokine release syndrome, thus suggesting that adequate debulking with bridging therapy prior to CAR T-cell infusion may help to decrease acute toxicity.[6]

Although these initial data from Pinnix et al suggest a role for bridging therapy, and specifically bridging RT, prior to CAR T-cell therapy, the unknowns remain. The International Lymphoma Radiation Oncology Group (ILROG) has created an RT/CAR T-cell Consortium to study the questions highlighted by this series in a coordinated and collaborative way. Until more data are available, the most salient lesson learned appears to be that CAR T-cell candidates benefit from an early referral for care coordination, particularly if bridging therapy is being considered. A silver lining in the era of the COVID-19 pandemic is the strengthening of virtual tumor boards and telemedicine capabilities. With reduced barriers to multidisciplinary care and tertiary referrals to expert centers, CAR T-cell therapy will hopefully be optimized for each patient, whether via appropriate bridging or the decision to pursue CAR T-cell therapy at all.

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