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The Bottom Line

Late Events After CD-19 CAR-T Treatment

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Conventional therapy for patients with relapsed/refractory CD19$^+$ lymphomas and leukemias has unacceptably low long-term progression-free survival. Enthusiasm for using CD19 chimeric antigen receptor (CAR) T cell therapy for treating these patients is based on the impressive results in patients with Acute B Lymphoblastic Leukemia (complete response [CR] rates ≥70% in multiple trials) and Diffuse Large B-cell Lymphoma (DLBCL) (82% response rate/54% CR rate) [1,2]. These results have led to Food and Drug Administration approval for tisagenlecleucel (Novartis, Basel, Switzerland) for pediatric acute lymphoblastic leukemia (ALL) and adult DLBCL patients and axicabtagene ciloleucel (Kite-Gilead, Los Angeles, USA) for adults with DLBCL. A great deal of attention has been paid to the acute toxicities of CD19 CAR T cell therapy—namely, cytokine release syndrome and Immune Effector Cell-associated neurotoxicity syndrome, including their identification, grading, and management [3,4]. However, as experience with CD19-directed T cell therapy has grown, there is an increased awareness of the long-term adverse events. The article by Cordeiro et al. [5] fills an important gap in the literature by reporting on long-term adverse events in a cohort of patients with a variety of B cell malignancies (ALL, non-Hodgkin lymphoma, or chronic lymphocytic leukemia) treated with CD19 CAR T cells in a single-site phase I/II study (NCT01865617). The authors limited their analysis to a cohort of patients who survived at least a year after receiving CAR T cell therapy and excluded all patients who had subsequent lines of therapy, including allogeneic stem cell transplant. They defined long-term adverse events as complications developing after or persisting beyond day 90 following CAR infusion. Their analysis found that 16% of patients with ongoing CR had prolonged cytopenias lasting 15.2 to 21.7 months compared with 0% in the non-CR group. The cumulative incidence of hypogammaglobulinemia (HGG) was 74% in the CR group and 61% in the non-CR group. Late infections where reported for 54 patients, 23 with multiple infections. The rate of secondary malignancies was 15%, including 6 nonmelanoma skin cancers, 4 myelodysplastic syndromes, 1 melanoma, 1 noninvasive bladder cancer, and 1 multiple myeloma. The authors reported an 8% rate of immune-related events, categorized as lymphocytic alveolitis, skin rash, eosinophilic pneumonia, pneumonitis not otherwise specified, granulomatous disease not otherwise specified, persistent flu-like syndrome, and collagenous colitis. Graft-versus-host disease (GVHD) was reported in 3 patients (out of a total 15 who had previous allogeneic stem cell transplant before CAR infusion), all of whom were in CR. Neurologic and psychiatric events were reported in 10% of patients (n = 9), including 3 cerebrovascular accidents, 1 transient ischemic attack, Alzheimer dementia and peripheral neuropathy (2 patients developed both entities), and 8 patients with psychiatric events (4 newly diagnosed and 4 with exacerbation of previously known psychiatric diagnoses).

During the longitudinal care of CAR T cell patients, it is of great importance that clinicians increase their awareness of the long-term complications associated with CD19 CAR T cells. Most physicians experienced in treating patients with hematologic malignancies often encounter treatment-related cytopenias, HGG, persistent infections, secondary malignancies, immune-related phenomenon, and GVHD. However, the neurologic/psychiatric issues that can arise months to years after CAR T cell therapy are a concern. Currently, no guidelines exist to assist clinicians in the long-term care of CAR T cell patients, whether it is the surveillance plan for future malignancies/immune-related events/GVHD, the optimal management of persistent cytopenias/HGG, or how to screen for and address late-onset neurologic/psychiatrics issues. In the absence of committee-based guidelines, developing institutional practices to optimize CD19 CAR T cell patient care is critical. Certain institutions, including ours, model the care plan for CD19 CAR T cell patients after the care plan for autologous stem cell transplant patients. All patients considered for CAR T cell therapy have psychologic evaluations before CAR T cell infusion and regular follow-up to monitor for emerging neurologic or psychiatric events.

The real question is how the CD19 CAR T cell therapy can be improved to retain the high clinical response rates while limiting both short- and long-term adverse events [9]. Therefore, it is best to consider the adverse events associated with the preparative chemotherapy regimen separately from the CD19 CAR T cell adverse events. There are reports in animal models

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of strategies to maintain T cell persistence following adoptive transfer without the need for lymphodepletion [6,7]. Such strategies, if proven to not reduce the efficacy of the CD19 CAR T cells, would reduce any long-term non-B cell cytopenias, potential for secondary bone marrow-related malignancies, and the overall cost of the CD19 CAR T therapy. However, most investigators in the field have focused on strategies to improve the safety of the CD19 CAR T cells themselves [8,9]. There is clear evidence that the choice of CAR construct costimulatory cassette impacts the persistence and function of CAR T cells [10-12]. CD19 CAR T cell persistence is the likely culprit for many of the late-term adverse events reported by Cordeiro et al. [5], especially the persistent HGG as well as the late onset of infections, immune-related events, and neurologic/psychiatric events. One solution to long-term T cell persistence would be including a suicide gene into the vector [13-17]. However, early elimination of the CD19 CAR T cells could promote disease relapse. Alternatively, CAR constructs have been developed that require targeting more than CD19 alone to activate the CAR T cells, which should preserve normal B cells and eliminate HGG [18,19]. Another promising approach is to use universal CAR T cells [20,21]. Universal CAR T cells themselves persist long term but only function after they are loaded with a receptor/antibody in vivo. This single-site report by Cordeiro et al. [5] raises concerns about critical late adverse events in CD19 CAR T cell patients, but solutions are on the horizon. Further investigation using a larger patient cohort and other clinical grade CD19 CAR construct use by other investigators is required to improve the safety of CD19 CAR T cell therapy.

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