FDA-mandated CAR-T monitoring period could be halved, say researchers

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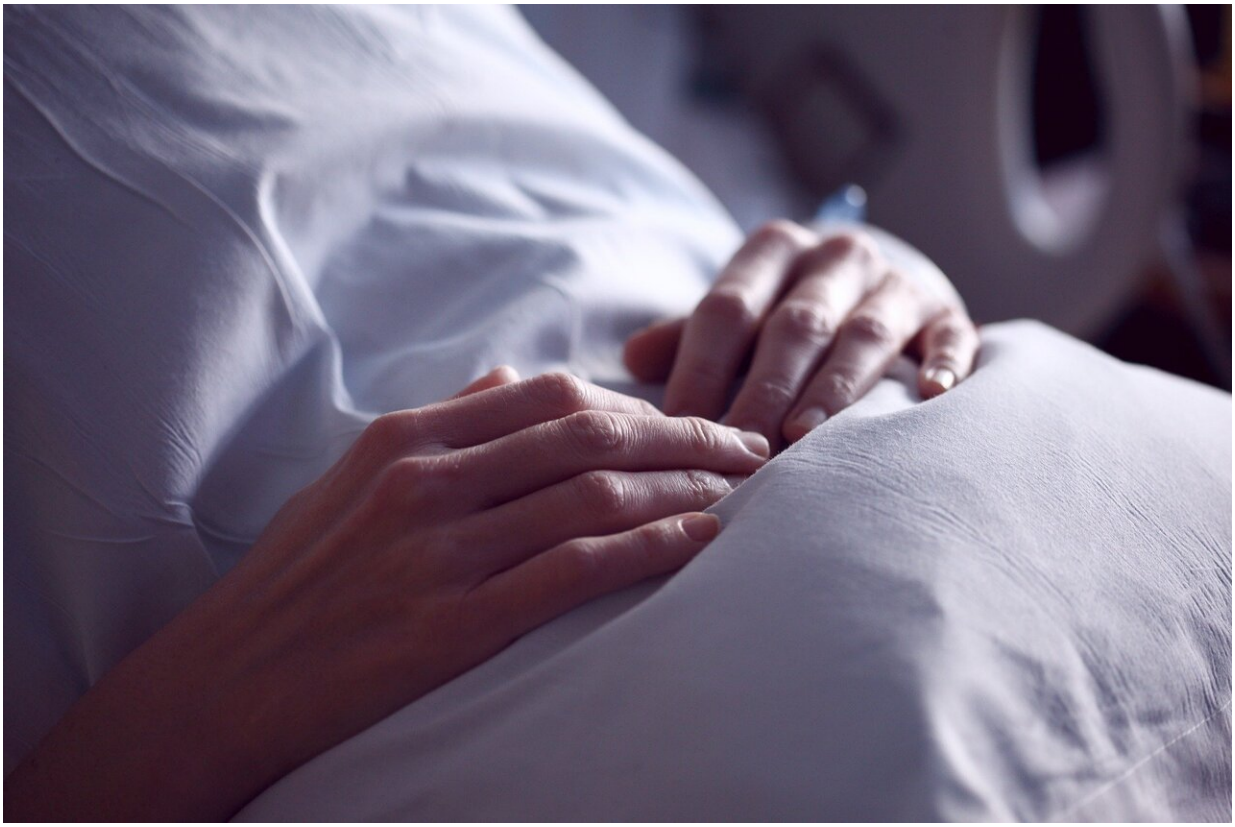

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In patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCL), the two hallmark post-chimeric antigen receptor (CAR)-T therapy toxicities are extremely rare after two weeks, supporting a shorter, more

flexible toxicity monitoring period, according to a study published in Blood Advances.

Currently, three CAR T-cell therapies—axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel)—are approved for treating DLBCL, a cancer that affects the white blood cells responsible for producing antibodies. However, patients receiving these therapies are at high risk of developing either cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS).

CRS is characterized by fever, as well as low blood pressure and/or oxygen levels in more severe cases. ICANS may cause temporary effects such as altered mental status and confusion, or even loss of consciousness and/or seizures in more severe cases. Both toxicities can also result in rapid decline and death.

To monitor and manage these toxicities, the U.S. Food and Drug Administration (FDA) established a Risk Evaluation and Mitigation Strategy (REMS) mandating that recipients of CAR-T therapy remain within a two-hour distance of their authorized treatment center (ATC) for four weeks after therapy and refrain from driving for eight weeks post-treatment.

Most ATCs have even stricter criteria than those directed by the REMS, requiring patients to stay within a 30- to 60-minute radius of their ATC and have a dedicated caregiver. In a recent study of 185 patients receiving CAR-T therapy, 65% lived more than 30 minutes away from the closest ATC.

"As a clinician that administers CAR-T, I've had many patients who have not been able to receive it because of barriers to access," said study author Nausheen Ahmed, MD, associate professor of hematologic

malignancies and cellular therapeutics, assistant director of cellular therapeutics, and medical director of the BMT Survivorship Program at the University of Kansas Medical Center.

"I have patients who are traveling for six or even eight hours to get treatment."

In a retrospective study across nine treatment centers, Dr. Ahmed and her colleagues investigated the onset and duration of CRS, ICANS, and other non-relapse causes of death post-CAR-T therapy to determine if the monitoring period and driving restriction might be shortened to increase treatment accessibility.

The first-of-its-kind study investigated 475 patients who underwent infusion therapy between March 2018 and May 2023. Of the 475 patients evaluated, 216 (45%) received axi-cel, 158 (33%) received tisa-cel, and 101 (21%) received liso-cel. Most of the study participants (69.8%) received CAR-T as third-line or later therapy.

Across all patients, the incidence of any grade of CRS was 60%, while the incidence of any grade of ICANS was 32.4%. In the first seven days after CAR-T infusion, new-onset CRS occurred in 57.5% of patients and new-onset ICANS occurred in 25.4%.

During the eight- to 12-day period following treatment, 5.4% of patients experienced new-onset CRS and 9.3% experienced new-onset ICANS. After 12 days post-infusion, there were no recorded cases of new-onset CRS and only one case of new-onset ICANS reported in a tisa-cel recipient.

The study showed that most patients who developed CRS or ICANS did so within the first two weeks following infusion. After this period, no new-onset CRS cases were reported and only 0.7% of patients exhibited

new-onset ICANS.

According to the researchers, these results support downgrading from the standard four-week monitoring period to a two-week one (with the option to extend, dependent on patient status), as well as instituting a shorter driving restriction.

Results also showed that after two weeks, infections, which developed in 14.5% of patients within the 28 days post-infusion, were the most common cause of death.

Two infection-related deaths occurred in the first 28 days following CAR-T infusion, while five such deaths were reported between days 29 and 90. Bacterial infections were most common during the period closely following CAR-T infusion, while viral infections were most prevalent after four weeks post-infusion.

"We are learning that infection may be driving a lot of the non-relapse mortality and toxicity within the first few months after CAR-T infusion, so we have to shift our focus to preventing and managing infections after those two weeks," Dr. Ahmed said. To do this, she suggested a hybrid model of care, which would also shorten the restriction periods for patients.

"Instead of the ATC trying to keep the patient locally for a long time, we could collaborate with and train community hematologists/oncologists and referring physicians to identify, initiate treatment for, and collaborate with the ATC to manage infections and other less common side effects."

Shortening restriction periods can help mitigate the challenges associated with CAR-T therapy for both patients and their families, as well as prevent patients from having to resort to more accessible therapies when

CAR-T could be curative, Dr. Ahmed said.

This could make an especially big difference in the lives of patients from minority backgrounds and of lower socioeconomic status, who are disproportionately affected by barriers to access, she added.

Studies have shown that 25% to 60% of patients eligible for CAR-T therapy must relocate during the required REMS monitoring period, depending on their ATC's requirements. Further, treatment-adjacent expenses are not always covered by insurance or the ATC.

There were a few limitations to the study. Each ATC had individual guidelines that influenced patient eligibility and management of CRS and ICANS, and some variables were unable to be captured, including late-onset neutropenia and hypogammaglobulinemia, patient-reported outcomes, and caregiver education practices. Additionally, the study was limited to patients with DLBCL and the therapies tested.

The researchers have published similar results in a study of the CAR-T therapies idecabtagene vicleucel and ciltacabtagene autoleucel for the treatment of multiple myeloma.

More information: *Blood Advances* (2024). ashpublications.org/bloodadvan … dadvances.2023012549

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