

CAR T-Cell Therapy and Secondary T-Cell Malignancies: What the Data Reveal

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Chimeric antigen receptor (CAR) T-cell therapies have transformed the treatment landscape for certain hematologic malignancies. However, recent post-marketing reports have raised questions about the potential for secondary T-cell malignancies. This article summarizes the current understanding and regulatory perspective on this emerging concern.

KEY TAKEAWAYS

- **The Pivot:** The FDA is investigating a potential risk of secondary T-cell malignancies, including lymphomas, following CAR T-cell therapy, prompting a label update for all approved products.
- **The Data:** As of January 2024, fewer than 20 confirmed cases of secondary T-cell malignancies have been reported globally among hundreds of thousands of patients treated.
- **The Action:** Clinicians should monitor patients receiving CAR T-cell therapy for new malignancies and report any suspected cases to the FDA and manufacturers.

Background on CAR T-Cell Therapy and Emerging Concerns

Chimeric antigen receptor (CAR) T-cell therapies are a type of immunotherapy that involves genetically engineering a patient's own T cells to recognize and attack cancer cells. These therapies have demonstrated significant efficacy in treating specific B-cell lymphomas, multiple myeloma, and B-cell acute lymphoblastic leukemia that are refractory to other treatments or have relapsed¹. Six CAR T-cell products are currently approved by the U.S. Food and Drug Administration (FDA) for various indications.

In late 2023, the FDA announced an investigation into reports of secondary T-cell malignancies, including T-cell lymphoma and leukemia, in patients who had received CAR T-cell therapy. This led to a class-wide label change requiring manufacturers to add a warning about the risk of secondary primary T-cell malignancies and to conduct 15-year follow-up studies for all patients treated with these products¹.

Regulatory Oversight and Data Collection

The FDA's Center for Biologics Evaluation and Research (CBER) maintains a robust post-marketing surveillance system for all approved biological products, including CAR T-cell therapies. This system includes adverse event reporting databases, such as the FDA Adverse Event Reporting System (FAERS), and mandatory long-term follow-up studies for gene therapy products¹. Manufacturers are required to submit annual reports on safety and efficacy, and any serious adverse events must be reported promptly.

The current investigation into secondary T-cell malignancies is part of this ongoing surveillance. The FDA is actively

collecting and evaluating all available information from clinical trials, post-marketing reports, and real-world data sources to understand the incidence, characteristics, and potential mechanisms of these events¹.

Reported Cases and Incidence

As of January 2024, the FDA has identified fewer than 20 confirmed cases of secondary T-cell malignancies globally among patients treated with CAR T-cell therapies. These cases include both T-cell lymphomas and T-cell leukemias. It is important to note that hundreds of thousands of patients have received CAR T-cell therapy worldwide since the first approval in 2017¹.

The reported cases represent a very small fraction of the total patient population treated. The latency period between CAR T-cell infusion and the diagnosis of a secondary T-cell malignancy has varied, with some cases occurring several years post-treatment. The specific CAR T-cell product involved, the underlying primary malignancy, and prior treatments are all factors being considered in the analysis of these events¹.

Potential Mechanisms Under Investigation

The exact mechanism by which CAR T-cell therapy might contribute to secondary T-cell malignancies is not yet fully understood and is a key area of investigation. Several hypotheses are being explored:

- **Insertional Mutagenesis:** The viral vectors used to introduce the CAR gene into T cells could potentially integrate into the host genome in a way that disrupts tumor suppressor genes or activates oncogenes, leading to malignant transformation. However, current vector designs are generally considered to have a low risk of insertional mutagenesis¹.
- **Chronic T-cell Activation/Dysregulation:** Persistent activation or dysregulation of T cells due to the CAR construct itself or the chronic inflammatory environment could potentially contribute to malignant transformation over time.
- **Pre-existing Clonal Hematopoiesis:** Patients receiving CAR T-cell therapy often have a history of extensive prior treatments, including chemotherapy and radiation, which can predispose them to secondary malignancies. Pre-existing clonal hematopoiesis, a common age-related phenomenon, could also play a role.
- **Off-target Effects:** While CAR T-cells are designed to target specific antigens, there is a theoretical possibility of off-target effects or unintended consequences of the genetic modification.

The FDA emphasizes that the CAR T-cells themselves are not always the source of the secondary malignancy; in some cases, the malignancy may arise from the patient's endogenous T cells¹.

Clinical Implications and Monitoring

Given the potential for secondary T-cell malignancies, clinicians should maintain a high index of suspicion and monitor patients who have received CAR T-cell therapy for signs and symptoms of new malignancies. This includes routine follow-up, physical examinations, and appropriate diagnostic testing if clinically indicated. Any suspected cases of secondary T-cell malignancies should be reported to the FDA and the respective product manufacturers¹.

Why this matters for clinical practice today

While the absolute number of reported secondary T-cell malignancies remains low relative to the number of patients treated, this emerging safety signal warrants careful attention. Clinicians should be aware of the updated prescribing information for all approved CAR T-cell products and integrate long-term monitoring for new malignancies into their post-treatment surveillance protocols. It is crucial to balance the significant benefits of CAR T-cell therapy for

life-threatening cancers against this potential, albeit rare, long-term risk. Open communication with patients about these risks and the importance of ongoing follow-up is essential for informed decision-making and patient safety.

Limitations and Future Directions

The primary limitation of the current understanding is the rarity of these events, which makes it challenging to establish a definitive causal link and fully elucidate the underlying mechanisms. Further research is needed to determine the true incidence, identify potential risk factors, and understand the pathogenesis of these secondary malignancies¹.

The FDA's requirement for 15-year follow-up studies will be crucial in gathering more comprehensive long-term safety data. Continued collaboration between regulatory agencies, academic researchers, and pharmaceutical companies will be essential to monitor these events, refine risk mitigation strategies, and ensure the safe and effective use of CAR T-cell therapies¹.

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1. Verdun N, Marks P. Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy. N Engl J Med. 2024;390(7):584-586. doi:10.1056/NEJMp2400209

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