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VIEWPOINT

T-Cell Lymphoma From CAR T-Cell Therapy—A New Safety Notice

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On November 28, 2023, a concerning safety signal was announced by the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research. Several patients undergoing chimeric antigen receptor (CAR) T-cell therapy for pediatric acute lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma developed T-cell lymphoma. The lymphoma in question contains the CAR construct, meaning that the drug product itself has transitioned into a malignancy. This finding, although rare (the FDA has yet to release the number of reports), has significant implications for all CAR T-cell therapy development programs. Herein is outlined what is known, residual uncertainties, and implications.[1]

The FDA's acknowledgment of a safety concern represents an important regulatory event. It is probable the T-cell lymphomas in question are causally related to infusion of the CAR T-cell product, given that the genetic signature of the construct is easily detectable in the malignant clone. That this has occurred for all approved CAR T-cell products suggests it is a class effect and not confined to the specific manufacturing process of a single company or the specific costimulatory domain of a single CAR T-cell therapy.[1] In fact, the FDA suspects this will be true for all CAR T-cell therapies that use integrating vectors, such as retroviral or lentiviral vectors, although admittedly, it may not occur for ongoing investigational products that use RNA, resulting in only transient expression of the CAR.

> Although rare, the malignant transformation of a cellular therapy is a concerning safety signal, and diligent efforts should be made to monitor it, ascertain the true incidence, and research efforts to avoid the risk.

The real incidence remains unknown but must be rare. Reports of CAR T-cell transformation remain scarce in the reported literature. Tens of thousands of products must have been administered since the original approval of tisagenlecleucel in 2016.[2] One preliminary analysis found just 12 cases of T-cell lymphoma reported in 17 700 infusions, a rate of 0.068%.[3] Yet this may be an underestimate because sequencing is unlikely to be universally performed when a subsequent T-cell lymphoma is observed.

The net effect of CAR T-cell therapy for approved indications likely remains favorable.[1] For diffuse large B-cell lymphoma, randomized data show that some CAR T-cell products result in improved overall survival over autologous stem cell transplant.[4] This fact alone means that any harms of CAR T-cell therapy must be smaller than benefits. Yet notably for myeloma, overall survival was not improved (to date) in randomized trials, nor in mantle cell lymphoma or follicular lymphoma. Some caution is required for cancer types that lack randomized data showing mortality benefit. Some investigators are studying CAR T-cell therapy in premalignant cases, such as smoldering myeloma (NCT05767359). These investigations should proceed with utmost caution, given potential to harm patients with lengthy life expectancy.

For forthcoming CAR T-cell products, approvals would ideally be based on data from randomized clinical trials. Initial approvals of tisagenlecleucel and other CAR T-cell therapies were based on nonrandomized data in pediatric acute lymphocytic leukemia, diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. Single-arm trials allow for these products to be offered earlier to patients who have exhausted all other options. Likely a greater reliance on randomized clinical trials is needed in confirmatory trials, permitting conversion from accelerated to regular approval, particularly because the product is offered earlier in disease courses.

The risk-benefit of CAR T-cell therapy pursued in noncancer indications or cancer with long survival times is entirely uncertain. With added time, the propensity for the cellular product to transform into malignancy—particularly if it is persistent—will increase. For diseases with short survival times, such as the aforementioned, it is likely the net benefit of CAR T-cell therapy will be positive, but for diseases such as lupus[5] or myasthenia gravis in which CAR T-cell therapy is being assessed, it is likely that harms may swell with decades of follow-up.

It is commendable that the FDA issued the safety alert promptly. Therapy with CAR T cells remains a promising avenue of investigation (**Table**),[6] and studies in patients with cancer and short life expectancy should not be halted. Yet patients should provide additional consent to acknowledge this risk. Drug development in noncancer conditions requires reassessment by institutional review boards pending better characterization of the risk.

Further biological studies are needed to understand the mechanism of malignant transformation and whether it can be abrogated by so-called kill switches or other mechanisms to remove or destroy the CAR T cells

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Table. Pivotal Trials Testing CAR T-Cell Therapies Leading to FDA Approval for Hematologic and Oncologic Indications

Trial	Product	Tumor type	Primary end point	Overall survival results	Response rate, %
KarMMa	Idecabtagene vicleucel	Multiple myeloma	ORR	NA	72
TRANSCEND	Lisocabtagene maraleucel	Large B-cell lymphoma	ORR	NA	73
TRANSFORM	Lisocabtagene maraleucel	Large B-cell lymphoma	EFS	Median OS: NR vs 16.4 mo (HR, 0.51; 95% CI, 0.26-1.00; *P* = .03)	86
PILOT	Lisocabtagene maraleucel	Large B-cell lymphoma	ORR	NA	80
ELARA	Tisagenlecleucel	Follicular lymphoma	CRR	NA	86
JULIET	Tisagenlecleucel	Large B-cell lymphoma	ORR	NA	50
ELIANA	Tisagenlecleucel	B-cell ALL	ORR	NA	83
ZUMA-1	Axicabtagene ciloleucel	Large B-cell lymphoma	ORR	NA	72
ZUMA-2	Brexucabtagene autoleucel	Mantle cell lymphoma	ORR	NA	87
ZUMA-3	Brexucabtagene autoleucel	B-cell ALL	Overall complete remission or complete remission with incomplete hematologic recovery	NA	65
ZUMA-5	Axicabtagene ciloleucel	Follicular lymphoma	ORR	NA	91
ZUMA-7	Axicabtagene ciloleucel	Large B-cell lymphoma	EFS	Median OS: NR vs 31.1 mo (HR, 0.73; 95% CI, 0.54-0.98; *P* = .03)	83
CARTITUDE-1	Ciltacabtagene autoleucel	Multiple myeloma	ORR	NA	98

Abbreviations: ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CRR, complete response rate; EFS, event-free survival; FDA, Food and Drug Administration; HR, hazard ratio; NA, not applicable; NR, not reported; ORR, overall response rate; OS, overall survival.

after infusion and response. Some non-DNA methods of CAR engineering are ongoing,[7] and these may better optimize the benefit-to-harm balance of CAR T-cell therapy.

The announcement by the FDA of the safety signal that the CAR T-cell product can itself become a cancer is a noteworthy step in the history of this product. This ability appears to be a class effect, affecting all products and approvals. Although rare, the malignant transformation of a cellular therapy is a concerning safety signal, and diligent efforts should be made to monitor it, ascertain the true incidence, and research efforts to avoid the risk. Many lives have been saved by CAR T-cell therapy and the product likely retains a net benefit in most approved indications.

ARTICLE INFORMATION

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