COMMENTARY

blood advances

TO THE EDITOR:

Answering the "Doctor, can CAR-T therapy cause cancer?" question in clinic

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On 28 November 2023, the Food and Drug Administration (FDA) released a statement regarding T-cell malignancies in recipients of chimeric antigen receptor T-cell (CAR T) therapies for hematologic malignancies.[1] Per media reports, the FDA is aware of 20 cases of T-cell malignancies in CAR T recipients of an estimated denominator exceeding 30 000 patients with large B-cell lymphoma (LBCL), multiple myeloma (MM), and other lymphoid malignancies.[2,3] The same week, an online-only abstract for the 2023 American Society of Hematology (ASH) meeting was published describing a case of T-cell lymphoma diagnosed 5 months after ciltacabtagene autoleucel (cilta-cel) for relapsed/refractory (R/R) MM. More than 90% of the cells in this patient's lymph node biopsy were CAR positive, but whole-exome sequencing showed a clonal loss-of-function *TET2* mutation unrelated to the *PBX2* gene in which CAR insertion had predominantly occurred.[4]

Many news organizations have already reported on the FDA's statement, with 1 headline in a leading newspaper declaring "Innovative Cancer Treatment May Sometimes Cause Cancer, FDA Says."[5] Many of our patients, both those who have already received CAR T therapy as well as those who may consider CAR T therapy in the near future, will likely see media coverage regarding the FDA statement or the ASH abstract. This includes patients being treated at community practices who are considering referrals to CAR T–capable centers. How can we best discuss the issue of second primary malignancies (SPMs) after CAR T therapy with our patients in light of these new updates?

We suggest a 3-part response that summarizes both the evidence we have at hand and the evidence we would need to see to confirm such an association between CAR T therapy and SPMs (Table 1). As a starting point for discussion, the benefits of CAR T therapy continue to far outweigh their risks in the setting of R/R malignancies. In several randomized studies, CAR T therapy has been associated with improved progression-free survival and/or overall survival.[6-10] Given the "one-and-done" nature of CAR T infusions coupled with their potential for rapid and durable remissions, several trials have also shown that CAR T outperforms standard therapies in terms of meaningful improvements in quality of life.[11,12] Even if one assumes a causal relationship with secondary T-cell malignancies to be true, 20 cases among tens of thousands of CAR T recipients represent a small risk relative to the potential benefit.

As a second point to discuss with patients, several other factors can explain why our patients develop SPMs. Pretransplant conditioning, bendamustine, and lenalidomide have all been associated with SPMs in large studies.[13,14] If one extrapolates from registry data analyzed through 2017, a longitudinal cohort of 25 000 patients with LBCL (similar to the current number of CAR T recipients for this B-cell malignancy)[3] would include 30 patients who developed secondary T-cell malignancies in the pre–CAR T era.[15] In MM, cilta-cel's package insert was recently updated to note that 10 of 97 patients in the CARTITUDE-1 trial had developed secondary myeloid malignancies with extended follow-up.[16] However, >95% of CARTITUDE-1 participants had received prior lenalidomide, a drug known to predispose patients to myeloid malignancies through its effects on hematopoietic progenitor cells.[17,18] In general,

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Table 1. Suggested discussion framework regarding SPMs after CAR T therapy

Discussion point	Supporting evidence
The benefits of CAR T therapy generally outweigh the risks	• CAR T therapy has been shown to extend PFS, OS, and QOL compared with traditional therapies in several cancers. • CAR T therapy offers a "one-and-done" treatment for patients with the potential for rapid and durable remissions.
A causal association is possible but many confounders exist	• Many other factors, including prior alkylating chemotherapy and immortal time bias, need to be examined carefully. • The presence of neoplastic CAR$^+$ T cells does not itself prove that the CAR "caused" the malignancy.
Patients' active cancers are often a bigger threat than a hypothetical cancer years later	• Even in patients who develop SPMs, their original malignancy can remain a cause of death. • T-cell malignancies are heterogenous, and some (e.g., T-LGL) may have excellent prognoses even if they occur.

OS, overall survival; PFS, progression-free survival; QOL, quality of life; SPM, second primary malignancy; T-LGL, T-cell large granular lymphocytic leukemia.

clonal hematopoiesis of indeterminate potential is present in 20% to 60% of patients at baseline before receiving CAR T.[19-21]

As future SPM case-control analyses emerge in coming years, the broad principle of immortal time bias must also be taken into account. Patients can only develop SPMs if they do not first die of their primary malignancies; as such, patients who receive effective cancer therapies will have higher rates of SPMs than patients who do not. This phenomenon explains why patients who do develop SPMs are paradoxically more likely to have achieved complete responses or to have lived longer than patients with MM who do not develop SPMs.[22,23] A way to word this confusing principle to patients might be: "even if studies someday show that those who do get CAR T develop a second cancer at higher rates than those who do not, this may be because CAR T allows for patients to live long enough that other issues might develop. To put it simply, one needs to be alive to be diagnosed with cancer."

That being said, the risk of T-cell malignancies from ex vivo gene therapy was first recognized more than 15 years ago.[24,25] Vector technology has advanced considerably since then, with large analyses showing no evidence of replication-competent lentivirus in the modern era.[26]

However, CAR T therapy requires lymphodepletion with drugs such as fludarabine that are known to increase the risk of SPMs.[27,28] Clonal (nonmalignant) CAR T expansion has rarely been observed due to vector insertion into oncogenes or tumor suppressor genes.[29,30] As a result, SPMs have already been a routine component of physician-patient CAR T discussions. In 2021, a phase 1 study of allogeneic CAR Ts (using a transposon platform not found in any FDA-approved therapies) was suspended after 2 patients developed CAR$^+$ T-cell lymphomas.[31] Subsequent analyses implicated high transgene copy numbers per cell rather than CAR insertion as a key factor associated with oncogenesis.[32] In the newly reported ASH abstract describing a T-cell lymphoma after cilta-cel,[4] workup revealed several acquired mutations (not due to CAR insertion) as well as a germline heterozygous *JAK3* p.V722I variant previously associated with T-cell lymphomagenesis.[33,34] As such, even the presence of neoplastic CAR$^+$ T cells does not itself prove that the CAR "caused" the malignancy.

As a third and final point to discuss with concerned patients, the active cancer at hand is generally a much larger threat than a hypothetical cancer years later. Patients with MM who develop SPMs after autologous transplantation are more likely to die from their underlying myeloma than from their SPMs, even in patients who specifically develop hematologic SPMs.[35] In an international discrete-choice study of patients designed to simulate the benefits vs serious risks of CAR T therapy (with the caveat that SPMs were not specifically queried), increasing the probability of 1-year survival was the most important factor to patients.[36] Even in the rare event that an SPM develops, not all T-cell malignancies are created equal. Certain types such as T-cell large granular lymphocytic leukemia are associated with excellent prognoses, whereas other types may be amenable to novel targeted therapies in the future.

We expect continued research to identify and operationalize "genomic safe harbors" for CAR insertion to add further layers of safety to this already safe process.[37,38] In the interim, registry-based studies will shed more light on risk factors of SPMs in CAR T recipients. The FDA already mandates 15 years of follow-up data in CAR T recipients,[39] a requirement that adequately minimizes the risk of patients being "lost to follow-up" before SPM diagnosis. Given the fivefold higher risk of T-cell malignancies in patients with LBCL than the general population (regardless of CAR T therapy),[15] any suspicious post–CAR T lesions should be biopsied to evaluate for malignant T cells even if a LBCL recurrence is suspected. Any treatment-emergent T-cell malignancies should be reported immediately, analyzed for presence of the CAR transgene, and sent for integration analyses and clonality testing.[1,39] Other testing should include vector copy number analyses, whole-genome sequencing of the malignancy and (if possible) unmanipulated leukapheresis product, and evaluation for preinfusion clonal hematopoiesis of indeterminate potential.

Until findings with this level of evidence are available, we suggest caution with drawing any definitive conclusions from the FDA's statement. This updated information should be included in discussions with patients considering CAR T therapy, particularly for trials of CAR T in earlier lines or nonmalignant indications for which the risk/benefit ratio is less certain. However, for patients and referring physicians who are concerned by recent news headlines suggesting that CAR T may cause cancer, we recommend cautious reassurance. Given the aforementioned confounders, current evidence does not support any significant new risk of T-cell malignancies in CAR T recipients. Although further research is ongoing, the benefits of CAR T therapy clearly outweigh the risks in patients with hematologic malignancies and should not be understated.

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