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GENE THERAPY

Comment on Elsallab et al, page 2099

Data mining for second malignancies after CAR-T

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In this issue of *Blood*, Elsallab et al report data mining and analysis of the Adverse Event Reporting System (FAERS) of the US Food and Drug Administration (FDA) to evaluate second primary malignancies after therapy with the 6 autologous chimeric antigen receptor T-cell (CAR-T) products currently approved by the FDA to treat CD19$^+$ leukemia and lymphoma and B-cell maturation antigen–positive myeloma.[1] The impetus for this analysis was an announcement by the FDA in November 2023 of an investigation on the risk of T-cell malignancies after CAR-T therapies and a subsequent report that the FDA was aware of 22 cases of T-cell cancers that occurred after treatment with commercial CAR-T products.[2] For 3 cases in which genetic sequencing was available, the CAR transgene was detected in the malignant clone, raising the possibility that gene transfer may have contributed to development of the T-cell malignancy.[2]

The report raised some questions. The Center for International Blood and Marrow Transplant Research, which has received follow-up data on >11 000 recipients of commercial CAR T cells, only had 3 reported T-cell malignancies, with none having expression of the CAR construct.[3] Similarly, 2 published reports evaluating incidence of secondary malignancies with CD19 CARs or investigational products did not indicate increased risks of subsequent malignancy in patients treated with genetically modified T cells compared with a control group of patients.[4,5] None of the patients who developed new malignancies, including 1 patient with T-cell lymphoma, had the transgene detected in tumor cells.[4] More recently, a study from the University of Pennsylvania reported a case of peripheral T-cell lymphoma in a patient diagnosed 3 months after infusion of axicabtagene ciloleucel.[6] The CAR transgene copies in the tumor biopsy were very low and next-generation sequencing analysis revealed that the malignant clone was present beforer the CAR-T infusion.[6] Another abstract report from the 2023 Annual Meeting of the American Society for Hematology described a CAR$^+$ T-cell lymphoma after treatment with ciltacabtagene autoleucel. The report concluded that the lymphoma could have been driven by genetic mutations, some of which may have been present before manufacturing.[7] In both cases, inflammation after CAR-T infusion may have contributed to the T-cell lymphomagenesis.

To provide additional information, Elsallab et al took advantage of the publically available FAERS database to quantify second primary malignancies after CAR-T therapies. They found that second primary malignancies were reported in 536 of 12 394 (4.3%) adverse events after CAR-T therapies in FAERS. Myeloid and T-cell neoplasms were disproportionately more frequent, with 208 reports of myelodysplasia and 106 reports of acute myeloid leukemias. The authors also identified 19 cases of T-cell malignancies (17 non-Hodgkin lymphoma and 2 T-cell large granular lymphocytic leukemia cases).

Patients eligible to receive the current commercial CAR products are mostly heavily pretreated for their underlying CD19$^+$ lymphoid malignancies or myeloma, and the risks of second malignancies are well defined in these populations. For example, patients with B-cell lymphoma have a 4.7-fold higher standardized incidence ratio of developing a second primary T-cell lymphoma.[8] In addition, clonal hemopoiesis is often present in patients before receiving CAR-T therapies and may expand during CAR-T cell treatment.[9,10]

Elsallab et al also identified 19 cases of T-cell malignancies in FAERS, whereas the FDA report indicates being aware of 22 cases.[2] This discrepancy illustrates that, although the FAERS database provides information on data on adverse events reported to the FDA, there are limitations to these data, as outlined on the FDA website. In particular, the information should not be used to estimate the incidence (occurrence rates) of the events reported due to issues such as duplicate report submissions, missing information, inability to establish causal relationships, and reporting bias. For example, a T-cell malignancy may be more likely to be reported to the FDA after CAR therapy than other types of cancer.

In conclusion, Elsallab and colleagues have provided additional information on the numbers of second malignancies reported after CAR therapies; however, we need additional data on the reported cases of T-cell malignancy to determine the true incidence and identify any cases in which the CAR product may have been a driver for the second malignancy. Clearly, the overall benefits of commercial CAR products for eligible patients continue to outweigh the potential risks. Nevertheless, it also illustrates the importance of long-term follow-up for CAR

recipients and the value of enrolling patients in prospective registries, such as the Center for International Blood and Marrow Transplant Research. This will allow us to determine the incidence and outcomes of second malignancies as has been done for patients who receive an allogeneic hemopoietic stem cell transplant.

Conflict-of-interest disclosure: H.E.H. has equity in Allovir and Marker Therapeutics, and has served on advisory boards for Tessa Therapeutics, GSK, and Fresh Wind Biotechnologies. ■

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