Umyarova *et al.*
Journal of Hematology & Oncology (2025) 18:30
https://doi.org/10.1186/s13045-025-01676-4

Journal of
Hematology & Oncology

CORRESPONDENCE

Open Access

Second primary malignancies following CAR T-cell therapy in patients with hematologic malignancies

Elvira Umyarova[1*], Charles Pei[1], William Pellegrino[1], Qiuhong Zhao[1], Nidhi Sharma[1], Don Benson[1], Francesca Cottini[1], Evandro Bezerra[1], Jonathan Brammer[1], Naresh Bumma[1], Hannah Choe[1], Nathan Denlinger[1], Srinivas Devarakonda[1], Abdullah Khan[1], Sam Penza[1], Ashley Rosko[1], Sumithira Vasu[1], Sarah Wall[1], Lapo Alinari[1], Robert Baiocchi[1], David A. Bond[1], Beth Christian[1], Walter Hanel[1], Kami Maddocks[1], John Reneau[1], Yazeed Sawalha[1], Alma Habib[1], Audrey Sigmund[1], Timothy J. Voorhees[1], Marcos de Lima[1] and Narendranath Epperla[1,2*]

Abstract

Chimeric antigen receptor T-cell (CAR-T) therapy has transformed the management of patients with relapsed/refractory (R/R) hematologic malignancies, including B-cell lymphomas and multiple myeloma (MM). While data pertaining to the efficacy and toxicity associated with CAR-T have been widely reported, there are limited data on long-term complications. We retrospectively analyzed 246 patients treated with CAR-T for R/R B-cell lymphoma (n = 228) and MM (n = 18) at Ohio State University from 2016 to 2022, with a minimum of two years of follow-up. The median age was 66 years, and the median number of prior treatments was four. With a median follow-up of 38 months (range 11–66), 21 patients (8.5%) developed a second primary malignancy (SPM), with non-melanoma skin cancer being the most common (52%), followed by hematologic malignancies (33%) and non-skin solid tumors (14%). Squamous cell carcinoma accounted for 38% of skin cancers, while myelodysplastic syndrome and acute myeloid leukemia were the predominant hematologic malignancies. Solid tumors included bladder, prostate, and breast cancer. The distinct pattern of SPMs suggests potential CAR-T-related risks, warranting vigilant post-treatment surveillance. Further studies are necessary to elucidate underlying mechanism and predictive factors and guide long-term management of SPM risk in CAR-T survivors.

Keywords Second primary malignancies, SPM, CAR-T, LBCL, MM

To the Editor,

Chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized the treatment of relapsed/refractory (R/R) hematologic malignancies, including B-cell acute lymphoblastic leukemia, B-cell lymphomas, and multiple myeloma (MM). The durable remissions associated with CAR-T in these challenging cases have established it as a transformative option for patients with limited

*Correspondence:
Elvira Umyarova
Elvira.Umyarova@osumc.edu
Narendranath Epperla
naren.epperla@hci.utah.edu
[1] Division of Hematology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA
[2] Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84103, USA

alternatives [1]. There are limited data regarding the long-term complications of CAR-T particularly second primary malignancies (SPMs) with varied incidence rates and different duration of post-CAR-T follow-up across studies [2–6].

We conducted a retrospective analysis of adults (≥18 years) with R/R B-cell lymphoma or MM treated with CAR-T at Ohio State University from January 1, 2016, to September 1, 2022 with a minimum of two years of post-CAR-T follow-up. A total of 246 patients were included in the study (n = 228 R/R lymphoma and n = 18 R/R MM). With a median follow-up of 38 months (range 11–66), 21 patients (8.5%) developed SPMs (Table 1). The median age at CAR-T infusion was 66 years (range 28–76), with a median of four prior lines of therapy (range 2–23). The most commonly used CAR-T product was axicabtagene ciloleucel (57%). The median time between the administration of CAR-T cells and the diagnosis SPM was 2.1 years (range 0.4–4.8).

Among 21 patients who developed SPM, non-melanoma skin cancer was the most frequently observed SPM, occurring in 52% (11/21) of the cases (Table 2). Of these, 8 patients (38%) developed squamous cell carcinoma, 2 patients (10%) had basal cell carcinoma, and 1 patient (5%) had undifferentiated skin cancer. Figure S1 outlines the detailed breakdown of risk factors. This predominance of skin cancers may suggest an increased vulnerability in CAR-T recipients, potentially linked to factors such as prior radiotherapy, chemotherapy, or chronic immunosuppression post-CAR-T.

Table 1 Characteristics of Patients Who Developed SPMs After CAR-T Therapy

Characteristics	N = 21 (%)
Age at CAR-T (in years), median (range)	66 (28–76)
Number of lines of therapy prior to CAR-T, median (range)	4 (2–23)
Sex	
Male	14 (67)
Female	7 (33)
Disease type	
LBCL*	14 (67)
SLL/CLL transformed to DLBCL**	2 (10)
MCL	2 (10)
MM	2 (10)
PMBCL	1 (5)
Prior HSCT	8 (38)
LD chemotherapy	
Fludarabine + Cyclophosphamide	21 (100)
CAR-T product	
Axicabtagene ciloleucel	12 (57)
Tisagenlecleucel	4 (19)
Idecabtagene vicleucel	2 (10)
Brexucabtagene autoleucel	2 (10)
Lisocabtagene maraleucel	1 (5)

SPM—second primary malignancies, LBCL—large B-cell lymphoma, MCL—mantle cell lymphoma, MM—multiple myeloma, CLL—chronic lymphocytic leukemia, PMBCL—primary mediastinal B cell lymphoma, HSCT—hematopoietic stem cell transplantation

* LBCL includes DLBCL, NOS (n = 10), HGBL (n = 1), and transformed lymphomas (FL transformed to DLBCL, n = 3)

** Richter's transformation

Table 2 Second Primary Malignancy type

SPM	N = 21 (%)
Skin cancers	11 (52)
Squamous cell carcinoma	8 (38)
Basal cell carcinoma	2 (10)
Undifferentiated skin cancer	1 (5)
Hematologic malignancies	7 (33)
Myelodysplastic syndrome	4 (19)
Acute myeloid leukemia	2 (10)
Plasmacytoma	1 (5)
Solid tumors	3 (14)
Bladder cancer	1 (5)
Prostate cancer	1 (5)
Breast cancer	1 (5)

SPM- second primary malignancies

Hematologic malignancies were the second most common type of SPM, observed in 7 patients (33%). These included myeloid disorders such as myelodysplastic syndrome (MDS) in 4 patients (19%) and acute myeloid leukemia (AML) in 2 patients (10%). Additionally, one patient developed plasmacytoma. The occurrence of secondary hematologic malignancies is a recognized risk in patients who have received prior cytotoxic therapies or HSCT, making it challenging to disentangle the specific contribution of CAR-T versus prior treatments. It is possible that CAR-T therapy itself may exert selective signaling on hematopoietic cells or promote clonal hematopoiesis, thereby increasing the risk for secondary hematologic malignancies.

Solid organ tumors, excluding skin, were relatively rare, occurring in 14% (3/21) of patients with SPMs. There was one case each of bladder cancer, prostate cancer, and breast cancer. Although the small number of solid tumors limit definitive conclusions, these cases highlight the need for comprehensive long-term follow-up in CAR-T treated patients, considering the potential for cumulative cancer risks related to previous therapies, age, and other comorbidities.

The incidence of SPMs observed in our cohort is in line with prior studies evaluating second malignancy risk in other heavily pretreated cancer populations [5, 6]. However, the distinct pattern of SPMs, dominated by

skin cancers and hematologic malignancies may point to unique risk factors in the CAR-T treated population. The high rate of skin cancer in particular may warrant heightened dermatologic screening in survivors of CAR-T. Additionally, identifying predictive markers for the development of hematologic SPMs, such as the presence of clonal hematopoiesis of indeterminate potential (CHIP), could provide valuable insight for risk stratification and management.

It remains crucial for clinicians to maintain a high index of suspicion for new malignancies in CAR-T survivors, particularly those with extensive treatment histories. As CAR-T continues to be integrated into earlier lines of therapy and new indications emerge, further research will be necessary to clarify its long-term safety profile and guide optimal post-treatment surveillance strategies.

The study is limited by retrospective design and lack of detailed molecular methodologies such as single-cell transcriptome sequencing, etc. to explore the correlation and pathogenesis of CAR-T therapy and SPMs.

In conclusion, our study demonstrates an 8.5% incidence of SPMs in a cohort of patients treated with CAR-T for R/R aggressive lymphomas and MM and adds to the growing body of SPMs post-CAR-T literature. The predominance of skin cancers and hematologic malignancies highlights the importance of vigilant long-term follow-up. Further studies are needed to identify predictive factors and clarify the pathophysiology behind SPM development in this patient population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-025-01676-4.

Additional file 1.

Acknowledgements
Not applicable.

Author contributions
Conception and design: NE and EU Financial support: None Collection and assembly of data: CP and WP Data analysis: QZ, EU, and NE Interpretation: All authors Manuscript writing: First draft prepared by EU and NE. CP, WP, QZ, NS, DB, FC, EB, JB, NB, HC, ND, SD, AK, SP, AR, SV, SW, LA, RB, DAB, BC, WH, KM, JR, YS, AH, AS, TV, and MDL provided critical and insightful comments. Final approval of manuscript: EU, CP, WP, QZ, NS, DB, FC, EB, JB, NB, HC, ND, SD, AK, SP, AR, SV, SW, LA, RB, DAB, BC, WH, KM, JR, YS, AH, AS, TV, MDL, and NE.

Funding
Not applicable.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional review board at OSU and was conducted in compliance with the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

Received: 24 December 2024 Accepted: 16 February 2025
Published online: 18 March 2025

References

1. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. Nat Rev Clin Oncol. 2023;20(6):359–71.
2. Verdun N, Marks P. Secondary cancers after chimeric antigen receptor T-cell therapy. N Engl J Med. 2024;390(7):584–6.
3. Elsallab M, Ellithi M, Lunning MA, et al. Second primary malignancies after commercial CAR T-cell therapy: analysis of the FDA adverse events reporting system. Blood. 2024;143(20):2099–105.
4. Shen J, Hu R, Lin A, et al. Characterization of second primary malignancies post CAR T-cell therapy: real-world insights from the two global pharmacovigilance databases of FAERS and VigiBase. EClinicalMedicine. 2024;73:102684.
5. Tix T, Alhomoud M, Shouval R, et al. Second primary malignancies after CAR T-cell therapy: A systematic review and meta-analysis of 5,517 lymphoma and myeloma patients. Clin Cancer Res. 2024;30(20):4690–700.
6. Lorenc R, Shouval R, Flynn JR, et al. Subsequent malignancies after CD19-targeted chimeric antigen receptor T cells in patients with lymphoma. Transplant Cell Ther. 2024;30(10):990–1000.

Publisher's Note