377 DECADE-LONG EPITHELIAL CANCER REMISSIONS FROM CELLULAR THERAPY

[1]Scott M Norberg*, [1]Stacey Doran, [2]Krishnamurthy Subramanian, [2]Riya Joshi, [2]Antara Biswas, [2]Yoke-Chen Chang, [3]Sarah Radford, [1]Liang Cao, [1]Zhigang Kang, [1]James L Gulley, [2,4]Cristina Montagna, [2,4]Jian Cao, [2,4]Christian S Hinrichs. *[1]National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; [2]Rutgers Cancer Institute, New Brunswick, NJ, USA; [3]Duncan and Nancy MacMillan Cancer Immunology and Metabolism Center of Excellence, Rutgers Cancer Institute, New Brunswick, NJ, USA; [4]Rutgers Robert Wood Johnson Medical School, Piscataway, NJ, USA*

Background T-cell therapies have demonstrated curative potential in hematologic malignancies and melanoma, but not in epithelial cancers, the most common malignancy type. Here, we report ongoing complete tumor responses in two patients with metastatic cervical cancer 10 years after a single treatment with tumor-infiltrating lymphocytes (TIL) (NCT01585428). We investigated long-term T cell persistence, antigen heterogeneity, and antigen processing and interferon response pathway integrity in these responses.

Methods Two patients treated with TIL therapy for cervical cancer were assessed for evidence of cancer by computed tomography imaging and circulating cell-free tumor DNA (ccfDNA) 10 years post-treatment.[1] The long-term persistence of previously defined tumor-antigen-specific T cell clonotypes in peripheral blood was determined by T cell receptor repertoire sequencing.[2] The intratumoral heterogeneity of the antigens targeted by TIL and of gene alterations in antigen processing and interferon response pathways were assessed by genomic and transcriptomic sequencing and computational clonal architecture reconstruction.

Results Both patients demonstrated no evidence of disease at 10-year follow-up. Following infusion, tumor-antigen-specific T cell clonotypes expanded rapidly, peaked after 3-4 months, and then contracted to below baseline frequencies by 1-2 years.[2] Longitudinal analysis revealed negligible levels without re-expansion through 10 years. Clonotype response kinetics were similar regardless of CD4 versus CD8 subset, target antigen class, and antigen epitope. Tumor architecture analysis of four distinct tumor regions from a patient who received TIL targeting both neoantigens and HPV antigens revealed intratumoral heterogeneity with branched clonal evolution. Although the immunodominant TIL reactivity was against neoantigens [2], the targeted neoantigen mutations showed heterogeneity. One neoantigen mutation (ALDH1A1 N150I) was clonal, while two others (SETDB1 E21D and METTL17 E279K) were subclonal. However, clonal ALDH1A1 N150I did not show transcriptional expression, whereas the subclonal SETDB1 E21D and METTL17 E279K did. An examination of potential immunotherapy resistance genes showed a subclonal NLRC5 mutation in a single allele in 1 of 4 tumor regions and subclonal partial copy loss of B2M and JAK2 in 2 of 4 tumor regions.

Conclusions T cell therapy mediated ongoing 10-year complete tumor responses in cervical cancers supporting that the approach can be curative in epithelial malignancies. Anti-tumor T cell expansion and contraction without ongoing elevated persistence was sufficient for decade-long tumor response. Heterogeneous, partial alterations in potential immunotherapy resistance genes did not prevent complete tumor regression.

REFERENCES

1. Stevanović S, Draper LM, Langhan MM, Campbell TE, Kwong ML, Wunderlich JR, *et al*. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J Clin Oncol Off J Am Soc Clin Oncol*. 2015 May 10;**33**(14):1543–50.
2. Stevanović S, Pasetto A, Helman SR, Gartner JJ, Prickett TD, Howie B, *et al*. Landscape of immunogenic tumor antigens in successful immunotherapy of virally induced epithelial cancer. *Science* 2017 Apr 14;**356**(6334):200–5.

http://dx.doi.org/10.1136/jitc-2025-SITC2025.0377