Specific components of the tumor immune microenvironment may affect responses to BCMA CAR T-cell therapy

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Patients with myeloma whose tumor immune microenvironments had a more diverse baseline T-cell repertoire, fewer markers of immune cell

exhaustion, and distinct changes to immune cell populations were more likely to have longer progression-free survival (PFS) after treatment with BCMA-targeted T-cell therapy, according to results published in *Blood Cancer Discovery*.

The findings were concurrently presented at the International Myeloma Society Annual Meeting, held August 25–27, 2022.

"Two CAR T-cell therapies targeting the B-cell maturation antigen (BCMA) are now approved for the treatment of myeloma, but the challenge is that many of the responses to this therapy are not durable, and patients remain at risk for recurrence," said senior author Madhav Dhodapkar, MBBS, a professor at the Emory University School of Medicine and the director of the Center for Cancer Immunology at the Winship Cancer Institute of Emory University.

"A key goal in the field is to identify the factors that influence the durability of response so that we can improve treatment accordingly," he added.

In this study, which was a collaboration between teams at Emory University and the University of Pennsylvania (Penn), Dhodapkar and colleagues, including co-first authors Kavita Dhodapkar, MD, of Emory University and Adam Cohen, MD, of Penn, analyzed 28 pre- and post-treatment bone marrow samples from 11 patients who had clinical responses to BCMA-targeted CAR T-cell therapy in a previously reported phase I clinical trial led by Cohen and colleagues.

Samples were analyzed by single-cell approaches, including CITE-Seq, transcriptomics, mass cytometry, and T-cell receptor sequencing. Changes to the bone marrow microenvironment were compared between patients with short and long PFS (defined as less than six months and greater than six months, respectively).

Dhodapkar and colleagues found that in patients with long PFS, the proportion of T cells in the bone marrow increased after treatment, while myeloid cell proportions decreased. These changes were not observed among patients with short PFS. A higher proportion of myeloid cells may have contributed to recurrence in those patients by promoting cancer growth and/or suppressing antitumor immunity, Dhodapkar suggested.

The researchers also found that post-treatment CAR and non-CAR T cells from patients with long PFS had a distinct genomic signature with lower expression of immune checkpoint genes and other genes associated with T-cell exhaustion compared with those from patients with short PFS. Furthermore, T cells from patients with long PFS had higher expression of genes associated with bone marrow retention.

Baseline features were also associated with PFS: Greater T-cell receptor diversity, higher tumor expression of interferon response genes and mature plasma genes, and lower tumor expression of genes associated with epithelial-to-mesenchymal transition were observed in the pre-treatment samples from patients with long PFS.

"The major finding of this study is that the durability of response may be dependent on characteristics of non-CAR T cells and other immune cells in the tumor microenvironment," said Dhodapkar, noting that prior studies on response durability tended to focus on features of the CAR-T cells themselves. "This finding has broad implications for the CAR T-cell therapy field, as it emphasizes the importance of the patient's preexisting immune microenvironment as a determinant of durable responses."

Understanding the baseline factors that impact durable responses may allow clinicians to identify the patients who are most likely to benefit from BCMA-targeted CAR T-cell therapy, he explained. Moreover, the

results introduce opportunities to study combination therapies that target some of the markers or cell types associated with relapse.

A commentary simultaneously published in *Blood Cancer Discovery* noted that "the study by Dhodapkar and colleagues provides the first hints (and data set) that endogenous immunity may play a role in sustaining antitumor responses that are initiated by direct antitumor CAR T cells."

In the future, Dhodapkar and colleagues plan to utilize preclinical models to gain mechanistic insight into how the factors they identified affect response durability.

A limitation of the study is its small sample size. Dhodapkar noted that a larger, independent analysis is needed to confirm the findings, a point echoed by Cohen: "As a field, we need to pursue similar analyses of bone marrow cells from patients receiving commercially available BCMA-targeted CAR T-cell therapies to allow us to home in on those factors that remain most important for determining response durability," Cohen said.

An additional limitation is that immune cells were extracted from the bone marrow and examined externally, which precluded analysis of the spatial relationships between the cell types within the microenvironment.

More information: Kavita M. Dhodapkar et al, Changes in Bone Marrow Tumor and Immune Cells Correlate with Durability of Remissions Following BCMA CAR T Therapy in Myeloma, *Blood Cancer Discovery* (2022). DOI: 10.1158/2643-3230.BCD-22-0018

Charlotte E. Graham et al, CAR T cells Contend with Myeloma in the Bone Marrow Microenvironment, *Blood Cancer Discovery* (2022). DOI: 10.1158/2643-3230.BCD-22-0126

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