Clinical Trials

Major finding: Infusion of HPV-reactive tumor-infiltrating T cells can induce regression of metastatic cervical cancer.

Concept: T-cell HPV reactivity and frequency of HPV-reactive T cells in peripheral blood correlated with response.

Impact: Further evaluation of immunotherapy in patients with metastatic cervical cancer is warranted.

ADOPTIVE T-CELL THERAPY HAS CLINICAL ACTIVITY IN METASTATIC CERVICAL CANCER

Metastatic cervical cancer is a chemorefractory, generally incurable disease for which immunotherapy may hold promise because the vast majority of cervical cancers harbor immunogenic human papillomavirus (HPV) antigens. In an exploratory study in 9 patients with metastatic cervical cancer, Stevanović and colleagues evaluated whether a single intravenous infusion of autologous tumor-infiltrating lymphocytes enriched for those with reactivity against the HPV antigens E6 and E7 could induce tumor regression. Objective responses were observed in 3 of the 9 patients, including 2 patients who experienced complete regressions at all sites of disease and remained disease-free 15 and 22 months after treatment. No acute toxicity was observed, and the most common adverse events were hematologic and thought to be due to the single cycle of lymphocyte-depleting conditioning chemotherapy administered prior to adoptive T-cell transfer. Autoimmune adverse events were not observed and no patients experienced severe cytokine release syndrome. The frequency and degree of reactivity of HPV-reactive T cells, as measured by IFNγ production and CD137 upregulation, was highest in the 3 patients who experienced objective responses and was significantly correlated with clinical response overall. The responders also had the highest frequency of HPV-reactive T cells in their peripheral blood, and clinical response was correlated with the frequency of HPV-reactive T cells in the peripheral blood 1 month after adoptive T-cell transfer. The frequency of HPV-reactive T cells remained elevated in the responding patients at later timepoints after treatment, further suggesting that the adoptively transferred HPV-reactive T cells contributed to the clinical responses, although a role for infused tumor-infiltrating lymphocytes targeting different tumor antigens cannot be excluded. In addition to providing support for further evaluation of adoptive T-cell therapy in patients with metastatic cervical cancer, these results indicate that durable, complete responses to adoptive T-cell therapy can be achieved in an epithelial malignancy. ■

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 2015 Mar 30 [Epub ahead of print].

Leukemia

Major finding: Pharmacologic hyperactivation of SYK results in negative B-cell selection and cell death in ALL.

Concept: SYK activation above a maximum threshold engages a checkpoint to delete self-reactive B-cell receptors.

Impact: SYK hyperactivation may overcome drug resistance and improve survival in patients with Ph$^+$ ALL.

B-CELL RECEPTOR HYPERACTIVATION SUPPRESSES PRE-B LEUKEMOGENESIS

Negative selection of B cells with attenuated or hyperactivated B-cell receptor (BCR) signaling eliminates cells with nonfunctional or self-reactive BCRs to ensure an intermediate threshold of BCR signaling. Expression of the oncogenic BCR–ABL1 tyrosine kinase in Philadelphia chromosome–positive (Ph$^+$) acute lymphoblastic leukemia (ALL) results in constitutively active pre-BCR signaling, and most therapeutic strategies for ALL are aimed at inhibiting BCR–ABL1 signaling below a minimum threshold to induce cell death. Chen, Shojaee, and colleagues sought to determine whether pharmacologic hyperactivation of BCR signaling above a maximum threshold would elicit a negative selection checkpoint and result in the killing of ALL cells. Reactivation of immunoreceptor tyrosine-based activation motif–mediated pre-BCR signaling resulted in cell death in patient-derived Ph$^+$ ALL cells. In particular, expression of constitutively active SYK kinase was necessary and sufficient to stimulate cell death in pre-B ALL cells. In an effort to identify pharmacologic means to hyperactivate SYK, the authors found that the immunoreceptor tyrosine-based inhibitory motif (ITIM)–bearing receptors platelet/endothelial cell adhesion molecule 1, CD300A, and leukocyte-associated immunoglobulin-like receptor 1, which negatively regulate SYK, were upregulated in Ph$^+$ ALL and were associated with decreased overall and relapse-free survival. Deletion of ITIM-bearing receptors triggered pre-B ALL cell death *in vitro* and inhibited leukemia growth *in vivo*; genetic rescue experiments demonstrated that activation of protein tyrosine phosphatase nonreceptor type 6 (PTPN6) and inositol polyphosphate-5-phosphatase (INPP5D) by ITIM-bearing surface receptors was required for pre-B leukemogenesis in mice. Deletion of *Ptpn6* or *Inpp5d* or treatment with a small-molecule INPP5D inhibitor induced hyperactivation of SYK, resulting in subsequent cell death of patient-derived Ph$^+$ ALL cells, including tyrosine kinase inhibitor–resistant cells, and decreased leukemia burden in mouse models. In sum, these results suggest that hyperactivation of SYK engages negative selection of B cells and may be a viable therapeutic strategy to overcome drug resistance in Ph$^+$ ALL. ■

Chen Z, Shojaee S, Buchner M, Geng H, Lee JW, Klemm L, et al. Signaling thresholds and negative B-cell selection in acute lymphoblastic leukaemia. Nature 2015 Mar 23 [Epub ahead of print].