TCR gene therapy for HPV-associated epithelial cancers

Findings from a new study suggest that T-cell therapy is well tolerated and induces preliminary tumour regression in patients with human papillomavirus (HPV)-associated epithelial cancers.

For the phase 1/2 trial, Stacey Doran (National Cancer Institute, Bethesda, MD, USA) and colleagues treated 12 patients with metastatic HPV16-positive epithelial cancer who had previously received platinum-based therapy. Six patients had cervical cancer, four had anal cancer, one had oropharyngeal cancer, and one had vaginal cancer. All received autologous, genetically engineered T cells expressing a T-cell receptor (TCR) against HPV16 E6, at doses of 1×10^{9}, 1×10^{10}, 1×10^{11}, and $1–2\times10^{11}$ cells, a lymphodepleting conditioning regimen, and intravenous aldesleukin (720 000 IU/kg) infusion every 8 h. The primary objectives were to identify dose-limiting toxicities, when treatment would be stopped, and determine the maximum tolerated dose.

The patients received a median of 105×10^{9} (range $1–170\times10^{9}$) T cells. No dose-limiting toxicities were observed and the maximum tolerated dose was not established. The most common grade 3–4 adverse events were lymphopenia, neutropenia, and thrombocytopenia, which occurred in all patients, regardless of treatment group. "We gave doses in excess of 100 billion T cells per patient, far higher than what has been done with CAR T-cell therapy in haematological cancers, without being limited by cytokine storm or haemodynamic instability", explained coauthor Christian Hinrichs (National Cancer Institute).

1 month after treatment, all patients had high peripheral blood engraftment with E6 TCR T cells (median 30%, range 4–53). Two (17%) of 12 patients had objective tumour responses, one of whom had a complete regression of one tumour and partial regression of two tumours, which were subsequently resected. "We also gained some insight into resistance", said Hinrichs. One resistant tumour showed a frameshift deletion in interferon-γ receptor 1 and another showed loss of *HLA-A*02:01*.

Christian Ottensmeier (Southampton Experimental Cancer Medicine Centre, Southampton, UK) welcomed the findings. "The idea of targeting viral antigens that are not found in human cells is very appealing", he said. "It will be fascinating to see if the same patients who respond to T-cell therapy benefit from an anti-PD1 antibody." However, Ottensmeier was concerned that two patients had resistant tumours.

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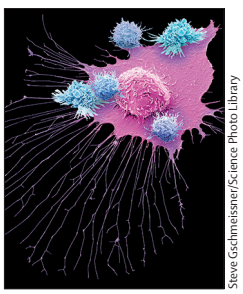

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For the **study by Doran and colleagues** see *J Clin Oncol* 2019; published online Aug 13. DOI:10.1200/JCO.18.02424