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BRIEF REPORTS

Activity of Mesothelin-Specific Chimeric Antigen Receptor T Cells Against Pancreatic Carcinoma Metastases in a Phase 1 Trial

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Pancreatic ductal adenocarcinoma (PDAC) is resistant to T-cell–mediated immunotherapy. We engineered T cells to transiently express a messenger RNA encoding a chimeric antigen receptor (CAR) specific for mesothelin, a protein that is overexpressed by PDAC cells. We performed a phase I study to evaluate the safety and efficacy of adoptive cell therapy with autologous mesothelin-specific CAR T cells (CARTmeso cells) in 6 patients with chemotherapy-refractory metastatic PDAC. Patients were given intravenous CARTmeso cells 3 times weekly for 3 weeks. None of the patients developed cytokine release syndrome or neurologic symptoms and there were no dose-limiting toxicities. Disease stabilized in 2 patients, with progression-free survival times of 3.8 and 5.4 months. We used ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography/computed tomography imaging to monitor the metabolic active volume (MAV) of individual tumor lesions. The total MAV remained stable in 3 patients and decreased by 69.2% in 1 patient with biopsy-proven mesothelin expression; in this patient, all liver lesions had a complete reduction in FDG uptake at 1 month compared with baseline, although there was no effect on the primary PDAC. Transient CAR expression was detected in patients' blood after infusion and led to expansion of new immunoglobulin G proteins. Our results provide evidence for the potential antitumor activity of messenger RNA CARTmeso cells, as well as PDAC resistance to the immune response.

Keywords: Immune Response Heterogeneity; Immune Therapy; Antitumor Immunity; Pancreatic Cancer Treatment.

Pancreatic ductal adenocarcinoma (PDAC) has demonstrated striking resistance to T-cell immunotherapy.[1–3] This resistance may reflect the lack of strong immunogenic neoantigens[4] in PDAC or ineffective priming of endogenous T cells in vivo.[5,6] To circumvent these issues, T cells can be synthetically modified to express a chimeric antigen receptor (CAR) that activates T cells on engagement with its cognate cell surface target protein.[7] However, the translation of CAR T cells to solid malignancies has been hampered by on-target off-tumor toxicities as a result of target antigen expression by normal healthy tissues.[8,9] To address this concern, we have used messenger RNA (mRNA) electroporation to engineer T cells to transiently express a CAR, so as to limit exposure and potential for toxicity. Here, we conducted a phase I study to evaluate adoptive cell therapy with autologous T lymphocytes (mesothelin-specific CAR T [CARTmeso] cells) genetically modified with mRNA to express a CAR recognizing mesothelin,[10] a protein that is overexpressed in most surgically resected PDACs[11,12] but also found on some normal tissues, including the lining of the peritoneum, pleura, and pericardium.

Six patients with chemotherapy-refractory metastatic PDAC received CARTmeso cells administered intravenously 3 times weekly for 3 weeks (Figure 1*A*, Supplementary Figure 1, and Supplementary Methods). Fifty-three of 54 planned CARTmeso cell infusions were administered. None of the patients experienced cytokine release syndrome or neurologic symptoms (Supplementary Table 1). There were no dose-limiting toxicities. Safety and tolerability of the infusions are described in Supplementary Methods.

The best overall response achieved with mRNA CARTmeso cells was stable disease by RECIST v1.1, with 2 patients (08212-100 and 08212-108) demonstrating progression-free survival lasting 3.8 and 5.4 months, respectively (Figure 1*B* and Supplementary Figure 1). We used ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography imaging to monitor the metabolically active volume (MAV) and maximum standardized uptake value of individual tumor lesions (Figure 1*C* and *D*). We found that the total MAV remained stable in 3

Abbreviations used in this paper: **CAR, chimeric antigen receptor; CARTmeso, mesothelin-specific CAR T cells; FDG, ^{18}F-2-fluoro-2-deoxy-D-glucose; IL, interleukin; MAV, metabolically active volume; mRNA, messenger RNA; PDAC, pancreatic ductal adenocarcinoma.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Chimeric antigen receptor (CAR)-modified autologous T cells are an effective way to target cancer cells particularly in hematological malignancies, but their application to solid malignancies such as pancreatic ductal adenocarcinoma (PDAC) remains ill-defined.

NEW FINDINGS

CAR T cells were safely administered to 6 PDAC patients with one patient showing a response in the liver, despite lack of activity against the primary lesion in the same patient.

LIMITATIONS

This study included a small cohort of patients, and CAR expression on autologous T cells was engineered to be transient, using mRNA electroporation for initial safety evaluation.

IMPACT

CAR T cells are a potentially valuable tool for evaluating mechanisms of immune resistance in PDAC.

patients but decreased by 69.2% in 1 patient (08212-113). For 08212-113, maximum standardized uptake value for all lesions was found to decrease with a complete reduction in FDG uptake seen in all liver lesions at month 1 compared with baseline, despite an increase in MAV within the primary pancreatic lesion (Figure 1*E* and *F*). This dramatic reduction in FDG uptake is atypical for the course of this disease and, thus, this observation is highly suggestive of the potential antitumor activity of mRNA CARTmeso cells.

CAR expression is transient in T cells when introduced as mRNA.[13] Consistent with this, we detected CAR transcripts transiently in the blood after each infusion in all patients (Figure 2*A*). To determine the impact of CARTmeso cell infusion on endogenous immune responses, we first examined serum cytokine levels within the peripheral blood after infusion. We found elevated levels of several inflammatory cytokines, including interleukin (IL)6, hepatocyte growth factor, IL1RA, and IL8, after starting therapy in patient 08212-113, but not in any of the other patients (Figure 2*B*). We also detected no significant levels of human anti-mouse antibodies in patients at baseline or at multiple defined time points after CARTmeso infusion. In contrast, human anti-chimeric antibodies were seen in some patients

A

Baseline patient demographics and clinical characteristics of treated patients		
Characteristic	**No.**	**Percent**
Age, years		
Median	61	
Range	50-71	
Sex		
Male	3	50%
Female	3	50%
ECOG PS		
0	4	67%
1	2	33%
Site of metastases		
Liver	2	33%
Lung	2	33%
Peritoneum	4	67%
No. of prior therapies		
1	0	0%
2	4	67%
≥3	2	33%

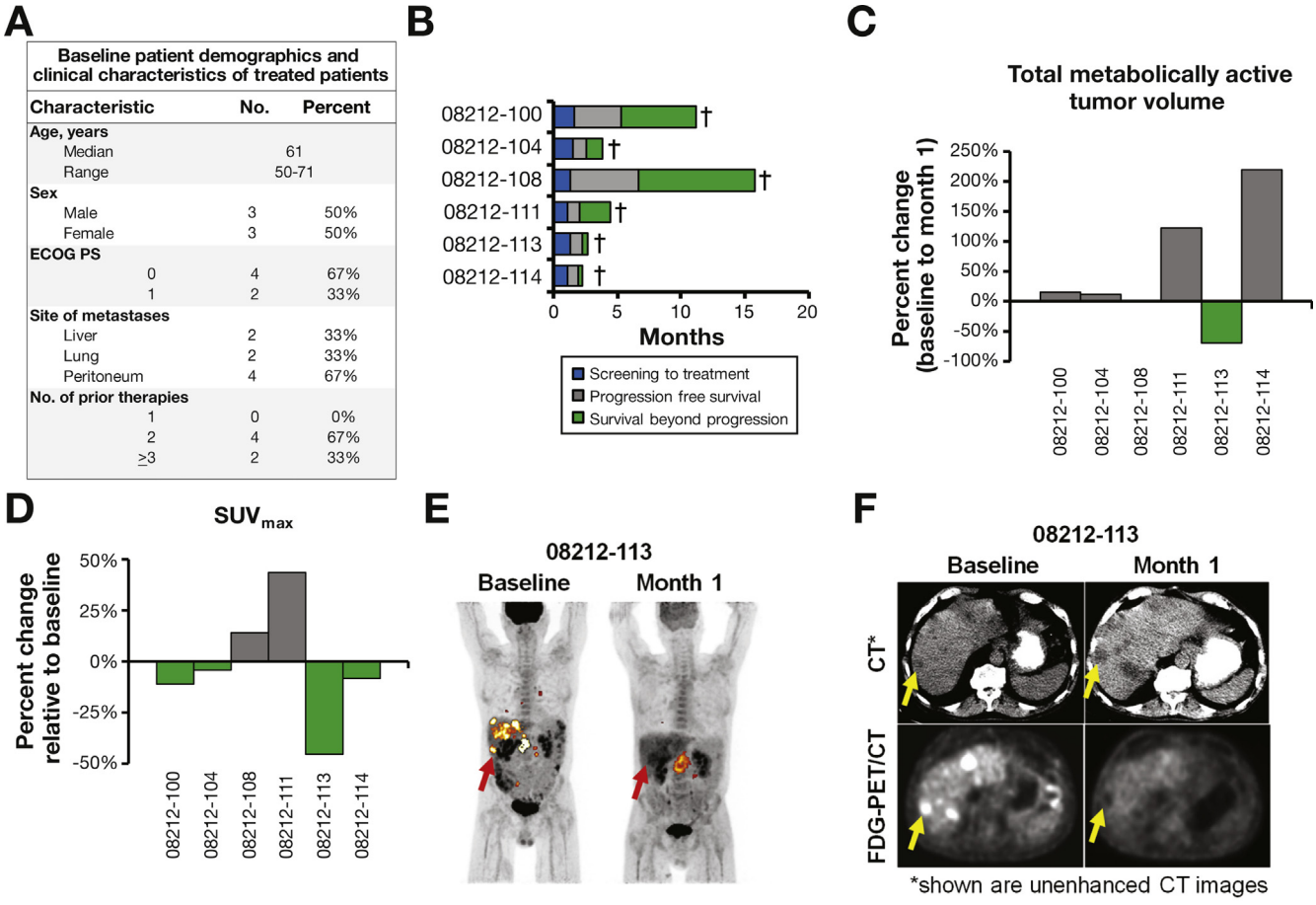

Figure 1. Clinical responses. (*A*) Baseline patient demographics. (*B*) Swimmer plot showing patient outcomes. Percent change at 1 month relative to baseline in (*C*) total MAV and (*D*) maximum standardized uptake value for tumor lesions detected using FDG–positron emission tomography/computed tomography (FDG-PET/CT) imaging. (*E*) Sequential coronal maximum intensity projection PET images and (*F*) sequential unenhanced CT and FDG-PET images for patient 08212-113. In (*E*), *red arrows* indicate liver and primary pancreatic lesions, respectively. In (*F*), *yellow arrows* mark a representative liver lesion.