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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Phase I First-in-Human Study on the Feasibility, Safety, and Antitumor Activity of CD4-Redirected Chimeric Antigen Receptor (CAR) T-Cell Therapy in Patients with CD4+ T-Cell Malignancies (TCM)

Rita Assi, MD¹, Nabil Hagag, PhD², Sherif Farag, MD PhD³, Robert V.B. Emmons, MD⁴, Allie Carter¹, Magdalena Czader, MDPHD⁵, Rafat Abonour, MD⁶, Lionel Apetoh, PhD⁷, Yupo Ma, MDPHD⁸, Huda S. Salman, MD PhD¹

¹Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

²State University of New York Stony Brook, Stony Brook, NY

³Melvin and Bren Simon Comprehensive Cancer Center, Division of Hematology and Oncology, Indiana University School of Medicine, Indianapolis, IN

⁴University of Louisville, Louisville, KY

⁵Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN

⁶IU Health University Hospital, Indiana University, Indianapolis, IN

⁷Indiana University Brown Center for Immunotherapy, Indianapolis, IN

⁸Stony Brook University Hospital, Stony Brook, NY

Background

TCM are aggressive diseases with poor outcomes. Translating the CAR T-cell therapy success from B-cell diseases to TCM has proven challenging. CD4 is an attractive therapeutic target, owing to its restricted expression on normal tissues. In this first-in-human phase I study, we investigate the autologous third generation CD4-redirected CAR T-cell safety, tolerability, manufacturing feasibility, trafficking and preliminary efficacy in patients with R/R CD4+ TCM who failed standard therapies.

Methods

The investigational construct is engineered with a single-chain variable fragment (ScFV) and dual co-stimulators (CD28; 4-1BB), fused to CD3zeta and CD8 leader sequence, packaged in lentivirus and transduced into T-cells. Patients received conditioning therapy with fludarabine and cyclophosphamide. CD4CAR product is administered in a 3+3 dose-escalation scheme. Dose-limiting toxicities (DLT) were monitored during the initial 42-days post-treatment. Treatment-emergent adverse events (AE) were graded by CTCAE v5.0

Results

Three patients with median age of 63 years (range, 18-68) were enrolled and treated at DL1 (2.0x10⁵/kg), including 2 (66%) women and 2 (66%) African-American. Median number of prior therapies was 3 (range, 2-4) (Figure). AEs included grade 3-4 hematologic toxicity in 3 (100%) patients, all present before enrollment. There was no protocol defined DLTs. All grade ≥3 lymphopenia reverted to grade 2 by day 30 and no related infections occurred between CAR infusion and hematopoietic stem cell transplantation (HSCT). Since infusion, the CAR T-cells percentage in peripheral blood had continued to expand. CD4CAR T-cells were detectable in all patients for at least 28 days post-infusion, meeting the primary endpoint, and on D111 in one patient. CD4CAR expansion was reflected on by a decrease in CD4/CD8 ratio and flow cytometry using ScFV Fab2 specific antibodies (Figure). Cytokine response analysis CD4CAR was associated with variable but significant production that seems to correlate with clinical responses (Figure; More data at meeting). No cytokine-mediated organ toxicities were observed. Bone marrow and peripheral blood flow cytometry confirmed complete remission (CR) in 2 patients at day 30 (PTCL and T-ALL). Patient 3 (mycosis fungoides) achieved hematological CR with stable skin lesions. Post-treatment day 30 skin biopsy demonstrated persistent disease with marked loss of CD4.

Conclusions

CD4CAR T-cell therapy is feasible in patients with R/R CD4+ TCM. 2/3 patients achieved CR and the third achieved hematological CR with stable skin disease. Toxicities were manageable without DLT upon completion of cohort 1. The cytokine response suggests immune activation and tumor recognition by CD4CAR T-cells. Dose escalation will proceed. NCT03829540

Disclosures Abonour: BMS, Janssen, Takeda: Consultancy; BMS, Janssen, Pfizer: Honoraria.

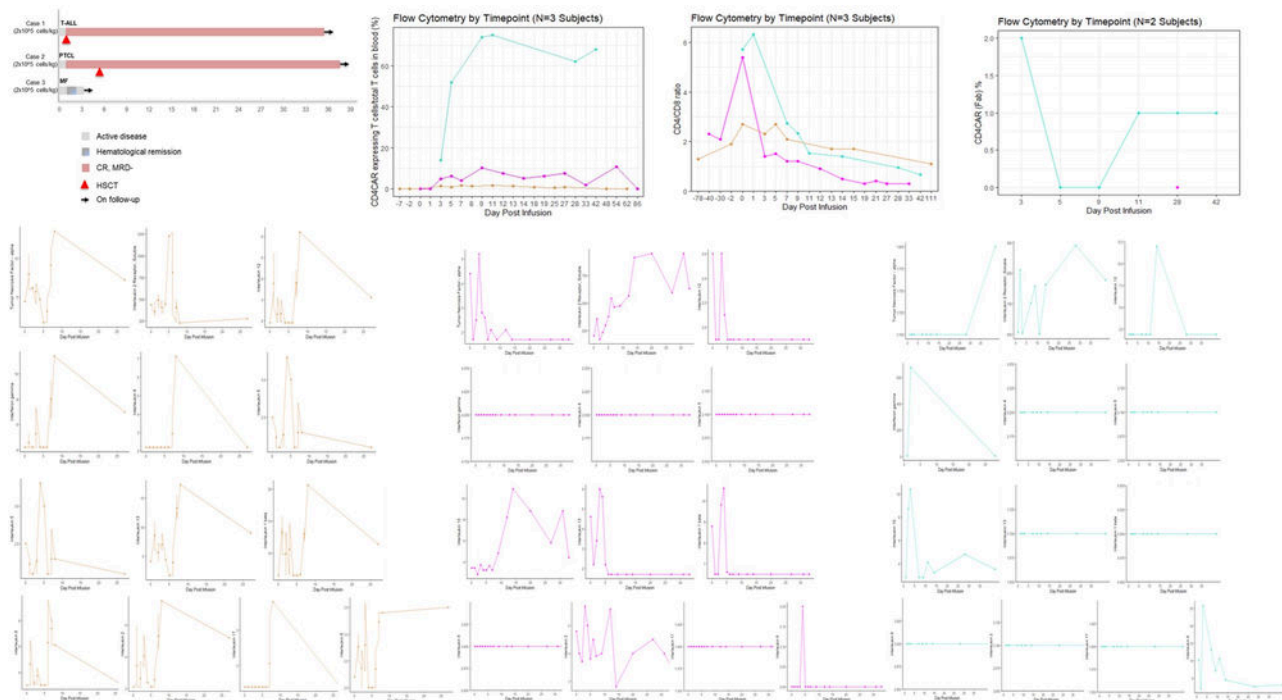


Figure 1

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