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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

CAR-T Cell Therapy in Patients with Refractory Systemic Autoimmune Diseases Exhibits Less Inflammation, Toxicities and Different Cellular Dynamics Compared to Patients with B Cell Lymphoma

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Chimeric antigen receptor (CAR) T-cell therapies have shown high efficacy in the treatment of B cell non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL) and are established as a standard treatment for patients with hematological malignancies. Aside from malignant B cells, autoreactive B cells can also cause great harm in patients with autoimmune diseases (AID), resulting in chronic inflammation, organ damage, and increased mortality. We have recently demonstrated that CD19-directed CAR-T cell therapy is feasible and effective in patients with refractory systemic lupus erythematosus (Mougiakakos et al, 2021; Mackensen et al., 2022), antisynthetase syndrome (Müller et al., 2023) and systemic sclerosis (Bergmann et al., 2023). Despite these promising data, there are many uncertainties in the treatment of AID patients with cellular therapies, which were primarily developed for the treatment of cancer patients.

Here, we analyzed the occurrence and severity of toxicities, inflammatory markers, and the cellular dynamics of 15 AID patients and 40 NHL patients undergoing CAR-T cell therapy. All patients were treated in our center with either commercial CAR-T cell products (Axicabtagenee ciloleucel, Tisagenlecleucel, Lisocabtagen maraleucel) or with the investigational medicinal product MB-CART19.1 (in-house manufactured 2 nd generation anti-CD19 CAR-T cells with a 4.1BB co-stimulatory domain; Kretschmann et al., 2023). Average peak expansion was reached at day 7 in both patient groups. Despite comparable average peak levels, patients with AID showed lower incidence and severity of cytokine-release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS) compared to the NHL cohort. Consistent with reduced toxicity, AID patients received less tocilizumab and glucocorticoid treatment. Bone marrow toxicity with severe and/or prolonged cytopenia is a frequent long-term CAR-T cell related adverse event. Of interest, AID patients demonstrated a less profound decrease of neutrophils, platelet counts, and hemoglobin after CAR-T cell therapy compared to NHL patients and a faster recovery to normal values. Occurrence and duration of severe neutropenia (<500 neutrophils/µl) also differed between both patient cohorts. There was no late bone marrow toxicity in AID patients, whereas 19 of 40 patients with NHL showed at least one > grade 3 blood count reduction. In line with the Hematotox-Score predicting bone marrow toxicity, baseline inflammation (e.g. C-reactive protein, ferritin) prior to CAR-T cell treatment was higher in lymphoma patients than in AID patients. While AID patients quickly returned to normal ferritin values, elevated ferritin levels often persisted in the NHL cohort after CAR-T cell therapy. Given that AID patients showed fewer late toxicity and lower long-term inflammation, we speculated that persistence of CAR-T cells was lower. In line, longitudinal monitoring of the patient's immune cells including CAR-T cell kinetics demonstrated a typical contraction of CAR-T cell numbers with low-level persistence in both cohorts. We did not observe a difference in absolute CAR-T cell numbers or dynamics within the first three months after treatment. In contrast to NHL patients in remission, AID patients did not develop long-term persistence of CAR-T cells as most patients lost CAR-T cells

within 1 year after cell infusion. Consistent with this observation, all AID patients showed B-cell reconstitution after loss of CAR-T cell persistence.
Taken together, we observed less toxicities and severe adverse events in AID patients than in NHL patients despite similar CAR-T cell expansion and dynamics. The lack of CAR-T cell persistence and the early recurrence of B cells in AID patients is so far not explained and could provide novel insights in the biological processes controlling long-term CAR-T cell persistence.

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