Results of ISIKOK-19 CAR T cell therapy in patients with relapsed/refractory acute lymphoblastic leukemia with extramedullary disease

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Short title: ISIKOK-19 CAR T cell in ALL with extramedullary disease

Background: The prognosis of relapsed/refractory acute lymphoblastic leukemia (ALL) patients with the extramedullary disease (EMD) is controversial. There is still no consensus and unmet medical need for these patients. Although several chimeric antigen receptor T cell products (CAR-T) have satisfactory response rates for bone marrow involvement, there is a lack of data about EMD.

Methods: A pilot clinical trial (NCT04206943) was designed to assess the safety and feasibility of ISIKOK-19 CAR-T therapy in patients with relapsed/refractory CD19-positive leukemia/lymphoma was conducted at Acıbadem Altunizade Hospital.

The academic CAR-T product presented in this study, ISIKOK-19, encodes the anti-CD19 CAR construct with the single-chain variable fragment (scFv) of an anti-CD19 monoclonal antibody (FMC63) conjugated with the CD8 hinge region, CD28 transmembrane (TM), and co-stimulatory domain, and the CD3ζ pro-activator signaling domain. Product characterization, in vivo expansion, and persistence of CAR-T were published before (Erdogan et al, 2022).

After a cyclophosphamide/fludarabine-containing lymphodepletion regimen, ISIKOK-19 CAR-T therapy was applied in three fractionated doses.

Results: A total of 15 patients (6 children, 9 adults) were enrolled in the ISIKOK-19 CAR-T study. Of this, 4 ALL patients (P1,P2,P3,P4) with the extramedullary disease were identified. The median age at infusion was 16 years (range, 5–22), including 2 pediatric patients.

The production phase was feasible with all the patients receiving the product within a median of two months from apheresis. The median total dose of ISIKOK-19 CAR-T was 4,7x10^6 CAR-T/kg (3,1-6,4 x10^6 CAR-T/kg) and all the products were applied in three fractions.

All the patients had cytokine release syndrome (CRS) and recovered. P1 and P2 who had grade 2 CRS needed tocilizumab treatment. Immune effector cell-associated neurotoxicity syndrome (ICANS) was observed only in P4 as grade 2 and this patient recovered after dexamethasone treatment. Besides CRS and ICANS, P4 had hemolytic anemia in the 4th month of CAR-T therapy and recovered after daratumumab treatment.

CAR-T was still detected in peripheral blood and CSF in P3 and P4 at 5 months and 6 months, subsequently. CAR-T was detected in peripheral blood in P1 and P2 until the subsequent HSCT (7 months and 3 months after CAR-T, respectively). B cell aplasia persisted for all the patients. All the patients had a response at the analysis of day 28. The breast involvement of P1 was significantly decreased at PET-CT and disappeared after 3 months. Bone marrow MRD was detected as negative for P1,P2, and P4. There were no residual blasts detected in the CSF analysis of P2, P3, and P4. Complete remission was still persistent for 12 months (P2) and 5 months (P3). P1 had an isolated bone marrow relapse after 13 months (received the second HSCT at the 7th month of CAR-T while in remission). P4 died due to infection in the 6th month of CAR-T while in remission for leukemia.

Patients	Age	Prior HSCT	Bridging Therapy	EMD Localization	Bone Marrow Involvement	Dose of ISIKOK-19	CRS/ICANS	Outcome
P1	22	yes	no	Breast	yes	6,4x10^6 CART/kg	CRS 2	Relapse after subsequent HSCT (CR in the 7th month of CART)
P2	5	no	no	CNS	yes	3,1x 10^6 CART/ kg	CRS 2	CR 12 months
P3	12	yes	yes	CNS	no	5,3 x10^6 CART/kg	CRS 1	CR 5 months
P4	20	yes	no	CNS	yes	4,1 x10^6 CART/kg	CRS 1/ICANS 2	Ex (CR in the 6th month of CART)

Conclusions: In conclusion, the administration of ISIKOK-19 CAR-T therapy in this small patient group with EMD achieved safety and efficacy outcomes. These preliminary results make us believe that ISIKOK-19 CAR-T constitutes a potential therapeutic option in such a high unmet medical need.

Clinical Trial Registry: A pilot clinical trial (NCT04206943) was designed to assess the safety and feasibility of ISIKOK-19 T-cell therapy in patients with relapsed/refractory CD19+ hematological malignancies.

Disclosures: "Nothing to declare"

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