Abstract: P1473

Title: CD7.PEBL-CART FOR PATIENTS WITH RELAPSED/REFRACTORY T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Abstract Type: Poster Presentation

Topic: Gene therapy, cellular immunotherapy and vaccination - Clinical

Background:

Prognosis of patients with relapsed/refractory (r/r) T-cell acute lymphoblastic leukemia (T-ALL) is dismal and there is urgent need to validate novel, more effective salvage therapies. The development of chimeric antigen receptor (CAR) T cells against T-ALL has been historically hampered by the difficulty of overcoming the fratricide induced by the expression of the target antigen on both blasts and healthy T-cells. To overcome this issue, Png et al. designed a 2nd-generation 41BB-CD3ζ CAR directed against the CD7 antigen associated with a protein expression blocker (PEBL) able to prevent CD7 expression on CAR T-cell surface (CD7.PEBL-CART) [Blood Adv 2017].

Aims:

At the Ospedale Pediatrico Bambino Gesù of Rome, we investigated the safety and efficacy of autologous CD7.PEBL-CART in a cohort of pediatric/young adult patients affected by r/r T-ALL, with at least 300 CD3+ cells/mL and less than 5% blasts in peripheral blood, treated in a hospital exemption setting.

Methods:

CD7.PEBL-CART were manufactured with a 12-day-long process, starting from cryopreserved leukapheresis and using a 2nd-generation lentiviral vector supplied by MediSix Therapeutics. Final drug products were cryopreserved and patients were treated with a single infusion after a cyclophosphamide/fludarabine-based lymphodepleting regimen (30 mg/sqm per 4 days and 60 mg/kg per 2 days, respectively). Prophylaxis against CMV reactivation with letermovir was employed in all patients.

Results:

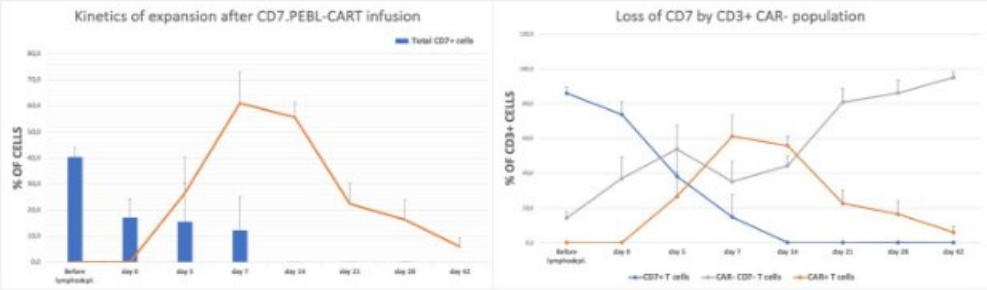
As of February 20 2024, 7 patients with r/r T-ALL received a median dose of 1x106 CD7.PEBL-CART cells/kg (range: 0.5-3, see Fig. 1 for details). CD7.PEBL-CART expanded in all patients, reaching a peak of 455.42+132.66 cells/ml and leading to the complete elimination of CD7-positive cells (Fig. 1). Cytokine release syndrome (CRS) occurred in 6/7 patients (Grade 1: 5; Grade 2: 1). No patient had immune effector cell-associated neurotoxicity syndrome (ICANS). Hematological toxicity (neutropenia Grade 4: 7/7; thrombocytopenia Grade 3-4: 7/7; anemia Grade 1-2: 3/7 – Grade 3: 4/7) developed after lymphodepleting chemotherapy in all patients. Reactivation of adenovirus, detected in both blood and stools, was observed in 1 patient and was successfully treated with twice-a-week infusions of cidofovir. BK virus infection occurred in 2 patients, causing hemorrhagic cystitis and CMV reactivation in 1 patient, successfully treated with foscarnet. No fungal infections were observed. All patients achieved a minimal residual disease (MRD)-negative complete remission (CR) 14 days after infusion of CD7.PEBL-CART. Four patients received an allogeneic hematopoietic stem cell transplantation (allo-HSCT) as consolidation treatment; allo-HSCT is pending for another patient. Of the 2 non-transplanted patients, one remains in molecular CR 4 months after CD7.PEBL-CART infusion and one had a relapse in the central nervous system (CNS). The latter received a second infusion of CD7.PEBL-CART cells, with a new expansion of the CAR T cells, and obtained a new CR. Noteworthy, both patients achieved T-cell reconstitution, consisting of CD7-negative T-cells that retain an antiviral response. With a median follow-up of 4 months (range: 1–6.7), 5/7 patients are alive and in CR, while 2/7 died in continuous CR for transplant-related toxicities (thrombotic microangiopathy and idiopathic pneumonia).

Summary/Conclusion: These data suggest that CD7.PEBL-CAR T-cells are effective in treating advanced r/r T-ALL and have manageable toxicity profile. A phase I/II clinical trial to expand and confirm these promising

results will be activated soon (NCT06064903).

Patient	Gender	Age at infusion	Diagnosis	Previous HSCT	Previous lines of therapy	PB blast % at leukapheresis	Extra-BM localization*	$CD7^+$ blast % BM*	Response at D+14	Response at D+28	HSCT post-CD7.PEBL-CART
1	M	15 y	*Non-ETP* T-ALL	no	2	0.1	no	70	CR (MRD-)	CR (MRD-)	Yes (D+39)
2	M	17 y	*ETP*-ALL	no	2	4.8% (CD4+/CD8-)	no	25	CR (MRD-)	CR (MRD-)	Yes (D+45)
3	M	18 y	*Non-ETP* T-ALL	no	2	0.15	no	12	CR (MRD-)	CR (MRD-)	Yes (D+52)
4	M	5 y	*Non-ETP* T-ALL	yes	2	1.2	no	2	CR (MRD-)	CR (MRD-)	No
5	F	11 y	*ETP*-ALL	yes	2	0.07	no	0.1	CR (MRD-)	CR (MRD-)	No
6	M	12 y	*Non-ETP* T-ALL	no	3	0.2	CNS2	58	CR (MRD-)	CR (MRD-)	Yes (D+49)
7	M	17 y	*Non-ETP* T-ALL	no	2	0.1	no	0.2	CR (MRD-)	CR (MRD-)	To be performed

HSCT: hematopoietic stem cells transplantation, PB: peripheral blood, BM: bone marrow, D: day, M: male, F: female, y: years, CR: complete remission, MRD: minimal residual disease, * before lymphodepleting therapy.



Keywords: Lentiviral vector, relapsed/refractory, T cell acute lymphoblastic leukemia, CAR-T