(PF515) OPTIMIZED CD33(FL33) CAR-T CELLS IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA: A PHASE 1/2CLINICAL TRIAL

Topic: 04. Acute myeloid leukemia - Clinical

Jing Pan*[1, 2], Bing Liu[3], Ang Zhang[4], Chen Liu[5], Yandong Gong[3], Wenjing Zhang[2], Shengnan Zhou[2]

[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical College, Sciences & Peking Union Medical College, Beijing, China; [2]Beijing Gobroad Hospital, Beijing, China; [3]State Key Laboratory of Experimental Hematology, Haihe Laboratory of Cell Ecosystem, Senior Department of Hematology, Fifth Medical Center, Medical Innovation Research Department, Chinese PLA General Hospital, Beijing, China; [4]Department of Comprehensive Basic Experiment, The Ninth Medical Center of Chinese PLA General Hospital, Beijing, China; [5]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China;

Background

Despite our previous optimized CD33 CAR-T therapy(FL33-01, J Pan, et al.Nature Communications, 2024) showed improved anti-leukemia efficacy in relapsed/refractory acute myeloid leukemia (r/r AML), grade 4 cytokine release syndrome (CRS) were identified, associated with elevated serum IL-6, IFN-γ, and TNF-α unresponsive to tocilizumab or corticosteroids. To address these safety issues, we upgraded our CD33 CAR structure (FL33-02 and FL33-03), adjusted lymphodepletion protocols,and defined bridging hematopoietic stem cell transplantation (HSCT)timing in a new trial.

Aims

Explore the safety and efficacy of optimized FL33 CAR-T therapy for r/r AML.

Methods

A multi-center, single-arm, open-label phase 1/2 trial (NCT06326021) of optimized CD33(FL-33) CAR-T cells (FL33-02 and FL33-03) was conducted in post-transplant and transplant-naïve r/r AML patients.Patients were assigned to three cohorts by CAR-T source: autologous (A),pre-transplant donor-derived(B), or new donor-derived(C).Using the BOIN12 design,phase I determined the optimal biological dose (OBD) via escalation,followed by phase II expansion. two dose levels (5.0×10^5 and 1.0×10^6cells/kg) were explored. Cohorts A/B received standard lymphodepletion (Bu 0.8-1.2mg/kg q6h×1d, VP-16 100mg/m²×1d, Fludarabine 30mg/m²×3d, Cyclophosphamide 250mg/m²×3d); Cohort C received enhanced lymphodepletion (Cyclophosphamide 30mg/kg×3d instead of 250mg/m² 3d). HSCT was guided by treatment response, remission, and recurrence. Primary endpoint: safety; secondary: efficacy.

Results

Seven patients were enrolled (5 males, 2 females, median age 13 years, range 7-46), with 3-7prior therapies and median baseline bone marrow tumor burden 20.44% (3.69%-86%). 1, 2, 4 patients were enrolled in cohort A, B, C, respectively, all received $0.5x10^6$(+20%) kg CAR-T cells. First 6 consecutive patients received FL33-02 with accepted safety profiles: 100% grade 1-2 CRS (median onset: day 6 post-infusion, range 1-8; median duration: 6.5days, range 3-12). 100% grade 3-4 neutropenia, onocytopenia and thrombocytopenia and obvious serum TNF-a increased (median peak: 62.89pg/ml, range 16.21-271.82), potentially due to CD33-expressing monocyte-macrophage activation, with median recovery 8.5 days after etanercept. CAR-T expansion was robust (median peak count: 2323 cells/ul,range0.8-313.6; median peak transgene: 3690.5 copies/ug, range 817-171145). Patient 7 received FL33-03. On the 7th day after infusion, patient 7 developed grade 2 CRS, which lasted for 5 days. The serum level of TNF-a slightly increased to 5.49 pg/ml, and the recovery time was 7 days. The expansion of CAR- T cells was even more significant (peak cell count: 103.79 cells per microliter, peak median transgenecopy number: 215,281 copies per microgram) All7 (100%) achieved CRi, 5/7 (71.4%) achieved MRD-Six responders underwent bridging HSCT (median 17.5 days post-infusion, range 12-35), one refused HSCT and died of Trichosporon asahii infection on day30. One patient died during pre-transplant conditioning. As of February 28, 2026, DFS rate was 71.4% (median follow-up 10.9 months, range0.6-15).

Summary/Conclusion

Optimized CD33(FL33-02 and FL33-03) CAR-T cells showed robust proliferation and potent anti-tumor activity in r/ AML FL33-03 structure have potent anti-tumor effects while also having the function of down-regulating TNFa and improving safety. However, infection remains a prominent safety concern, early bridging HSCT may reduce infection-related risks.