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Blood 142 (2023) 889–891

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Efficacy and Safety of Interleukin-6-Knockdown CD19-Targeted CAR T Cells(ssCART-19) for Relapsed/Refractory B-ALL

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Background:
Severe cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are significant challenges in the use of anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for patients with relapsed or refractory B-type acute lymphoblastic leukemia (r/r B-ALL). These complications limit the widespread adoption of CAR-T therapy. To address this issue, we developed a novel approach using anti-CD19 CAR T-cells incorporating a small hairpin RNA (shRNA) element to silence the interleukin-6 (IL-6) gene (ssCART-19). By reducing IL-6 expression levels in ssCART-19 cells, we aimed to decrease monocyte activation and pro-inflammatory cytokine release, thereby mitigating the incidence of severe CRS and neurotoxicity. In this phase 1/2 clinical trial conducted at two centers, we compared the efficacy and safety of ssCART-19 to classical CART-19 cells (cCART-19) in patients with r/r B-ALL (NCT03919240).

Methods:
Peripheral blood mononuclear cells were collected from patients through leukapheresis. ssCART-19 cells were generated by transducing anti-CD19 CAR with a shRNA-IL-6 gene silencing element into bulk peripheral T lymphocytes using a lentivirus vector. In contrast, cCART-19 cells were only transduced with an anti-CD19 CAR. Both cell types contained 4-1BB and CD3ζ co-stimulatory domains. Lymphodepletion (fludarabine at 30 mg/m ^{2}/day and cyclophosphamide at 300 mg/m ^{2}/day) was conducted on days -5, -4, and -3 before infusion. Each patient received a dose of 5×10^6CAR $^+$/kg. The primary endpoint was safety, with efficacy as the secondary endpoint for both ssCART-19 and cCART-19.

Results:
A total of 121 patients who had received at least two prior lines of treatment were screened for this study. A total of 47 patients received ssCART-19 and 40 patients received cCART-19 were included in the analysis. The median patient age of group ssCART-19 and group cCART-19 was 33(9-64) years and 24(2-68) years. At enrollment, ssCART-19 patients and cCART-19 patients had a median percentage of BM blasts of 4.0(0.01-86.0) % and 4.0(0.02-98.0) % by flow cytometry. ssCART-19 patients and cCART-19 patients had a median of 3 (2-8) and 4(2-9)prior lines of therapy(table 1).
The transfection efficiency was 44.66% (range: 13.70-84.66%) for ssCART-19 and 39.98% (range: 14.0-65.0%) for cCART-19. Adverse events within 28 days included grade 3-4 neutropenia in 14 patients (29.79%), thrombocytopenia in 17 patients (36.17%), grade 1-2 CRS in 25 patients (53.20%), grade 3-4 CRS in 7 patients (14.89%), and grade 1 ICANS in 2 patients (4.26%) in the ssCART-19 group. In the cCART-19 group, adverse events within 28 days included grade 3-4 neutropenia in 20 patients (50%), thrombocytopenia in 18 patients (45%), grade 1-2 CRS in 19 patients (47.5%), grade 3-4 CRS in 15 patients (37.5%), grade 1-2 ICANS in 4 patients (10%), and grade 3 ICANS in 2 patients (5%). The incidence of neutropenia, thrombocytopenia, grade 3-4 CRS, and ICANS in the ssCART-19 group was significantly lower than that in the cCART-19 group ($p < 0.05$)(Table 2). Furthermore, the peak levels of IL-6, IL-2 and TNF-α were significantly lower in the ssCART-19 group compared to the cCART-19

group ($p < 0.05$)(Fig.1). No significant differences were observed between the two groups in terms of the start time, peak value, duration and killing efficacy of CART cells ($p > 0.05$)(Fig.2).

As of the data cutoff on December 25, 2020, the median follow-up time was 12 months (range: 0.5-41.33). On day 28, with 91.49% of patients achieving complete remission (CR) or CR with incomplete hematological recovery (CRi) in ssCART-19, compared to 85% in the cCART-19 group. Median overall survival (OS) was not available for ssCART-19, while it was 32.93 months for cCART-19 (p=0.575). The median progression-free survival (PFS) was 14.17 months for ssCART-19 and 15.33 months for cCART-19 (p=0.339). Although no significant differences were observed in terms of 3-year OS and PFS, the 3-month PFS was higher in the ssCART-19 group compared to the cCART-19 group (82.3% vs 66.9%, p=0.045)(Fig.3).

Conclusion:

Our clinical studies demonstrated the safety and high efficacy of ssCART-19 with IL-6 gene silencing in patients with relapsed/refractory B-ALL. These findings support the potential of ssCART-19 as a promising therapeutic approach for this challenging patient population.

Disclosures No relevant conflicts of interest to declare.

Table1 Baseline Characteristics of All 87 Treated Patients and Subgroups

Characteristic	ssCART-19(n=47)	cCART-19(n=40)	P value
Male, No. (%)	24(51.06)	25(62.5)	0.5792
Median age (range), years	33(9-64)	24(2-68)	0.0787
Median lines of therapy(range)	3(2-8)	4(2-9)	0.4528
Allogeneic SCT, No. (%)	13(27.66)	6(15)	0.7865
Bone marrow blasts, %			
≥50%	6(12.77)	7(17.5)	0.8201
≥5% and <50%	14(29.79)	13(32.5)	
≥0.01% and <5%	13(27.66)	11(27.5)	
<0.01%	14(29.79)	9(22.5)	
Bone marrow blasts（range）	4.0(0.01-86.0)	4.0(0.02-98.0)	0.3399
High risk cytogenetic factors,No. (%)			
BCR/ABL(Ph+)	12(25.53)	9(22.5)	0.1641
TP53 gene mutation	1(2.13)	3(7.5)	0.9099

Ph+, Philadelphia chromosome-positive; SCT, Stem Cell Transplantation; TP53, TP 53gene mutation.

Table 2 AEs Among All 87 Treated Patients

Adverse events	ssCART-19(n=47)		cCART-19(n=40)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic event				
Anemia	32 (68.09)	15 (31.92)	28 (70)	15 (37.5)
Febrile neutropenia	8 (17.02)	6 (12.77)	6 (15)	6 (15)
Neutropenia	26 (55.32)	14 (29.79)	25 (62.5)	20 (50)
Thrombocytopenia	25 (53.20)	17 (36.17)	21 (52.5)	18 (45)
Cardiac disorders				
Sinus tachycardia	4 (8.51)	0 (0)	2 (5)	0 (0)
Heart failure	4 (8.51)	0 (0)	2 (5)	1 (2.5)
Gastrointestinal event				
Abdominal distension	5 (10.64)	0 (0)	4 (10)	0 (0)
Abdominal pain	1 (2.13)	0 (0)	6 (15)	0 (0)
Diarrhea	5 (10.64)	0 (0)	4 (10)	0 (0)
Nausea	11 (23.40)	0 (0)	10 (25)	0 (0)
Vomiting	7 (14.89)	0 (0)	9 (22.5)	0 (0)
General disorders				
Chill	11 (23.40)	0 (0)	7 (17.5)	0 (0)
Edema	6 (12.77)	0 (0)	2 (5)	0 (0)
Fatigue	20 (42.55)	0 (0)	16 (40)	0 (0)
Immune system disorders				
CRS	32 (68.09)	7 (14.89)	34 (85)	15 (37.5)
ICANS	2 (4.26)	0 (0)	6 (15)	2 (5)
Allergic reaction	0 (0)	0 (0)	0 (0)	0 (0)
Infections and infestations				
Unknown type infection	20 (42.55)	3 (6.38)	17 (42.5)	5 (12.5)
Lung infection	9 (19.15)	1 (2.13)	9 (22.5)	4 (10)
Laboratory tests				
Alanine aminotransferase increased	5 (10.64)	2 (4.26)	4 (10)	2 (5)
Aspartate aminotransferase increased	5 (10.64)	1 (2.13)	6 (15)	1 (2.5)
Alkaline phosphatase increased	5 (10.64)	0 (0)	8 (20)	0 (0)
Blood bilirubin increased	3 (6.38)	1 (2.13)	0 (0)	0 (0)
Creatinine increased	1 (2.13)	0 (0)	3 (7.5)	1 (2.5)
Hypokalemia	12 (25.53)	0 (0)	5 (12.5)	0 (0)
Nervous system disorders				
Headache	3 (6.38)	0 (0)	8 (20)	0 (0)
Epilepsy	2 (4.26)	0 (0)	6 (15)	2 (5)
Aphasia	0 (0)	0 (0)	1 (2.5)	0 (0)
Dysphonia	0 (0)	0 (0)	1 (2.5)	0 (0)
Cognitive disturbance	1 (2.13)	0 (0)	5 (12.5)	1 (2.5)
Respiratory, thoracic and mediastinal disorders				
Cough	10 (21.28)	0 (0)	6 (15)	1 (2.5)
Dyspnea	5 (10.64)	0 (0)	5 (12.5)	1 (2.5)
Hypoxia	6 (12.77)	1 (2.13)	15 (37.5)	1 (2.5)
Skin and subcutaneous tissue disorders				
Rash	4 (8.51)	0 (0)	3 (7.5)	0 (0)
Vascular disorders				
Hypotension	18 (38.30)	6 (12.77)	25 (62.5)	7 (17.5)

NOTE. Data are No. (%).

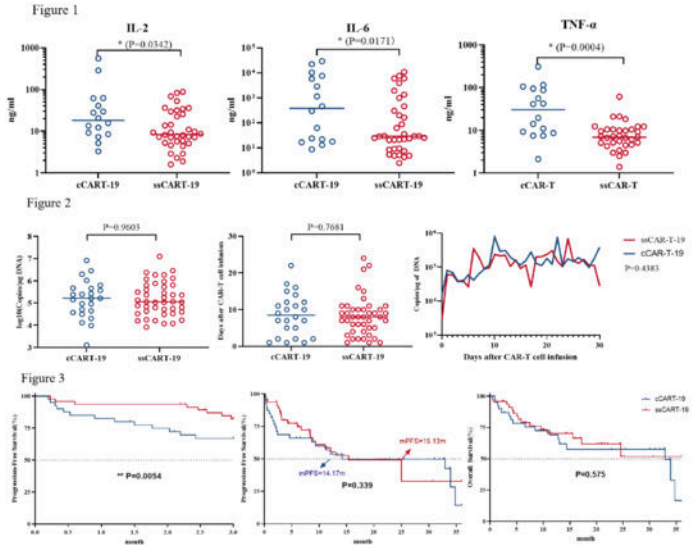

Figure 1

https://doi.org/10.1182/blood-2023-172615