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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Long-Term Follow-up of Humanized and Murine CD19 CAR-T Cell Therapy for B-Cell Malignancies

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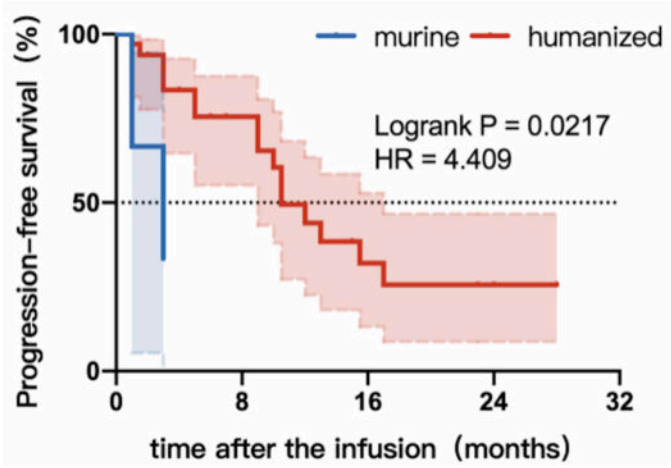
Aim:
CD19 chimeric antigen receptor T cell (CAR-T) therapy is a revolutionary treatment for relapsed/refractory (R/R) B-cell hematologic malignancies. However, the safety and efficacy of murine CAR-T cells which have been widely used as commercialized products still need to be improved. Similarly, murine CAR-T encountered the problem that CAR-related immunogenicity existed after the infusion, which led to the failure of the re-infusion of CAR-T cells. As an improved generation of murine CAR-T cells, whether humanized CAR-T therapy can overcome the above shortcomings remains to be explored.
Methods:
In this study, the differences in safety, efficacy, and long-term follow-up results of murine and humanized CD19 CAR-T cells in patients with B-cell malignancies were collected and analyzed. A total of 130 patients were enrolled, including 35 patients with murine CAR-T and 95 with humanized CAR-T cells (NCT 02965092, NCT 04008251).
Results:
The proportion of patients with cytokine release syndrome (CRS) in the murine and humanized groups was 54.3%(19/35) and 61.1%(58/95), respectively. A significantly higher proportion of patients suffered from severe CRS in the murine group than that in the humanized CAR-T group (17.14% vs. 7.4%, P=0.0233), and one patient in each group died of Grade 5 CRS. The incidence of grade 1-2 Immune effector cell-associated neurotoxicity syndrome (ICANS) was 11.4% (murine: 4/35) and 5.3% (humanized: 5/95), but high-grade ICANS was not observed.
Among patients receiving murine CAR-T cells, 80% achieved objective response (OR), 71.43% achieved complete response (CR) and the CR rate of patients with leukemia was 74.19%. The OR rate and CR rate of patients in the humanized group were 75.79% and 63.16%, respectively, while the CR rate of patients with leukemia receiving humanized CAR-T cells was 89.58%. The median follow-up time of patients in the murine and humanized groups was 7 months (0.6-75 months) and 5.5 months (0.5-34 months), respectively. The median progression-free survival (PFS) of patients with murine CAR-T cells was 11 months and that of patients with humanized CAR-T products was 12 months. Both of the median overall survival (OS) were not reached. Among the 48 patients with a bone marrow burden over 20% at baseline, humanized CAR-T therapy was associated with a higher OS rate (84.64% vs. 59.26%, P=0.1479) and a significantly improved PFS (43.94% vs. 33.33%, P=0.0217, Figure 1).
Bridging transplantation was an independent factor in prolonging OS (x^2=8.017, p=0.0046) and PFS (x^2=6.584, p=0.0103) of patients with leukemia. Neither species of chimeric antigen receptor nor common risk factors such as age, recurrence, bone marrow burden, BCR-ABL fusion gene had significant effect on patients' long-term follow-up outcomes (Table 1). Four patients received CAR-T therapies more than once. Three of them still achieved varying degrees of long-term remission after multiple humanized CAR-T infusions. However, one patient relapsed as soon as one month after his second infusion of murine CAR-T cells.
Conclusion:
Results indicate that humanized CAR-T therapy showed better safety and durable efficacy, especially in patients with higher tumor burden in bone marrow. Moreover, it could overcome immunogenicity-induced CAR-T resistance, providing treatment options for patients' failures of CAR-T therapies.

Disclosures No relevant conflicts of interest to declare.

Figure 1. PFS of patients with high tumor burden



Impact of murine CAR-T cells vs. humanized CAR-T cells on progression-free survival of patients with higher tumor burden (P = .0217). HR, hazard ratio.

Table 1. Univariate analysis for OS and PFS of patients with leukemia

Factors	No.	1-year OS (%)	x^2	P	1-year PFS (%)	x^2	P
Sexual			1.033	0.3094		0.7011	0.4024
male	42	84.884			49.352		
female	38	76.695			31.535		
Age			0.404	0.5248		0.1325	0.7159
⩾30y	38	82.943			44.342		
<30y	42	79.381			41.974		
R/R			1.839	0.1751		0.6238	0.4297
relapse	42	80.251			37.863		
refractory	38	86.044			46.952		
Tumor burden*			0.35	0.5561		0.6248	0.4293
⩾20%	45	83.137			41.493		
<20%	35	79.461			44.822		
BCR-ABL			0.004	0.9466		0.0678	0.7946
yes	16	86.154			48.951		
no	64	70.583			50.863		
Bridging transplantation			8.017	0.0046		6.584	0.0103
yes	18	100			66.406		
no	62	73.157			31.83		
Species of CAR			0.082	0.7740		0.6012	0.4381
murine	31	78.375			44.094		
humanized	49	82.413			42.074		

* Percent of bone marrow blasts measured by flow cytometry

Figure 1

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