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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Sequential Umbilical Cord Derived Mesenchymal Stromal Cells (MSCs) for the Third-Line Salvage Treatment of Steroid-Refractory Acute GvHD: A Multicenter, Open Label, Phase 1b/2 Trial

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Background and Aim: Acute graft-versus-host disease (aGVHD) is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), particularly if treatment is refractory. Human mesenchymal stromal cells (MSCs) have demonstrated safety and efficacy in steroid refractory acute graft versus host disease, due to their well-described immunosuppressive properties, however, clinical trials have resulted in variable success and an optimal source of MSC has yet to be defined. Based on the importance of maternal-fetal interface immune tolerance, the umbilical cord may provide a superior tissue source of MSC to mediate immunomodulation in aGVHD (SR-aGVHD). This study aimed to investigate the safety and efficacy of MSCs delivered as third-line salvage therapy for SR-aGVHD who had received at least two-lines of steroid-containing immunosuppressive therapy.
Method: This phase1b/2, multicenter, open-label clinical trial of a third-party, off-the-shelf preparation of human umbilical cord derived mesenchymal stromal cells (hUC-MSCs) (ChiCTR2200061603) enrolled grades II to IV steroid-refractory aGVHD patients who had been treated with at least two-lines of steroid-containing immunosuppressive therapy. This trial consist of 2 parts:a phase Ib dose escalation part using a standard 3+3 design, which planed biweekly i.v. infusions of hUC-MSCs, at 0.5×10^6 per kg, 1.0×10^6per kg and 2.0×10^6 per kg for 3 weeks, to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D). Phase II of this work is an expansion cohort study of hUC-MSCs at RP2D 1.0×10^6 per kg with 15 patients. The primary endpoint of the study was safety and RP2D. The key secondary endpoints were efficacy of the overall response rate (ORR) at Day 28 and Day 56 defined per the 2014 NIH consensus criteria.
Results: From June 23, 2022, through June 12, 2023, a total of 25 patients were enrolled with the median follow up period of 106 (10,210) days. Of the included 25 cases 11 patients (44.0%) were grade III/IV and 14 patients (56.0%) were grade II aGVHD at enrollment. Median patient age was 37.0 (range:24.5-47.0) years, 44.0% male. hUC-MSCs was well tolerated without dose-

limiting toxicities in aforementioned three dosages. The reported adverse events (AEs) potentially associated with hUC-MSCs were hypofibrinogenemia (12.0%), upper respiratory tract infection (4.0%), leukopenia (4.0%) and anemia (8.0%) within the median follow-up period of 106 (10, 210) days. Grade 3 or higher AEs were reported in 6 patients (6/25, 24%) with 11 events, all of them were supposed uncorrelated with hUC-MSC. Three patients unfinished the administration:1 was due to withdrawn ICF; 1 was SAE and 1 was due to participate another trial. Up to date of June 12, 2023, twenty of the initial included 25 patients were still in group. And the RP2D of this trial was identified as 1.0×10^{6} per kg. At Day 28, 20 patients (80.0%, 95% CI:59.3%-93.2%) had an overall response, including 10 (40.0%) with complete responses. And at day 56, only one patient loss response, while another non-response patient at day 28 in the dose of 1.0×10^{6} per kg achieved late responses at day 56 (**Table 1**). Responses were observed across skin (19/19, 100%), gastrointestinal tract (7/11,72.7%), and liver (2/2, 100.0%) at day 28. Durable overall response at day 56 was 76% (19/25), **Figure 1**. The median follow-up time after the initiation of hUC-MSC treatment was 106 (10,210) days with the cutoff date of 180 days after recruitment. The probability of 180-day overall survival (OS) and non-relapse mortality was 88.0% (95% CI, 68.8-97.5%) and 8.0% (95% CI, 1.0-26.0%), respectively. The 180-day cumulative incidence of relapse of primary hematologic disease was 8.0% (95%CI,1.0-26.0%). The percentage of total T lymphocyte, neutrophil, cytokine IL-10, IP-10 were statistically decreased in CR group, while CD8+central memory T cell was significantly increased compared to non-CR groups 24h or 96h after hUC-MSC administration ($P<0.05$).

Conclusion: Collectively, our results support hUC-MSCs as an effective salvage treatment for SR-aGVHD with safe profile.

Key words: Acute graft-versus-host disease; allogeneic hematopoietic stem cell transplantation; mesenchymal stromal cells

Disclosures No relevant conflicts of interest to declare.

Table 1. Overall response at Day 28 and Day 56 of different dosage

Response	0.5×10^{6}cells/kg (N=5)	1×10^6 cells/kg (N=17)	2×10^{6}cells /kg (N=3)	Total (N=25)
Day 28				
N (N, Miss)	5 (0)	17 (0)	3 (0)	25 (0)
CR [n, (%)]	3 (60.0)	5 (29.4)	2 (66.7)	10 (40.0)
PR [n, (%)]	1 (20.0)	8 (47.1)	1 (33.3)	10 (40.0)
PD [n, (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NR [n, (%)]	1 (20.0)	4 (23.5)	0 (0.0)	5 (20.0)
ORR(95%CI)	80.0 (28.4, 99.5)	76.5 (50.1, 93.2)	100.0 (29.2, 100.0)	80.0 (59.3, 93.2)
Day 56±2				
N (N, Miss)	5 (0)	17 (0)	3 (0)	25 (0)
CR [n, (%)]	4 (80.0)	7 (41.2)	2 (66.7)	13 (52.0)
PR [n, (%)]	0 (0.0)	7 (41.2)	0 (0.0)	7 (28.0)
PD [n, (%)]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NR [n, (%)]	1 (20.0)	3 (17.6)	1 (33.3)	5 (20.0)
ORR(95%CI)	80.0 (28.4, 99.5)	82.4 (56.6, 96.2)	66.7 (9.4, 99.2)	80.0 (59.3, 93.2)

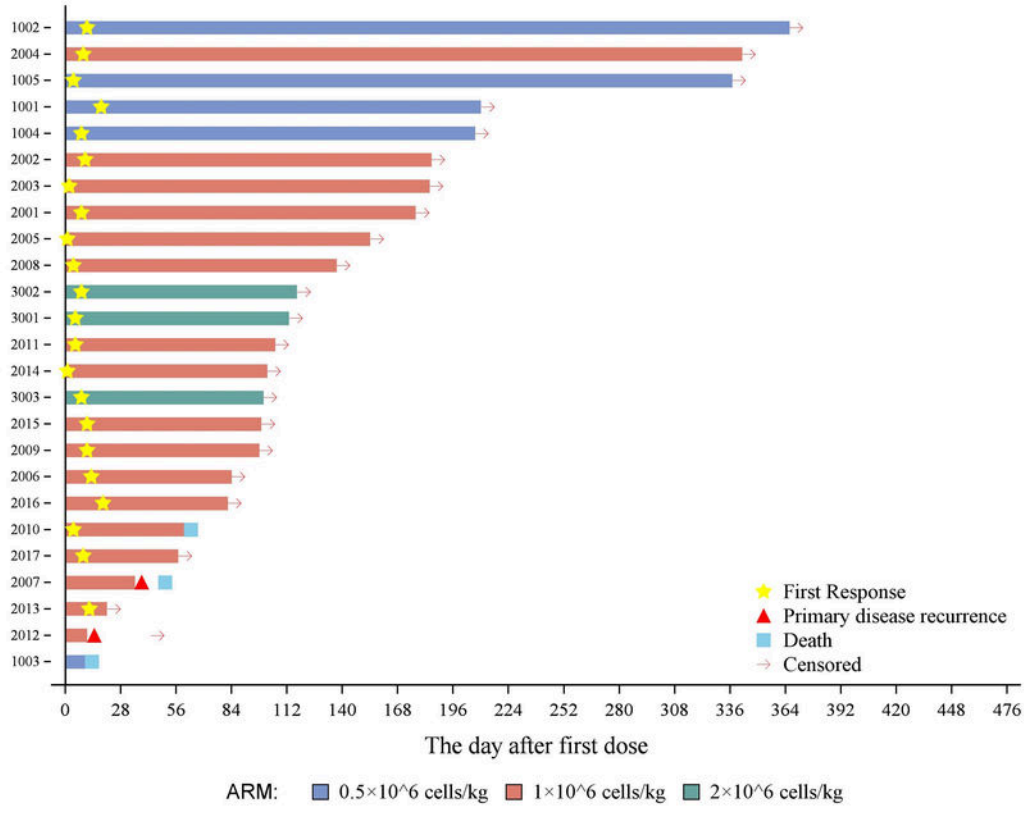

Figure 1. Treatment response, outcomes and primary disease recurrence over time in 25 patients. The first responses, primary disease recurrence, and death of the 25 patients with different infusion doses (0.5×10^6 cells/kg, 1.0×10^6 cells/kg, and 2.0×10^6 cells/kg) are shown in the swimmer plot.

Figure 1

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