GvHDHub

cGvHD

Clinical features of cGvHD following cord blood infused haploidentical transplantation

Iqra Farooq | May 07, 2019

Chronic graft-versus-host disease (cGvHD) is a major cause of morbidity after haploidentical hematopoietic stem cell transplantation (haplo-HSCT). Strategies to help reduce the incidence of cGvHD are urgently needed.

Tao Tao, from the Department of Respiratory Medicine, The Fifth People's Hospital of Suzhou, CN, and colleagues conducted a study[1] to investigate whether cord blood infusion following haplo-HSCT, can reduce the incidence of cGvHD.

The open-label, multicenter, non-randomized, single-arm, prospective study looked at the clinical profiles of cGvHD according to the National Institutes of Health[2] (NIH) criteria.

Patient characteristics

- N = 300
- Median age 25 (range, 2—55)
- Males, n = 187 (62.3%), females, n = 113 (37.7%)
- All patients met the following criteria:
  - First time HSCT
  - Age: ≤55 years: <18 = 68 (22.7%); ≥18 = 232 (77.3%)
  - Myeloablative conditioning regimen adopted
  - Haploidentical donor combined umbilical cord blood transplantation
  - Expected survival after transplant >100 days
  - Eastern Cooperative Oncology Group (ECOG) score <2

Diagnosis	**N (%)**
AML	114 (38)
ALL	124 (41.3)

MDS	28 (9.3)
HAL	12 (4)
CML	8 (2.7)
NHL	5 (1.7)
Others	9 (3)

Table 1: Diagnosis of patients

Methods

- Haploidentical donors were parents, children, or siblings
- Donors received:
  - Granulocyte colony-stimulating factor 5mg/kg/day, for 5 consecutive days before stem cell harvesting
  - If bone marrow $CD34^+$ cells were $<2x10^6$/kg additional peripheral blood stem cells were collected
- Participant received a modified myeloablative conditioning regimen:
  - Day -10: simustine 250mg/m^2
  - Day -9 and -8: cytarabine 4g/m^2/day
  - Day -7 to -5: oral busulfan 4mg/kg/day
  - Day -4 and -3: cyclophosphamide 1.8g/m^2/day
- Median follow-up 26.4 months (range, 0.2—61.8) from initiation of transplantation
- First-line treatment of cGvHD: prednisone, 1mg/(kg · d), with or without a calcineurin inhibitor
- Second-line treatment options included: mycophenolate mofetil (MMF), methotrexate (MTX), tacrolimus, sirolimus, imatinib and rituximab
- Scoring of cGvHD syndromes evaluated according to NIH consensus and Seattle criteria

Key findings

Factor	**N (%)**
Graft type of haplo-identical donor	

• Bone marrow	47 (15.7)
• Peripheral blood	12 (4)
• Bone marrow & peripheral blood	241 (80.3)
Median MNC cells, range, 10^8/kg	9.93 (1.28—28.52)
Median $CD34^+$ cells, range, 10^6/kg	3.46 (0.81—9.46)

Table 2: Transplantation characteristics for all patients

Follow-up data on all patients, n = 300 (95% CI)				
Time post-HSCT (years)	**OS (%)**	**DFS (%)**	**GRFS (%)**	**NRM (%)**
1	71.5 (68.9~74.1)	66.6 (63.7~69.5)	50.8 (47.9~53.7)	30.8 (28.1~33.5)
2	65.7 (62.9~68.5)	64.2 (61.4~67)	45.6 (42.7~48.5)	35.8 (33.0~38.6)
3	61.1 (58.1~64.1)	58.3 (55.0~61.6)	44.5 (41.5~47.5)	38.2 (35.5~41.1)

Table 3: Follow-up data on all patients, n = 300, 95% CI for all values. OS = overall survival; DFS = disease-free survival; GRFS = GvHD-free, relapse free survival; NRM = non-relapse mortality

Acute GvHD incidence, severity and survival

- Incidence of aGvHD, n = 113 (37.6%)
  - Classic, late-onset aGvHD, n = 90 (79.6%)
  - Persistent aGvHD (n = 15, 65.2%), recurrent aGvHD (n = 2, 8.6%) and *de novo* late aGvHD (n = 6, 26%)
- Cumulative incidence of grades II—IV aGvHD on day 100 after transplantation: 36.7% (95% CI, 33.9%~39.5%)

GvHD type	**2-year survival (%)**

Classic aGvHD	60.6	95% CI, 55.2%~66.0%
Persistent late aGvHD	37.0	95% CI, 24.1%~49.9%
De novo late aGvHD	33.3	95% CI, 14.1%~52.5%
Recurrent late aGvHD	0.0	*P* = 0.05

Table 4: 2-year survival of patients who developed aGvHD

Chronic GvHD incidence, severity and survival

- Incidence of cGvHD (NIH criteria), n = 73 (24.3%)
  - Classic cGvHD, n = 64 (87.7%)
  - Overlap cGvHD, n = 9 (12.3%)
- Of the 73 patients with cGvHD:
  - Mild cGvHD, given topical glucocorticoids, n = 17
  - Treated with systemic immunosuppressive agents, n = 56
  - Achieved complete remission (CR), n = 35
  - Received second-line treatments, n = 21 (Table 5)
- Median time to onset of cGvHD post-transplantation: 6 months (range, 3—40)
- Median survival time after GvHD onset: 23.3 months (range, 1—53.3)

Treatment	**N**
Tacrolimus	8
MMF	6
Imatinib	2
Ruxolitinib	2

Sirolimus	1
MTX	1
Rituximab	1

Table 5: Treatments for patients with cGvHD receiving second-line treatments.

Cause	**N (%)**
Disease relapse	6 (30)
BOS	4 (20)
Multi-organ failure	3 (15)
IFD	3 (15)
Hepatic failure	2 (10)
Interstitial pneumonitis	1 (5)
Intracranial hemorrhage	1 (5)
Total	20 (27.4)

Table 6: Cause of death for patients with cGvHD. BOS: bronchiolitis obliterans syndrome; IFD: invasive fungal disease.

According to the Seattle criteria, 89 patients were diagnosed with cGvHD, with onset at a median of 5.7 months (range, 3.6—42).

Years	**GOS (%)**	

1	76.5	95% CI; 71.6~81.5
2	71.6	95% CI; 66.2~77.0
3	67.6	95% CI; 61.2~74.0

Table 7: cGvHD overall survival (GOS)

Multivariate analysis

Risk factor	**Multivariate analysis**		
	Hazard ratio	**95% CI**	***P***
$CD34^+$ ($\geq 3.46x10^6$/kg vs ,$3.46x10^6$/kg)	0.178	0.05~0.62	<0.05
BOS (yes vs no)	10.93	2.43~49.16	<0.05
Platelet count ($\geq 100x10^9$/L vs $<100x10^9$/L)	13.23	2.99~58.55	<0.05
cGvHD response to first-line treatment	5.25	1.48~18.71	<0.05
Disease relapse (yes vs no)	17.89	2.79~114.67	<0.05

Table 7: Cox multivariate model of factors predicting survival for patients with cGvHD (n=73). A nomogram was developed to predict GOS using the five independent covariates identified in the final Cox model.

Conclusion

Relapse, thrombocytopenia, BOS and SR-cGvHD were independent risk factors for GOS, with $CD34^+ \geq 3.46x10^6$/kg found to be a protective factor affecting GOS. A prognostic model and nomogram were proposed to be used to predict outcomes for patients and could be useful for clinicians and for future research.

Despite several studies demonstrating the unique tolerogenic properties of the fetal lymphoid system and the immunomodulatory effects of cellular components in the umbilical cord, the question on whether the cord has a functional role in preventing cGvHD remains. The limitations of this study has led to the requirement of randomized, controlled studies in order to validate the findings.

References

1. Tao, T., *et al*. Clinical features of chronic graft-versus-host disease following haploidentical transplantation combined with infusion of a cord blood. *Stem Cells Dev*. 2019 Apr 12. DOI: 1089/scd.2018.0259

2. Arora, M. *et al*. Late acute and chronic graft-versus-host disease after allogenic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016 Mar 1. 1:22(3):449—455. DOI: 1016/j.bbmt.2015.10.018
