GvHDHub

Haploidentical *vs* haplo-cord transplant in adults receiving fludarabine and melphalan conditioning

Iqra Farooq | Jul 24, 2019

For a number of patients, it can be difficult to identify matching donors for allogeneic human stem cell transplantation (allo-HSCT). Typically, these include patients from ethnically diverse backgrounds, small families, or those who are older. Haploidentical transplantation (haplo) using $CD34^+$ cells from partially matched related donors, followed by post-transplant cyclophosphamide (PTCy) is one choice emerging as an appealing option for patients who do not have matching donors.[1]

Another option is umbilical cord blood (UCB) transplant with partially matched peripheral cord blood cells (haplo-cord), which has been shown to cause less chronic graft-*versus*-host disease (cGvHD), and could mediate superior graft-versus-leukemia (GVL) effects.[2] The addition of antithymocyte globulin (ATG) is necessary to prevent violent rejection of the haplo-graft before UCB engraftment.[3]

Koen van Besien, from Weill Cornell Medical College, New York, US, and colleagues compared the use of each haplo versus haplo-cord in patients under 60. Both procedures used a melphalan-based reduced-intensity conditioning (RIC).

Study design

This retrospective study identified patients between the ages of 18–59 who underwent haplo or haplo-cord transplantation, using melphalan-based RIC. A total of 137 patients received haplo-cord transplantation between 2007 and 2016, at Weil Cornell Medical College, and the University of Chicago, US. These patients were treated with ATG, tacrolimus, and mycophenolate as GvHD prophylaxis. They were compared with 170 patients who underwent haplo transplantation between 2009 and 2016, at MD Anderson Cancer Center, and received GvHD prophylaxis that included PTCy, tacrolimus, and mycophenolate. Trials were registered as NCT01810588 and NCT01050946.

Patients with second transplants were excluded.

Haplo-cord: donor selection criteria, stem cell processing, conditioning, and GvHD prophylaxis

- Cord blood selected based on HLA-typing and total nucleated cell (TNC) count (matching over TNC)
- Additional supportive administration of CD34+ from peripheral blood of first- or second-degree relatives (target dose of 3 to 5 x 10^6 $CD34^+/kg_{rec}$
- Conditioning consisted of 30mg/m^2 x 5 fludarabine, 140mg/m^2 melphalan and 1.5mg/kg thymoglobulin for 3 or 4 doses; 25 patients were also treated with total body irradiation (TBI)
- Post-transplant GvHD prophylaxis consisted of tacrolimus until day 180 and mycophenolate until day 60 (until day 28 for more recent patients)

Haplo: donor selection criteria, stem cell processing, conditioning, and GvHD prophylaxis

- Donors were first-degree relatives, where apheresis began on day 5 and continued until at least 5 x 10^6 $CD34^+$ cells/kg_{rec} were collected
- As the haploidentical donor source, 7% received peripheral blood, while 93% received bone marrow
- Conditioning consisted of 140mg/m^2 melphalan (100mg/m^2 for patients older than 55/significant comorbidities), 40mg/m^2 fludarabine (x 4 days); 26 patients were treated with TBI and 101 patients received thiotepa.
- GvHD prophylaxis included 50mg/kg PTCy on days +3 and +4, tacrolimus until day 180 and mycophenolate until day 90

Endpoints

- Neutrophil engraftment: first of three consecutive days with an absolute neutrophil count of 0.5 x 10^9/L
- Platelet engraftment: first of seven consecutive days with a count of 20 x 10^9/L without platelet transfusion
- NRM: death without evidence of progression or relapse

Results

Similar results were achieved for NRM, survival, and relapse in both groups, with almost two-thirds of patients alive at one year (table 1). OS and PFS did not differ between the two groups, after adjusting for prognostic factors, with the researchers identifying that disease risk influenced outcomes more than donor platforms. Despite many studies2 describing the unique effects of UCB, a difference in the rates of disease recurrence was not identified.

Table 1: Relapse, PFS and OS analyses

	Haplo	Haplo-cord
Cumulative incidence of relapse at 1 year	27% (95% CI)	27% (95% CI)
Progression-free survival (PFS) at 1 year	56%	55%
PFS at 4 years	45%	40%
Overall survival (OS) at 1 year	65%	63%
OS at 4 years	49%	50%

The incidence of GvHD was lower, and neutrophil and platelet recovery was quicker after haplo-cord than haplo transplant, and despite PTCy-based GvHD prophylaxis, GvHD remains a more serious problem with haplo transplants (Table 2).

Table 2: Engraftment and GvHD

	Haplo	Haplo-cord	*p*
Median follow-up (months)	54	41	
Median days to ANC*	18 (16–20)	11 (10–14)	0.001
Median days to platelet	25 (20–32)	22 (17–36)	0.025
Cumulative incidence of grade II–IV acute GvHD (aGvHD, 100 days)	33% (27–39)	16% (9–23)	0.0001
Cumulative incidence of grade III–IV aGvHD (100 days)	9% (5–13)	5% (1–9)	0.275
Cumulative incidence of cGvHD (1 year)	16% (12–20)	4% (0–10)	0.0001

*ANC, absolute neutrophil count

Univariate analysis showed that NRM was close to being the same in both groups, 18% (95% CI, 12–24) in the haplo-cord arm and 19% (95% CI, 13–25) in the haplo arm at one year (table 3).

Thirty-seven patients receiving haplo-cord transplants, and 39 receiving haplo transplants died of non-relapse causes, with fatal GvHD occurring in nine patients with haplo transplants and only one patient with haplo-cord transplant (Table 4). Epstein-Barr virus (EBV) was addressed by systematic surveillance in haplo-cord transplant patients, every two weeks in the hospital and at every clinic visit. This led to pre-emptive treatment with rituximab in 30 patients. Surveillance was not conducted in patients with haplo transplantation.

Table 3: NRM analysis

NRM	n	HR (95% CI)	*p* value
Study cohort			0.36

Haplo	170	1.00	
Haplo-cord	137	1.34 (0.83–2.16)	

Table 4: Nonrelapse deaths

	Haplo (n=170)		Haplo-cord (n=137)	
	N (%)	Cumulative incidence at 1 year	N (%)	Cumulative incidence at 1 year
Fatal infection	13 (7)	7.6	20 (15)	6.6
GvHD	9 (5)	3.5	1 (1)	0.0
aGvHD	7 (4)	2.3	1 (1)	0.0
cGvHD	2 (1)	1	0	0
PTLD	0	0	4 (3)	2.9
Graft rejection/poor graft function	3 (1.5)	1.8	8 (6)	5
Unknown	5 (3)		0	
Other	9 (5)		5 (3.5)	

Conclusion

Both haplo and haplo-cord transplantation provide alternatives to patients who lack HLA-matched related or unrelated donors. The researchers mention that doctors should choose between haplo or haplo-cord transplant based on the patient's need and long-term outcomes, the availability of cord blood, as well as the cost and strain on hospital resources and their own expertise. These approaches can move patients quickly when a HLA donor is not available.

References

1. CiureaO., et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015 Aug 20;126(8):1033-40. DOI: 10.1182/blood-2015-04-639831
2. Milano, et al. Cord-blood transplantation in patients with minimal residual disease. New England Journal of Medicine. 2016 Sep 8;375(10):944-53. DOI: 10.1056/NEJMoa1602074
3. van Besien K., et al. Haploidentical vs haplo-cord transplant in adults under 60 years receiving fludarabine and melphalan conditioning. Blood Advances. 2019 Jun 25;3(12):1858-67. DOI: 1182/bloodadvances.2019000200