GvHDHub

aGvHD, cGvHD

Impact of donor type on outcomes of allogeneic transplant

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Human leukocyte antigen (HLA)-matched sibling donors (MSD) are the ideal donors for allogeneic hematopoietic stem cell transplantation (allo-HSCT), however, MSDs are only available in 30% of cases.[1] Using other donor types increases the risk of graft-*versus*-host disease (GvHD) and non-relapse mortality (NRM), though may promote an allo-immune effect against the tumor, thereby reducing the risk of relapse. Overall, diagnosis and disease status at time of transplant remain the main drivers of transplant outcome. [1]

The development and increased clinical usage of reduced-intensity conditioning (RIC) regimens and GvHD prophylactic agents have made transplantation an option for more patients. Roni Shouval, Joshua A Fein, and colleagues, hypothesized that the effect on overall survival (OS) and NRM due to the genetic disparity between donor and recipient may have diminished over time. Therefore, they conducted an analysis of adult patients who underwent allo-HSCT for a hematological malignancy between 2001 and 2015, using the European Society for Blood and Marrow Transplantation (EBMT) registry. The stem cell source was either peripheral blood (PB), bone marrow (BM) or umbilical cord blood (UC). They aimed to determine the impact of the donor source on OS, NRM, relapse incidence, progression-free survival (PFS), acute GvHD (aGvHD), chronic GvHD (cGvHD) and GvHD-free relapse-free survival (GRFS).

Study design and patient characteristics

- Retrospective, multicenter study of 106,188 patients receiving allo-HSCT
- Median follow-up: 4.1 years (interquartile range: 1.7–7.7)
- Patients were arranged into three epochs based on when they received their transplant:
  - 1: 2001–2005 (n= 23,249)
  - 2: 2006–2010 (n= 35,348)
  - 3: 2011–2015 (n= 47,591)
- Donor types:
  - MSD; matched at *HLA-A, HLA-B,* and *HLA-DRB1*
  - Matched unrelated (MUD); matched at *HLA-A, HLA-B, HLA-C,* and *HLA-DRB1*
  - Mismatched unrelated (MMUD); unrelated donor with ≥ one mismatch in: *HLA-A, HLA-B, HLA-C, HLA-DRB1*
  - Haploidentical (HD); sibling or relative with ≥ two mismatches at *HLA-A, HLA-B,* and *HLA-DRB1*
  - Cord blood (CD); unrelated
- Most patients received allo-HSCT for acute leukemia (epoch 1 *vs* 2 *vs* 3): 50.2% *vs* 57.8% *vs* 57.8% and most were low risk (epoch 1 *vs* 2 *vs* 3): 52.9% *vs* 51.8% *vs* 53.2%

- The proportion of patients receiving transplant from unrelated donors increased, with mismatched sibling donor transplants decreasing (**Table 1**)

Table 1. Transplant stem cell source and donor type, by epoch

Epoch	**1 (%)**	**2 (%)**	**3 (%)**
Donor type			
MSD	59.5	44.1	34.4
MUD	3.3	24.6	32.7
MMUD	2.3	8.8	8.6
Unrelated, HLA unknown	32.5	15.6	15.2
HD	1.2	2.6	6.3
CD	1.3	4.3	2.8
Cell source			
PB	73.7	81.5	84.8
BM	24.4	13.3	12.0
PB and BM	0.6	0.8	0.5
UC	1.3	4.3	2.8

Results

The investigators compared the outcomes between epochs one and two, and two and three. Some of these were statistically significant ($p < 0.05$), as indicated in **Table 2**.

Three-year OS:

- Increased across all epochs
- Increased in MSD transplant
- Increased between epochs 2 and 3 for MUD, HD, and CD transplants

Three-year NRM:

- Decreased in epoch 3, especially in HD, and somewhat in MSD, MUD and MMUD transplant
- For CD transplant, NRM was similar across the epochs, but was reduced between epochs 2 and 3
- Proportion of patients experiencing relapse over time did not differ
- Main causes of NRM in epoch 3:
  - Infection in HD (33.7%) and CD (31.1%)
  - GvHD in MSD (36.3%), MUD (31.7%) and MMUD (32.0%)
- Graft rejection in epoch 3 as cause of NRM (HD *vs* MMUD *vs* CD *vs* MUD *vs* MSD): 9.5% *vs* 6.4% *vs* 5.7% *vs* 5.4% *vs* 3.5%

Table 2. Outcomes by epoch and donor type

		Estimate (%)			FDR-adjusted Cox *p* value	
	n	Epoch 1 (2001-05)	Epoch 2 (2006-10)	Epoch 3 (2011-15)	Epoch 1 *vs* 2	Epoch 2 *vs* 3
Three-year OS	106,188	46.3	48.7	50.5	**<0.0001**	**<0.0001**
MSD	45,489	51.2	54.0	54.6	**0.0005**	**0.0083**
MUD	24,939	46.0	49.1	51.6	0.25	**<0.0001**
MMUD	7,722	41.4	37.4	41.3	0.34	**0.0033**
HD	4,174	23.0	34.5	44.2	0.46	**0.0033**

CD	3,130	37.1	36.3	43.7	0.46	**0.0086**
Three-year NRM	105,332	27.2	25.3	23.5	**<0.0001**	**<0.0001**
MSD	45,094	22.6	19.8	18.1	**<0.0001**	**<0.0001**
MUD	24,825	24.4	26.3	24.8	0.081	**<0.0001**
MMUD	7,685	31.3	36.6	33.4	0.82	**0.028**
HD	4,142	59.3	39.8	27.3	0.12	**0.0033**
CD	3,105	38.4	34.1	33.0	0.16	0.15
Three-year relapse incidence	105,332	34.0	33.6	34.1	**0.045**	0.46
MSD	45,094	34.5	35.6	36.8	0.47	0.44
MUD	24,825	37.1	31.8	31.0	0.45	0.36
MMUD	7,685	35.8	30.6	32.4	0.069	0.33
HD	4,142	21.8	31.6	33.2	0.051	0.87
CD	3,105	30.8	34.7	28.7	0.85	**0.0001**
Three-year PFS	105,332	38.8	41.0	42.4	**<0.0001**	**<0.0001**
MSD	45,094	42.9	44.6	45.0	0.054	0.10
MUD	24,825	38.4	41.9	44.2	0.22	**<0.0001**

MMUD	7,685	32.9	32.8	34.3	0.24	**0.023**
HD	4,142	19.0	28.6	39.5	0.82	0.055
CD	3,105	30.7	31.2	38.2	0.44	**0.0001**

GvHD

- Full analysis of outcomes for GvHD by donor type and epoch are shown in **Table 3**
- Severe aGvHD (grade III-IV):
  - Decreased moderately between MSD transplant recipients between epochs 1 and 2
    - Epoch 1 *vs* 2: 9.7% (95% CI, 9.2–10.3) *vs* 8.4% (95% CI, 7.9–8.8), *p*= 0.0002
  - Increased amongst CD recipients between epochs 2 and 3
    - Epoch 2 *vs* 3: 11.1% (95% CI, 9.4–12.8) *vs* 14.8% (95% CI, 12.7–16.8), *p*= 0.046
- Extensive cGvHD
  - Modest reduction led to increase in GRFS
- GRFS: improved with all donor types in epoch three

Table 3. GvHD outcomes by epoch and donor type

		Estimate (%)			FDR-adjusted Cox *p* value	
	n	Epoch 1 (2001-05)	Epoch 2 (2006-10)	Epoch 3 (2011-15)	Epoch 1 *vs* 2	Epoch 2 *vs* 3
One-year grade ≥ II aGvHD	99,625	27.1	25.0	25.4	**<0.01**	0.84
MSD	42,525	26.2	22.0	22.3	**<0.01**	0.84
MUD	23,741	33.0	26.5	27.8	0.51	0.56
MMUD	7,368	34.1	30.9	29.4	**<0.01**	0.19

HD	3,966	16.4	22.0	25.2	0.21	0.19
CD	2,940	24.6	29.0	33.5	0.33	0.17
One-year grade ≥ III aGvHD	99,625	10.4	9.4	9.7	**<0.01**	0.68
MSD	42,525	9.7	8.4	8.6	**<0.01**	0.78
MUD	23,741	13.2	9.1	10.1	0.25	0.82
MMUD	7,368	15.8	13.0	12.0	**0.01**	0.07
HD	3,966	4.7	8.1	8.9	0.25	0.25
CD	2,940	8.8	11.1	14.8	0.43	0.05
Three-year extensive cGvHD	93,864	14.1	13.9	11.9	0.28	**<0.01**
MSD	40,160	15.7	16.2	14.2	0.57	**<0.01**
MUD	22,021	19.5	14.0	12.3	0.72	0.07
MMUD	7,035	12.1	12.5	11.4	**<0.01**	**<0.01**
HD	3,856	7.4	7.8	7.2	0.97	0.07
CD	2,912	4.2	5.8	7.7	0.44	0.47
Three-year GRFS	86,408	25.8	27.8	30.7	**<0.01**	**<0.01**
MSD	36,492	27.9	28.9	31.1	**0.02**	**<0.01**

MUD	20,522	23.3	29.3	32.4	0.46	**<0.01**
MMUD	6,558	24.3	22.7	24.3	**<0.01**	**<0.01**
HD	3,660	14.8	20.6	33.2	0.82	**0.02**
CD	2,659	21.3	23.6	27.4	0.45	**0.02**

Risk stratification model

The authors developed a risk stratification scheme, categorizing patients in low-, intermediate-, and high-risk based on their disease, time from diagnosis, disease status, and cytogenetics. Using MSD as a reference category, the authors also compared outcomes by donor type within the risk categories. Epoch 3 served as the validation cohort, with results of multivariate analysis as below:

Overall mortality and NRM

- Intermediate- and high-risk: associated with increased hazard ratio (HR) for overall mortality
  - Intermediate-risk: HR= 1.24, (95% CI, 1.20–1.28)
  - High-risk: HR= 2.29, (95% CI, 2.21–2.38)
- MSD transplants had lowest overall mortality risk over all risk categories
- Hazard for all-cause mortality in the low- and intermediate-risk groups was higher with MUD:
  - Low-risk: HR= 1.22, (95% CI, 1.16–1.28), $p< 0.0001$
  - Intermediate-risk: HR= 1.12, (95% CI, 1.05–1.20), $p= 0.0004$
- NRM was higher with MUD in all categories but particularly in the low-risk group (HR= 1.45, (95% CI, 1.34–1.56), $p< 0.0001$)

Risk of Relapse

- Decreased risk of relapse was observed with low- and intermediate-risk MUD:
  - Low-risk: HR= 0.89, (95% CI, 0.84–0.95), $p= 0.0003$
  - Intermediate-risk: HR= 0.86, (95% CI, 0.80–0.92), $p< 0.0001$
- HD transplant showed a lower risk of relapse compared to MSD in the low- and intermediate-risk groups indicating a graft-*versus*-tumor effect. However, this benefit was not seen in the high-risk group possibly due to immune surveillance escape
  - Low-risk: HR= 0.83 (95% CI, 0.73–0.96), $p= 0.011$
  - Intermediate-risk: HR= 0.85, (95% CI, 0.74–0.99), $p= 0.033$
  - High-risk: HR= 1.14, (95% CI, 1.0–1.3), $p= 0.053$

- MUD transplant: across all risk categories, patients were less prone to relapse
    - Indicates graft-*versus*-tumor effect

Conclusions

OS has improved over time, across all donor types which appears to be driven by a decrease in NRM. The authors hypothesized that this is due to the use of RIC regimens and better supportive care. The biggest reduction in NRM was in patients receiving HD transplant, likely due to the use of post-transplant cyclophosphamide (PTCy) over anti-thymocyte globulin (ATG). PTCy appears to be an effective way to overcome HLA disparities.

In epoch 3 (transplant between 2011 and 2015), 24–33% of patients achieved an optimal outcome, were alive and relapse free without extensive GvHD at three-years post-transplant. Patients categorized as low- or intermediate-risk, who received an MSD transplant, had the lowest hazard for mortality. In high-risk disease though, similar hazards for mortality were observed between recipients of MUD and MSD transplant.

The incidence of cGvHD declined across the epochs, which the authors hypothesized is due to the use of ATG. ATG was used in 75% of HD transplants in epoch 2, whilst PTCy was used in 76% in epoch 3 indicating both are valid strategies to prevent GvHD.

Despite this, GRFS is only achieved by ~30% of patients. Current strategies to increase GRFS include;

- High-resolution HLA-matching
- Biomarker-driven approaches
- Modification of the microbiome
- Targeting immunosuppression

The authors concluded that the traditional hierarchy of donors (MSD, MUD and then other donors) remains true. The findings of this analysis may help guide further studies, and lead to the development of an algorithm to aid the selection of the most appropriate donor.

References

1. Shouval R., Fein J.A., *et al.* Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. Lancet Haem. 2019 Aug 30. DOI: 10.1016/S2352-3026(19)30158-9