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EBMT 2019 | No association between graft-versus-leukemia effect and graft-versus-host disease in patients with acute myeloid leukemia receiving haplo-identical stem-cell transplantation with post-transplant cyclophosphamide

Emily Smith | Apr 08, 2019

Previous studies have shown an association between a graft-*versus*-leukemia (GvL) effect and graft-*versus*-host disease (GvHD) in human leukocyte antigen (HLA)-matched donor transplants, but there is only limited data investigating this effect in T the T-replete haploidental stem cell transplant (haplo-SCT) setting. Separating the GvL and GvHD effect in this setting is therefore of great interest.

During the presidential symposium of the 45th European Society for Blood and Marrow Transplantation (EBMT) meeting in Frankfurt, Germany, Avichai Shimoni, Chaim Sheba Medical Center, Tel-Hashomer, IL, presented the results from a study by the acute leukemia working party (ALWP) of the EBMT. The study investigated the GvL effect in patients with acute myeloid leukemia (AML) who had undergone haplo-SCT with post-transplant cyclophosphamide (PTCy).[1]

Background

Allogeneic stem cell transplant (allo-SCT) may be a curative treatment for patients with AML, but is closely associated with GvHD. Due to the lack of a HLA-matched donors in many situations, haplo-SCTs from an HLA-mismatched donor are becoming increasingly common. In order to reduce the risk of GvHD in patients receiving haplo-SCT, T-cell depletion of the donor graft can be used; however, this has been shown to lead to high rates of non-relapse mortality (NRM). Recently, it has become possible to use non T-cell depleted haplo-SCT, in combination with PTCy, and achieve similar outcomes to transplants from HLA-matched donors.

It was also hypothesized that in in T-cell replete haplo-SCT with PTCy, natural killer (NK) cell alloreactivity may improve patient outcomes based on the absence of killer cell immunoglobulin-like receptor (KIR) ligands in the recipient that were present in the donor. However, the results of this study recently published in *Leukemia* failed to find a positive effect of NK alloreactivity in the PTCy setting with patients having similar relapse rates with, or without, KIR ligand mismatching.[2]

This aims of this study by the ALWP of the EBMT were to assess the impact of acute GvHD (aGvHD) and chronic GvHD (cGvHD) on haplo-SCT outcomes with PTCy.

Study design and patient characteristics

- Adult patients with AML (N = 605)
- Regimen:
  - Conditioning regimen (myeloablative *vs* reduced intensity): 71% *vs* 29%
  - Non T-cell depleted haplo-SCT with PTCy

    - GvHD prophylaxis: calcineurin inhibitor/mycophenolate mofetil: 87%
- Stem cell source (bone marrow *vs* peripheral blood stem cells): 51% *vs* 49%
- Median age: 53 years (18–76)
    - Median donor age: 37 years (13–72)
- Disease status:
    - Complete remission 1 (CR1): 73%
    - CR2: 27%
- Cytogenetics (good *vs* intermediate *vs* poor *vs* missing): 6% *vs* 43% *vs* 16% *vs* 35%
- aGvHD was assessed at day +100
- cGvHD was assessed at day +180 and +360

Transplant outcomes

The analysis of 605 patients at a median follow-up of 18 months (0.4–95) was consistent with previous studies that haplo-SCT with PTCy can provide similar outcomes to transplants from HLA-matched donors. This is true for aGvHD and cGvHD rates and two-year relapse, NRM, leukemia-free survival (LFS) and overall survival (OS) rates.

Univariate analysis at day +100 in 509 patients who remained alive and leukemia-free found no statistical significance between the rates of relapse and aGvHD. However, some factors showed statistical significance (**Table 1**):

- NRM was higher in patients with prior aGvHD grade II
- LFS and OS were lowest in the group with prior aGvHD grades III–IV
- The rates of cGvHD were higher in patients with prior aGvHD grades III–IV

Table 1: univariate analysis of outcomes of patients alive and leukemia-free on day + 100 (n = 509)

	N	Relapse (%)	NRM (%)	LFS (%)	OS (%)	cGvHD (%)
No aGvHD	366	20.3	10.3	69.4	73.6	32.7
aGvHD grade II	107	18.3	19.0	62.6	66.2	37.5
aGvHD grade III–IV	36	11.9	35.7	52.4	54.1	72.0
P value	-	0.6	<0.001	0.01	0.005	<0.001

In multivariate analysis, again, no significant association was found between any grade of aGvHD and relapse; however, there were significant associations between (**Table 2**):

- aGvHD grades III-IV and higher NRM, lower LFS and higher cGvHD

Table 2: multivariate analysis of outcomes of patients alive and leukemia-free on day +100

	Relapse		NRM		LFS		cGvHD	
No acute GvHD	1.00		1.00		1.00		1.00	
aGvHD grade II	1.02 (0.58–1.79)	0.93	1.79 (0.91–3.55)	0.09	1.28 (0.63–1.96)	0.27	1.15 (0.72–1.84)	0.55
aGvHD grade III–IV	0.92 (0.33–2.57)	0.87	5.23 (2.46–11.09)	0.003	2.35 (1.34–4.13)	0.003	4.85 (2.60–9.05)	0.001

In 366 patients alive and leukemia-free at day +180, univariate analysis showed significant associations between extensive cGvHD and higher NRM, lower LFS and OS (**Table 3**).

Table 3: univariate analysis of outcomes of patients alive and leukemia-free on day + 180 (n = 366)

	N	Relapse (%)	NRM (%)	LFS (%)	OS (%)
No cGvHD	316	14.3	7.3	78.4	82.6
Limited cGvHD	55	9.2	10.4	80.4	83.2
Extensive cGvHD	22	23.9	31.7	44.4	49.5
P value		0.58	0.003	0.007	0.0003

Multivariate analysis at day +180 (and similarly at day +360) showed no statistically significant association between cGvHD of any grade and relapse; however, it did show significant associations between extensive cGvHD and higher NRM and reduced LFS.

Table 4: multivariate analysis of outcomes of patients alive and leukemia-free on day +180*

	Relapse		NRM		LFS	
No cGvHD	1.00		1.00		1.00	
Limited cGvHD	0.68 (0.26–1.80)	0.45	1.43 (0.44–4.65)	0.56	0.88 (0.42–1.86)	0.74
Extensive cGvHD	1.45 (0.42–4.96)	0.56	5.77 (1.75–18.99)	0.004	2.75 (1.23–6.13)	0.01

* Analysis at day +360 showed similar results as to day +180.

Conclusion

This study by the ALWP of the EBMT has found no association between aGvHD or cGvHD of any grade and relapse. It did find however that aGvHD (grade III–IV) and extensive cGvHD were associated with higher rates of NRM and lower rates of LFS. In this setting, the ALWP conclude that GvL is not related to GvHD. One hypothesis to explain this is that PTCy may separate the GvL effect from GvHD. With GvHD a significant ongoing issue, further studies into prophylaxis and prevention strategies are warranted.

References

1. Shimoni A. *et al.* Graft-versus-leukemia effect after haplo-identical stem-cell transplantation with post-transplant cyclophosphamide in AML – no association with graft-versus-host disease: a study of the acute leukemia working party of the EBMT. Abstract GS2-3. 2019 March 25. 45th Annual Meeting of the European Society of Blood and Marrow Transplantation (EBMT), Frankfurt, DE
2. Shimoni A. *et al.* Killer cell immunoglobulin-like receptor ligand mismatching and outcome after haploidentical transplantation with post-transplant cyclophosphamide. Leukemia. 2018 June 15. DOI: 10.1038/s41375-018-0170-5