Journal of Hematology & Oncology

CORRESPONDENCE

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GVHD occurrence does not reduce AML relapse following PTCy-based haploidentical transplantation: a study from the ALWP of the EBMT

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Abstract

The association between graft-versus-host disease (GVHD) occurrence and acute myeloid leukemia (AML) relapse in patients treated with HLA-haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-HCT) with post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis has remained debated. Here, we addressed this issue in patients with active AML at transplantation. 2-year cumulative incidences of relapse and leukemia-free survival (LFS) were 49% and 32.3%, respectively. There were no associations between acute nor chronic GVHD of any grade and lower relapse incidence. However, grade I acute GVHD was associated with better LFS (HR = 0.71, 95% CI 0.51–0.99, $P = 0.04$). In contrast, grade III–IV acute (HR = 3.09, 95% CI 1.87–5.12, $P < 0.0001$) as well as extensive chronic (HR = 3.3, 95% CI 1.81–6.04, $P = 0.0001$) GVHD correlated with higher nonrelapse mortality leading to lower LFS (HR = 1.36, 95% CI 0.99–1.86, $P = 0.056$ and HR = 1.97, 95% CI 1.35–2.89, $P = 0.0004$, respectively). In conclusion, these data suggest a dissociation of graft-versus-leukemia effects from GVHD in patients with active AML treated with PTCy-based Haplo-HCT.

Keywords AML, Acute myeloid leukemia, HLA-haploidentical, Mismatched unrelated donor, Post-transplant cyclophosphamide, PTCy

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To the Editor

Allogeneic hematopoietic stem cell transplantation (allo-HCT) has remained the best option for patients with relapsed/refractory acute myeloid leukemia (AML) [1]. This approach relies on graft-versus-leukemia (GVL) effects for leukemia eradication. In patients receiving grafts from HLA-matched donors, numerous studies have demonstrated a tight association between occurrence of graft-versus-host disease (GVHD) and lower risk of relapse [2–4].

Post-transplant cyclophosphamide (PTCy)-based GVHD prophylaxis has revolutionized the field of human leukocyte antigen (HLA)-haploidentical hematopoietic cell transplantation (Haplo-HCT) [5, 6]. Consequently, Haplo-HCT is nowadays frequently used as treatment for relapsed/refractory AML patients [7]. A recent systems biology analysis in patients with PTCy-based GVHD prophylaxis demonstrated different signatures associated with GVHD and GvL effects [8]. In addition, another study observed different T-cell phenotypes associated with GVHD or GvL in PTCy-Allo-HCT recipients [9]. These observations prompted us to perform a large retrospective study in the EBMT registry aimed at assessing whether PTCy given in the Haplo-HCT setting might dissociate GVL effects from GVHD in patients with active AML at transplantation, a subgroup of patients who particularly rely on GVL effects for leukemic cell eradication. Population selection criteria included ≥ 18 years of age at transplantation, Haplo-HCT between 2010 and 2020 with PTCy, no prior allo-HCT, and primary refractory or relapsed AML (i.e. all patients had active disease at the time of transplant conditioning initiation).

The analyses were carried out in a total of 670 patients (Additional file 1: Table 1). The 180-day incidences of grade II-IV and grade III-IV acute GVHD were 30.8% (95% CI 27.4–34.3%) and 13.3% (95% CI 10.9–16%), respectively. These incidences were 21% and 8%, respectively, in BM recipients versus 35% ($P=0.001$) and 16% ($P=0.008$), respectively, in PBSC recipients. The 2-year cumulative incidences of chronic and extensive chronic GVHD were 26.8% (95% CI 23.4–30.3%) and 13% (95% CI 10.5–15.8%), respectively. There was no impact of stem cell source on chronic GVHD incidence. However, in vivo T-cell depletion was associated with a lower incidence of chronic GVHD (17% versus 28%, $P=0.027$).

The impact of GVHD on transplantation outcomes was assessed using dynamic landmarking *i.e.* a method including a series of landmark analyzes at each time interval of 30 days from allo-HCT to day 365 (Table 1, see Additional file 1 for more details) [10].

There was no impact of acute nor of chronic GVHD on relapse incidence (Table 1 and Fig. 1). There were

Table 1 Final model stratified on landmark at time intervals from day of allo-HCT to day + 360 by 30 days

	RI		NRM		LFS		OS	
	HR	*P*	HR	*P*	HR	*P*	HR	*P*
No acute GVHD ($n=320$, ref.)	1		1		1		1	
Acute GVHD I ($n=144$)	0.82 (0.56–1.21)	0.32	0.53 (0.27–1.01)	0.055	0.71 (0.51–0.99)	0.042	0.68 (0.48–0.97)	0.032
Acute GVHD II (=117)	0.83 (0.54–1.26)	0.38	0.78 (0.4–1.52)	0.46	0.8 (0.56–1.15)	0.23	0.86 (0.6–1.24)	0.42
Acute GVHD III–IV ($n=89$)	0.87 (0.55–1.36)	0.54	3.09 (1.87–5.12)	< 0.0001	1.36 (0.99–1.86)	0.056	1.32 (0.88–1.97)	0.17
No cGVHD (reference)	1		1		1		1	
Limited cGVHD	0.8 (0.43–1.49)	0.48	1.23 (0.54–2.81)	0.63	0.93 (0.57–1.52)	0.77	0.84 (0.48–1.49)	0.56
Extensive cGVHD	1.34 (0.74–2.42)	0.33	3.3 (1.81–6.04)	0.0001	1.97 (1.35–2.89)	0.0004	1.95 (1.29–2.94)	0.001
Age (per 10 y)*	0.9 (0.82–0.99)	0.038	1.56 (1.27–1.92)	< 0.0001	1.03 (0.94–1.13)	0.48	1.07 (0.98–1.18)	0.14
Sec. AML*	0.79 (0.54–1.15)	0.22	0.87 (0.52–1.46)	0.61	0.85 (0.63–1.15)	0.3	0.94 (0.69–1.28)	0.7
Adverse cytogenetics*	1.83 (1.37–2.45)	< 0.0001	1.33 (0.86–2.06)	0.2	1.68 (1.32–2.13)	< 0.0001	1.65 (1.28–2.12)	0.0001
Year of HCT*	0.97 (0.92–1.03)	0.3	0.97 (0.88–1.07)	0.55	0.97 (0.93–1.02)	0.27	0.98 (0.93–1.03)	0.42
KPS90*	0.88 (0.67–1.16)	0.37	0.61 (0.4–0.93)	0.022	0.82 (0.65–1.02)	0.08	0.82 (0.64–1.04)	0.11
Female to male*	0.8 (0.56–1.15)	0.23	1.43 (0.9–2.28)	0.13	0.97 (0.74–1.26)	0.8	1.08 (0.81–1.44)	0.58
Patient CMV positive*	1.19 (0.84–1.68)	0.32	1.01 (0.63–1.64)	0.96	1.12 (0.85–1.48)	0.42	1.11 (0.83–1.47)	0.49
Donor CMV positive*	1.14 (0.85–1.53)	0.37	0.73 (0.47–1.14)	0.17	1 (0.78–1.27)	0.97	1.02 (0.79–1.33)	0.86
PB vs BM*	0.94 (0.69–1.28)	0.72	1.66 (1.01–2.72)	0.046	1.07 (0.83–1.39)	0.58	1.1 (0.84–1.45)	0.47
RIC vs MAC*	1.11 (0.83–1.5)	0.48	0.88 (0.52–1.46)	0.61	1.06 (0.82–1.38)	0.64	1.15 (0.87–1.52)	0.33
In vivo TCD*	1.59 (1.03–2.44)	0.035	0.89 (0.4–1.97)	0.78	1.34 (0.9–1.99)	0.15	1.28 (0.86–1.92)	0.22

*Co-variates in the multivariate models; *Ref.* Reference; *RI* incidence of relapse; *NRM* nonrelapse mortality; *LFS* leukemia-free survival; *OS* overall survival; *GVHD* graft-versus-host disease; *cGVHD* chronic GVHD; *HCT* hematopoietic cell transplantation; *CMV* cytomegalovirus; *PB* peripheral blood stem cells; *BM* bone marrow; *RIC* reduced-intensity conditioning; *MAC* myeloablative conditioning; in vivo *TCT* in vivo T-cell depletion. There was no interaction between stem cell source (PB vs. BM) and the impact of GVHD on transplantation outcome

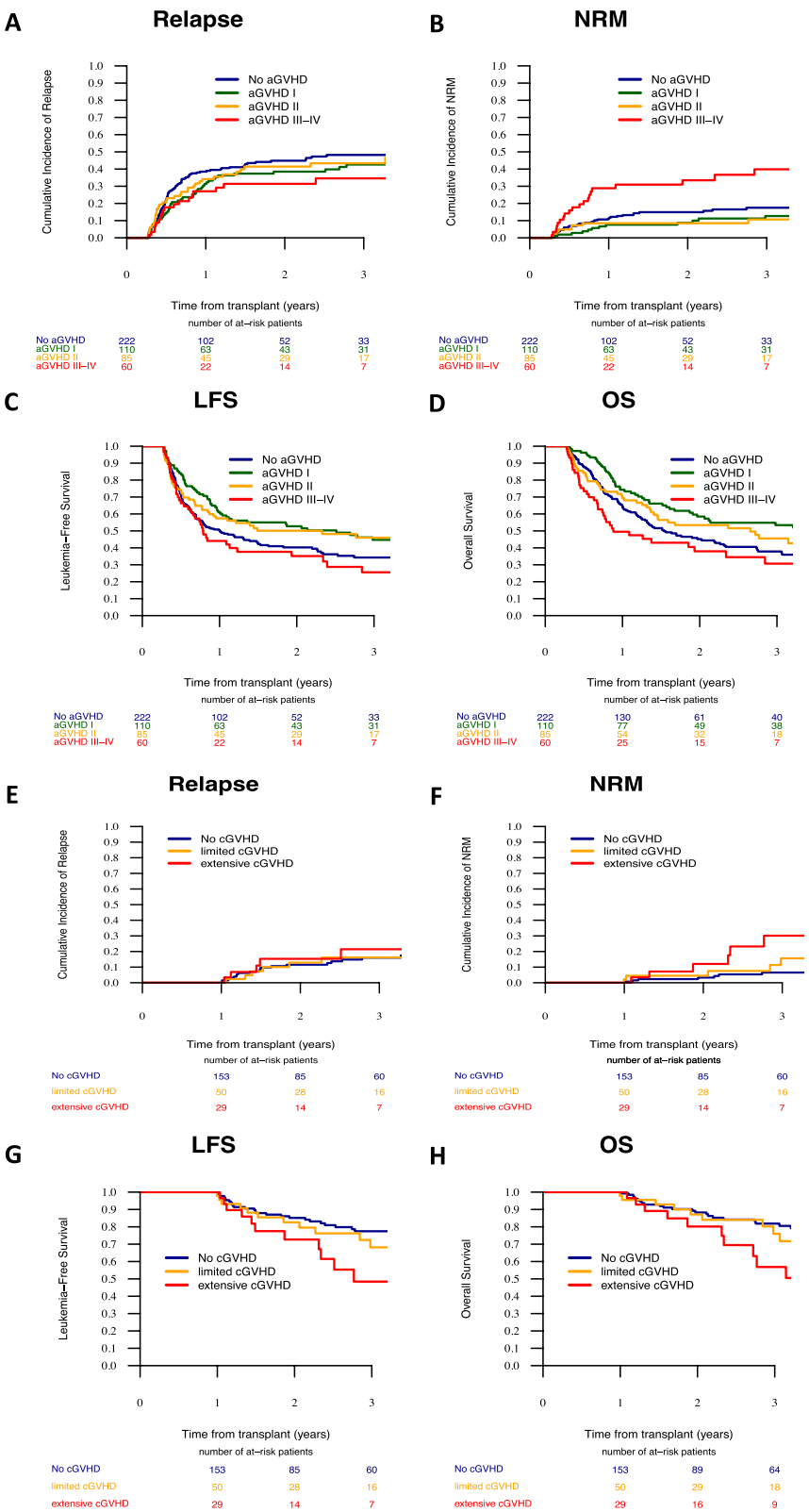

Fig. 1 **A**–**D** Day-100 landmark analyses ($n=477$) showing the impact of grade I, II and grade III–IV acute GVHD on: **A** relapse incidence ($P=0.39$); **B** incidence of nonrelapse mortality (NRM, $P=0.001$); **C** Leukemia-free survival (LFS, $P=0.005$); **D** overall survival (OS, $P=0.002$). **E**–**H** Day-365 landmark analyses ($n=234$) showing the impact of limited and extensive chronic GVHD on: **E** relapse incidence ($P=0.8$); **F** NRM ($P=0.021$); **G** LFS ($P=0.11$); **H** OS ($P=0.014$)

no associations between either grade II acute GVHD nor limited chronic GVHD on NRM, LFS nor OS in dynamic landmarking models (Table 1). However, grade III-IV acute GVHD was associated with higher NRM (HR = 3.09, 95% CI 1.87–5.12, $P < 0.0001$) and a statistical trend for lower LFS (HR = 1.36, 95% CI 0.99–1.86, $P = 0.056$) (Fig. 1). In contrast, grade I acute GVHD was associated with a trend for lower NRM (HR = 0.53, 95% CI 0.27–1.01, $P = 0.055$) and better LFS (HR = 0.71, 95% CI 0.51–0.99, $P = 0.042$) and OS (HR = 0.68, 95% CI 0.48–0.97, $P = 0.032$). We do not have a biological explanation for the lower NRM in patients with grade 1 acute GVHD. Future studies needed to evaluate whether this is due to a better immune reconstitution in patients with grade I acute GVHD. Finally, extensive chronic GVHD was associated with higher NRM (HR = 3.3, 95% CI 1.81–6.04, $P < 0.0001$) and lower LFS (HR = 1.97, 95% CI 1.35–2.89, $P = 0.0004$) and OS (HR = 1. 95, 95% CI 1.29–2.94, $P = 0.001$) (Fig. 1).

Our results differ from what has been observed by the Baltimore group in patients receiving Haplo-HCT with PTCy-based GVHD prophylaxis after nonmyeloablative conditioning as treatment of various hematological malignancies ($n = 340$) [11]. Indeed, in that study, grade II acute GVHD was associated with a lower risk of relapse. Our observations are, however, concordant with recent observations in another large population of patients treated with Haplo-HCT as treatment for AML in CR ($n = 805$) [10] and with data in humanized mouse models of GVHD in which it was demonstrated that PTCy attenuated GVHD without abrogating graft-versus-leukemia effects [12].

The absence of association between GVHD occurrence and the risk of relapse might suggest that in vivo T-cell depletion could be particularly suitable in the Haplo-HCT PTCy setting. However, we observed that ATG was associated with higher relapse incidence in multivariate analysis, without significantly affecting OS and LFS.

In conclusion, we demonstrated in a cohort of patients with active AML at transplantation treated with PTCy-based T-cell repleted Haplo-HCT that occurrence of GVHD did not decrease the risk of relapse suggesting a dissociation of GvL effects from GVHD in this transplantation setting.

Abbreviations

Allo-HCT	Allogeneic hematopoietic stem cell transplantation
AML	Acute myeloid leukemia
ATG	Anti-thymocyte globulin
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia effect
Haplo-HCT	HLA-haploidentical stem cell transplantation
LFS	Leukemia-free survival
NRM	Nonrelapse mortality
OS	Overall survival
PTCy	Post-transplant cyclophosphamide

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-023-01403-x.

Additional file 1. Supplemental data.

Acknowledgements
We thank Emmanuelle Polge from the office of the ALWP of the EBMT.

Author contributions
FB wrote the manuscript, designed the study and interpreted the data. ML designed the study, performed the statistical analyses, interpreted the data and edited the manuscript. MM and FC designed the study, interpreted the data, and edited the manuscript. JT, AMR, JV, DB, PC, FS, RF, PC and AN reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

Funding
FB is senior research associate at the Fonds National de la Recherche Scientifique (FNRS), Grant # T.0016.20.

Availability of data materials
ML and MM had full access to all the data in the study. Data are available upon reasonable request. Please contact Dr Myriam Labopin (myriam.labopin@upmc.fr).

Declarations

Ethics approval and consent to participate
The scientific board of the ALWP of the EBMT approved this research project. The study was conducted according to the Declaration of Helsinki, and Good Clinical Practice guidelines. EBMT centres commit to obtain informed consent according to the local regulations applicable at the time of transplantation and report pseudonymized data to the EBMT.

Consent for publication
Not applicable.

Competing interests
FB has received travel grants and/or speaker honoraria from Pfizer, Celgene, Abbvie, Novartis and Sanofi. The other authors declare that they have no relevant conflict of interest.

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Received: 5 December 2022 Accepted: 20 January 2023
Published online: 13 February 2023

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