Allogeneic Hematopoietic Stem Cell Transplantation in Patients Older than 65 Years with Acute Myeloid Leukemia and Myelodysplastic Syndrome: A 15-Year Experience

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Abstract

Background. Median age of occurrence of acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS) is 65 years and older. Nevertheless, the use of allogeneic stem cell transplant (allo-HCT) has been historically limited to younger population, namely due to excess in non-relapse-mortality (NRM) in elders.

Methods. In the present study, we analyzed all consecutive patients aged ≥ 65 y diagnosed with AML (71, 81%) or MDS (19, 19%) who received transplants from adult donors at our center from January 2005 to December 2019.

Results. Median age was 68.29y (65.02-76.54), 26pts (29%) aged ≥ 70 y. Thirty-three (37%) pts received a HLA-matched donor. Conditioning regimen was myeloablative in 46pts (51%). The 3-year overall survival (OS) was 53+/-6%, and disease free survival (DFS) 45+/-6% (Figure 1). Day-100 and 3-year NRM was 17+/-2% and 29+/-2%, respectively. The 3-year CI of relapse was 22+/-2%. Day-100 CI of aGvHD was 21+/-2% for grade II-IV, 14+/-1% for grade III-IV. The 3-year CI of cGvHD was 35+/-3%, extensive 20+/-2%. In multivariate analysis, the Karnofsky Performance Status (KPS) $< 90\%$ was associated with lower OS (HR: 2.999, CI: 1.477- 6.691; $p=0.002$), DFS (HR: 3.155, CI: 1.593 - 6.250; $p=0.001$) and higher NRM (HR: 2.997, CI: 1.344-6.682; $p=0.041$). HCT-CI ≥ 3 was also associated with higher NRM (HR: 2.949, CI: 1.166-7.462, $p=0.022$). Diagnosis of MDS and receiving a matched donor with PTCy were associated with longer OS (HR: 0.3440, CI: 0.1029-0.915; $p=0.033$; HR: 0.197, CI: 0.042-0.934; $p=0.041$).

Conclusions. Age alone should not limit transplant eligibility for AML and MDS. KPS and HCT-CI proved to be useful for patient selection among the elderly. The use of HLA-matched donors with PTCy improved OS compared to ATG in our consecutive series.

Introduction

Allogeneic stem cell transplantation (allo-HCT) is the only curative option for intermediate and high-risk adult acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS). Despite the median age of occurrence of these diseases (> 65 y)¹, the majority of patients older than 65y had historically been excluded from this potentially curative option for both changes in tumor biology (conferring treatment resistance) and patient characteristics (decreasing allo-HCT tolerance)² that translated into lower survival rates. Advances in allo-HCT using non-myeloablative/reduced-intensity conditioning (NMA/RIC) regimens allowed more widespread HCT application.^{3,4} Furthermore, when compared with conventional myeloablative conditioning (MAC) regimens, RIC yields comparable or lower peri-HCT toxicities but higher relapse rates.^{5,6} Data on patients older than 65y who received conditioning regimens intended to be myeloablative but with reduced toxicities, such as treosulfan-based, are limited. Understanding which older patients are likely to benefit from allo-HCT versus low-intensity therapies or supportive care is critical. Identifying the most suitable type of conditioning regimen, type of donor, and most effective

graft-versus-host disease (GvHD) prophylaxis is challenging. We here report our large, 15-year experience of allo-HCT in patients diagnosed with AML or MDS and older than 65 y.

Methods

Patients

Inclusion criteria of this retrospective analysis were: age > 65 years; diagnosis of either AML or MDS, both de novo and secondary; all disease status at allo-HCT, not ex-vivo T-cell depletion. All types of adult donors were included: matched related (MRD), matched unrelated (MUD), mismatched unrelated (MMUD), or haploidentical (haplo) donors. Patients could have received both peripheral blood (PB) or bone marrow (BM) as source of stem cells (SC). Only first allo-HCT were analysed (previous autologous HCT was allowed). All patients underwent transplantation between January 2005 and December 2019 at San Raffaele Hospital in Milan. The last updated follow-up was on December 31th 2020. A written informed consent was provided by all patients, allowing the retrospective use of medical records for research, in line with the Declaration of Helsinki. All experimental protocols were approved by the ethical committee of IRCCS San Raffaele Scientific Institute.

Definitions

Primary endpoints were overall survival (OS), disease free survival (DFS) and non-relapse mortality (NRM). Secondary endpoints were incidence of neutrophils and platelets engraftment, relapse incidence (RI), acute and chronic GvHD incidence. OS was defined as time from date of transplant to death from all causes. DFS was defined as time to death or relapse/progression whichever came first. NRM was defined as death without evidence of relapse. Acute GvHD was graded according to the modified Seattle Glucksberg criteria⁷, and chronic GvHD according to the revised Seattle criteria.⁸

Engraftment was defined as the first of three consecutive days with an absolute neutrophil count $>0.5 \times 10^9/L$, with no evidence of patient autologous reconstitution.

Myeloablative full intensity conditioning regimens (MAC) were defined as treosulfan (any dose) plus another alkylating agent (Melphalan 140mg/m² or Thiotepa 10mg/kg), treosulfan (42g/mq) plus TBI 4Gy, busulfan $\geq 9.6\text{mg/kg}$,⁹ and were compared to all other regimens (busulfan $\leq 6.4\text{mg/kg}$, treosulfan/fludarabine or treosulfan/clofarabine). Patient comorbidities were classified during pre-transplant assessment using the hematopoietic stem cell transplantation comorbidity-index (HCT-CI) according to Sorror et al.¹⁰ The Disease Risk Index was assigned at the time of transplant according to Armand et al.¹¹

Hematopoietic chimerism was assessed monthly in samples of bone marrow aspirate with the use of short-tandem-repeat amplification and genomic HLA typing in parallel until 2011 as previously reported¹² or with the use of real-time quantitative polymerase chain reaction from June 2011.¹³ Full donor chimerism was defined as the percentage of recipient cells less than 1%.

Statistical analysis

OS and DFS were estimated by the product-limit method of Kaplan-Meier.¹⁴ Cumulative incidence (CI) functions were used to estimate engraftment, aGvHD, cGVHD, RI and NRM.¹⁵ Competing risks were as follows: death without engraftment for engraftment; death without relapse for RI; relapse for NRM; death without GvHD for aGvHD and cGVHD. Univariate analyses were done using log rank test¹⁶ for OS and DFS and Gray's test¹⁷ for CI function. The following variables were assessed via univariate analysis: diagnosis (AML vs MDS), bone marrow blast count before allo-HCT ($<5\%$ vs $\geq 5\%$), intensity of conditioning regimen (MAC vs others), patient age ($<$ or ≥ 70 y), in-vivo T-cell depletion (posttransplant cyclophosphamide - PtCy vs no PtCy), HCT comorbidity index (HCT-CI) ($0-2$ vs ≥ 3), year of transplant according to the median value (< 2015 vs ≥ 2015). Given the lack of statistically significant differences in all transplant outcomes between matched donors (MRD vs MUD) (data not shown), which was in line with Devine et al¹⁸, and the low number of patients receiving an MRD, we grouped together the matched donors and compared their outcomes to those of the mismatched donors (haplo and MMUD).

Multivariate analysis were performed using the Cox proportional-hazard model.¹⁹ We looked for interactions between the type of donor (matched vs mismatched) and type of in-vivo T-cell depletion (PTCy vs no PTCy). All factors known to influence outcome and factors associated with a univariate analysis p-value < 0.10 were first included in the model. Then, a stepwise backward procedure was used with a cut-off significance level of 0.10 for deleting factors from the model. The type I error rate was fixed at 0.05 for determination of factors associated with time to event.

Analyses were performed using SPSS 26 and the R statistical software version 3.2.3 (R Development Core Team, Vienna, Austria).

Results

Patient and Donor characteristics

Between January 2005 and December 2019, 90 consecutive adult patients aged more than 65y received an allo-HCT for AML or MDS at our center. Patients' and disease characteristics are described in Table 1. Patients' median age was 68.29y (65.02-74.38), with no difference for AML and MDS ($p=0.479$). Median interval from diagnosis to transplant was 9.85mo (0.72-120.89). Donors' median age was 38y (18-74): 64y (55-74) for sibling, 39y (20-58) for haplo, 30y (19-50) for MUD and 32y (18-52) for MMUD. Median CD34 $\times$ 106/kg cells infused was 6 (1.51-9.57): 5 (1.55-7.50) for sibling, 6.47 (3.23-9.57) for haplo, 5.01 (1.51-7.85) for MUD and 6.01 (4.61-8.16) for MMUD.

Conditioning regimens and GvHD prophylaxis are described in Table 2. The conditioning regimen was treosulfan-based in 78pts (87%). as single alkylating agent or in association to thiotepa or melphalan. Eighty-five (94%) pts received in-vivo T-cell depletion: in 54 (63%) with antithymocyte globulin (ATG) and in 31 (37%) with posttransplant cyclophosphamide (PTCy). Five pts (6%) received neither ATG nor PTCy;

all 5 of which received an MRD. Forty-four (49%) pts had an HCT-CI of 0, 31 (34%) pts of 1 or 2 and 15 (17%) pts ≥ 3 . Disease Index Risk was high or very high in 49 (44%) pts and these patients were more likely to receive a MAC regimen ($p=0.032$).

Engraftment and chimerism

All patients engrafted, except one who was rescued by a second allo-HCT. Median time from transplant to neutrophil engraftment was 21 days (11-49). The CI of neutrophil engraftment was $78\pm 2\%$ at day-30 and $90\pm 1\%$ at day-100 from transplant. The latest patient engraftment occurred on day-49. Intensity of conditioning regimen (MAC vs others) was not correlated to time for neutrophil engraftment ($p=0.658$). At day-30 CI of platelet engraftment $> 20000/\text{mmc}$ was $62\pm 3\%$, while $79\pm 2\%$ at day-100. Four patients reached a platelet count higher than $20000/\text{mmc}$ after day-100: 2pts at day-109, 1pt at day-127 and 1pt at day-271. All patients had HSV6 reactivation with organ involvement during the first 100 days following transplant. Immune reconstitution data were available for 48 out of 72 (67%) surviving patients at day +90 and for 36 out of 52 (69%) survivors at 1 year from transplant. At day +90 and +365, the median count of CD3+ cells/mcl was 660 (42-2524) and 1298 (251-5879), of CD4+ cells/mcl was 174 (32-675) and 329 (75-1431), of CD8+ cells/mcl was 424 (7-2021) and 835 (143-4547), of CD19+ cells/mcl was 6 (0-144) and 134 (0-678), respectively. Among the 72 pts alive at day 100, chimerism was full donor in 67 (93%). Median time from transplant to full donor chimerism was 40 days (21-853), 2 pts had a full donor chimerism after day 365.

Acute and Chronic Graft-versus-Host Disease

Day-100 CI of aGvHD was $21\pm 2\%$ for grade II-IV (Figure 1A) and $14\pm 1\%$ for grade III-IV (Figure 1B). Skin was involved in 36pts (86%), gut in 15pts (36%) and liver in 6pts (14%).

The 3y overall incidence of cGvHD was $35\pm 3\%$ (Figure 1C). Extensive cGvHD incidence was $20\pm 2\%$ at 3 years (Figure 1D). Twelve out of 17 (71%) pts that developed extensive cGvHD were still alive: 7 (58%) pts with resolved cGvHD and free from IST, one (8%) pt with resolved cGvHD still on ruxolitinib, 3 (26%) pts with stable cGvHD in systemic immunosuppressive therapy (ruxolitinib, prednisone, ruxolitinib plus prednisone) and 1pt (8%) with cGvHD on local therapy for eye involvement.

Relapse Incidence

The 3-year CI of relapse was $22\pm 2\%$ (Figure 2C). Nineteen patients received posttransplant treatment for their disease: 1 (5%) prophylactic, 4 (21%) pre-emptive, and 14 (74%) for haematological relapse. Three out of 19 (16%) relapsed patients are still alive (2 in complete remission), 14 (74%) pts died from disease progression and 2 (10%) for causes other than haematological disease. Median time for relapse occurrence was 6mo (1.15-60-13).

Non Relapse Mortality

CI of day-100 and 3-year NRM was 17+/-2% (Figure 2A), and 29+/-2% (Figure 2B), respectively. In univariate analysis day-100 NRM was lower in patients with an HSCT-CI less than 3 (5+/-3% vs 18+/-6%, p=0.006) and receiving a matched donor (6+/-4% vs 24+/-6%, p=0.034).

Twenty-six patients died from transplant related causes. Sixteen pts died from infection (15 AML and 1 MDS), 7pts from GvHD, 1 from multi-organ failure, 1 from cardiac toxicity, 1 for unknown cause.

In MVA, KPS < 90% (HR: 2.997, CI: 1.344-6.682, p=0.007) (Figure 3A) and HCT-CI $\geq$ 3 (HR: 2.949, CI: 1.166-7.462, p=0.022,) (Figure 3B) were independently associated with higher risk of NRM. There was a trend for lower NRM in patients receiving a matched donor (p=0.052).

Overall Survival and Disease Free Survival

Median follow-up among survivors was 35.08 months (2.82-104). Median duration of hospitalization among survivors was 48 days (24-198). The 3y OS was 53+/-6% (Figure 4A). In univariate analysis, diagnosis and KPS were associated to outcome: 3y OS of 89+/-7% for MDS compared to 47+/-6% for AML (p=0.024) and 3y OS of 62+/-6% for KPS $\geq$ 90% compared to 26+/-10% for KPS < 90% (p=0.001). In MVA (Table 3) risk factors for a higher 3y OS were diagnosis of MDS vs AML (HR: 0.3440, CI: 0.1029-0.915; p=0.033), having received a matched donor with PTCy as GvHD prophylaxis (HR: 0.197, CI: 0.042-0.934; p=0.041). KPS < 90% was a risk factor for lower 3y OS (HR: 2.999, CI: 1.477-6.091; p=0.002). Patients transplanted with a matched donor using PTCy had a 3y OS of 79+/-11%.

The 3y DFS was 45+/-6% (Figure 4B). In univariate analysis higher 3y DFS was found in patients with a KPS $\geq$ 90% (53+/-7% vs 22+/-10%) (p=0.0002). In MAV the only risk factor for a lower 3y DFS was KPS < 90% (HR: 3.155, CI: 1.593-6.250; p=0.001).

Discussion

The maximum age of patients receiving allogeneic hematopoietic stem cell transplantation (allo-HCT) has been increasing over time^{20,21}. Nevertheless, consistent data on allo-HCT outcome and risk factors for better selecting patients more likely to benefit from this procedure are still scarce.

In the current retrospective study, we report our 15-year experience on allo-HCT, analyzing 90 consecutives adults patients older than 65 years affected by AML or MDS.

The majority of our patients received a treosulfan-based conditioning regimen and a rapamycin-based GvHD prophylaxis. Our approach was in line with the regimens we previously described in younger patients,^{22,23} but quite different from other reports about allo-HCT in elderly patients in the literature.^{24,25,18,26,27} The myeloablative properties of the treosulfan/fludarabine conditioning regimen have already been demonstrated in several publications^{28,29,30,31,32} and our data confirms prompt engraftment, rapid achievement of full-donor hematopoietic chimerism, as well as a low relapse incidence. Neutrophil engraftment was not a major concern as all but one patient engrafted.

The intensity of conditioning regimens used in our patients is another remarkable difference from all previous reports on older patients so far. Indeed, in half of our patients we attempted to increase the intensity of conditioning regimen with a second alkylating agent or with TBI, a well-known strategy to improve OS and lower RI.^{33,34} In addition, almost all patients received in-vivo T-cell depletion. NRM was not affected by increased intensity or by in vivo T-cell depletion strategies; this may be a result of the low toxicity profile of treosulfan-based conditioning regimen^{32,35} and the prevalent use of PTCy for T-cell in-vivo depletion strategy.^{36,9,37,38} Both day-100 and 3-y NRM were in line with previous reports of leukemic/myelodysplastic even younger patients.^{18,39,3,11,40} Day-100 NRM was largely below 10% in both HCT-CI < 3 and KPS > 90% patients indicating that we can easily identify older patients with a transplant risk comparable to that of younger ones using these scores. Matched donors, already associated with a lower incidence of NRM,³ seemed to be of help in reducing NRM in our study.

Despite the percentage of high/very high risk disease, relapse incidence was lower than expected compared to both younger patients receiving treosulfan-fludarabine²⁸ and older populations as previously reported^{3,18,41}. One possible explanation could be the addition of a second alkylating agent/TBI to treosulfan-fludarabine according to DRI, which would suggest that optimizing the pretransplant strategy may be critical to posttransplantation outcomes. Moreover, it has been reported that patients with advanced disease performed better after transplant if treosulfan was administered as part of their conditioning regimen.^{31,42} Finally, half of the patients in the present study received a transplant from a haploidentical donor, a factor that is already associated to lower RI using PTCy.^{9,43} Only a minority of patients received a prophylactic or preemptive posttransplant therapy.

The nearly exclusive use of PBSC did not increase the incidence of aGvHD II-IV, and the incidence of grade III-IV was similar to that of previous reports in older patients.^{3,24} These results confirm the efficacy of a rapamycin-based GvHD prophylaxis and may support the more favorable cytokine production due to treosulfan use compared to busulphan²⁹ and the positive influence of in-vivo T-cell depletion,^{9,44} especially with PTCy in mismatched cases.^{36,45} Of note, most of the extended cGvHD resolved and patients restored a good quality of life withdrawing all IST. A minority of patients are still on IST with a compromised quality of life.

These encouraging results in terms of NRM, RI, and GvHD, resulted in a surprisingly high OS and DFS at 3 years in our older population, far better than the first reports about allo-HCT in the elderly^{24,18,46} and higher than more recent reports as well.^{4,25,26} In contrast to previous data^{4,46} but according to Ustun,⁴⁷ we didn't find any difference in transplant outcomes in patients younger or older than 70 years. Despite high KPS in our patient populations, these patients suffered from several comorbidities and the majority had an HCT-CI of at least 3. Both of these scores confirmed to be useful for patients selection, but they are not superimposable. Improved identification of patients more likely to benefit from transplant could be derived from adding a geriatric assessment for frailty, which has already been shown to predict survival in older transplantation recipients.²¹ Patients diagnosed with AML resulted in a reduced survival after transplant, probably as a result of higher numbers of death from infections. Therefore, it should be

suggested to proceed to transplantation as soon as possible if the patient has an indication for allo-HCT and is determined to be fit for this procedure. According to our data, choosing a matched donor and using PTCy as back-bone for GvHD prophylaxis seems to be the best choice for improving survival in the elderly.

Conclusions

Our results confirm that age should not be the only criteria for excluding AML/MDS patients older than 65y from allo-HCT. By taking into consideration patient KPS, HCT-CI, DRI, and HLA-matching, we could design the ideal transplantation procedure in terms of survival for these patients, limiting relapse and GvHD without increasing NRM. Multicentric and larger studies with similar platforms are needed to confirm our results.

Abbreviations

AL	acute leukemia
AML	acute myeloid leukemia
SCT	stem cell transplantation
EBMT	European Society for Blood and Marrow Transplantation
OS	overall survival
CR	complete remission
RI	relapse incidence
HCT-CI	Hematopoietic cell transplantation - specific comorbidity index
PB	peripheral blood
BM	bone marrow
NRM	non relapse mortality
RIC	reduced-intensity conditioning regimens
MAC	myeloablative conditioning regimens
HLA	human leukocyte antigen
GVL	graft vs leukemia

ALWP	Acute Leukaemia Working Party
MED-A	minimum essential data A
GvHD	graft vs host disease
TBI	total body irradiation
PTCy	Posttransplant Cyclophosphamide
ATG	antithymocyte globulin
EMR	extramedullary relapse
TKI	tyrosine kinase inhibitors
DLI	donor leukocyte infusion
LFS	leukemia free survival
KPS	Karnofsky Performance Status

Declarations

ETHICS APPROVAL AND CONSENT FOR PUBLICATION

A written informed consent was provided by all patients, allowing the use of medical records for research in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIA

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare no competing financial interests.

FUNDING

The authors declare that they have no competing interests

AUTHORS' CONTRIBUTIONS

S.P. designed research, checked the data, analysed data and wrote the paper;; L.L. collected the data and wrote the paper; A.R. analysed the data and wrote the paper. All the other authors wrote the paper.

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Tables

Table 1. Patients', Host/Donor characteristics

		AML 71 (79%)	MDS 19 (21%)	p-value
Year of transplant		2015 (2005-2019)	2015 (2008-2019)	
Age at SCT	median (range)	68.10y (65.02-74.38)	68.5y (65.81-76.53)	0.479
Time diagnosis-transplant		10.36mo (0.72-120.89)	7.61mo (1.28-36.30)	0.254
Patient sex	Female	50 (70%)	15 (79%)	0.572
	Male	21 (30%)	4 (21%)	
Donor/Host sex	Female/Male	18 (25%)	6 (32%)	0.572
BM blasts pre Tx	<5%	39 (55%)	11 (58%)	1.000
	≥ 5%	32 (45%)	8 (42%)	
sAML		33 (46%)	NA	
ELN Risk (2017)	Low	3 (4%)	NA	
	Intermediate	45 (63%)		
	Adverse	23 (33%)		
IPSS-R	Intermediate	NA	3 (25%)	
	High		4 (33%)	
	Very High		5 (42%)	
	Unknown		7	
Disease Risk Index	Low	1	0	0.908
	Intermediate	31	9	
	High	33	9	
	Very High	6	1	
PS Karnosky	≥ 90%	53 (75%)	17 (90%)	0.223
	≤ 80%	18 (25%)	2 (10%)	
Sorrer	HCT-CI 0	14 (20%)	4 (21%)	0.315
	HCT-CI 1-2	15 (21%)	7 (37%)	
	HCT-CI ≥3	42 (59%)	8 (42%)	
Donor age	median (range)	37y (19-74)	40y (18-66)	0.192
Donor type	MRD	8 (11%)	5 (26%)	0.383
	Haplo	36 (51%)	8 (42%)	
	MUD	17 (24%)	3 (16%)	
	MMUD	10 (14%)	3 (16%)	
Host/Donor CMV status	neg/neg	2 (3%)	0	0.420
	neg/pos	1 (1%)	1 (5%)	
	pos/neg	20 (29%)	3 (16%)	
	pos/pos	46 (67%)	15 (79%)	
	missing	2	0	
Stem cell source	BM	2(3%)	3 (16%)	0.061
	PB	69 (97%)	16 (84%)	

Table 2. Conditioning regimens, GvHD prophylaxis and stem cell source

		AML (71pts)	MDS (19pts)
Conditioning regimen	Treo-Flu	27 (38%)	6 (32%)
	Clo-Treo	1 (1%)	0
	Treo-Flu-TBI 4Gy	3 (4%)	1 (5%)
	Thio-Treo-Flu	8 (12%)	2 (10%)
	Treo-Flu-Mel	25 (35%)	6 (32%)
	Flu-Bu2	6 (9%)	4 (21%)
	Thio-Bu (9.6)-Flu	1 (1%)	0
Tresulfan dose (g/mq)	10	5 (8%)	1 (7%)
	12	14 (22%)	4 (27%)
	14	44 (70%)	10 (66%)
		tot. 63	tot. 15
Melfalan dose (g/mq)	80	1 (40%)	0
	100	12 (48%)	4 (66%)
	120	3 (12%)	1 (17%)
	140	9 (36%)	1 (17%)
		tot. 25	
Thiotepa dose (g/mq)	5	3 (33%)	1 (50%)
	6	1 (11%)	1 (50%)
	8	1 (11%)	0
	10	4 (44%)	0
		tot. 9	tot. 2
Conditioning regimen intensity	NMA/RIC	34 (48%)	10 (53%)
	Full intensity	37 (52%)	9 (47%)
GvHD prophylaxis	Sirolimus	5 (7%)	2 (10%)
	Sirolimus-MMF	51 (72%)	12 (64%)
	CSA-MTX	15 (21%)	5 (26%)
In vivo T-cell depletion	none	2 (3%)	3 (16%)
	ATG, no PTCy	24 (34%)	7 (37%)
	PTCy, no ATG	45 (63%)	9 (47%)

Table 3. Multivariate analysis of NRM, OS and DFS

NRM	95.0% CI for Exp(B)			
	Exp(B)	Lower	Upper	Sig.
MDS vs AML	0.422	0.098	1.822	0.248
HCT-CI ≥ 3 vs < 3	2.949	1.166	7.462	0.022
KPS $< 90\%$ vs $\geq 90\%$	2.997	1.344	6.682	0.007
Matched Donor vs Mismatched Donor	0.401	0.159	1.007	0.052

OS	95.0% CI for Exp(B)			
	Exp(B)	Lower	Upper	Sig.
HCT-CI ≥ 3 vs < 3	1.203	0.645	2.243	0.561
Matched Donor vs Mismatched Donor	1.068	0.422	2.703	0.889
PtCy vs no PtCy	0.982	0.453	2.130	0.964
KPS $< 90\%$ vs $\geq 90\%$	2.999	1.477	6.091	0.002
DRI High-Very High vs Low-Intermediate	1.474	0.758	2.866	0.253
MDS vs AML	0.344	0.129	0.915	0.033
PTCy*Matched Donor	0.197	0.042	0.934	0.041

DFS	95.0% CI for Exp(B)			
	Exp(B)	Lower	Upper	Sig.
HCT-CI ≥ 3 vs < 3	1.040	0.557	1.940	0.903
Matched Donor vs Mismatched Donor	1.258	0.502	3.152	0.625
PtCy vs no PtCy	0.982	0.453	2.130	0.964
KPS $< 90\%$ vs $\geq 90\%$	3.155	1.593	6.250	0.001
DRI High-Very High vs Low-Intermediate	1.382	0.721	2.647	0.330
MDS vs AML	0.506	0.201	1.272	0.147
PTCy*Matched Donor	0.259	0.062	1.080	0.064

Figures

Figure 1

CI of grade II-IV aGvHD (A); grade III-IV aGvHD (B); cGvHD overall (C), extensive cGvHD

Figure 2

CI of NRM at day 100 (A) and at 3 years (B), CI of relapse at 3 years

A **B** **Figure 3**

NRM according to HCT-CI (A) and to KPS (B)

A **B** **Figure 4**

3-year Overall Survival (A) and Disease Free Survival (B)