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ARTICLE

Impact of patient: donor HLA disparity on reduced-intensity-conditioned allogeneic stem cell transplants from HLA mismatched unrelated donors for AML: from the ALWP of the EBMT

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Abstract

Patients with acute myeloid leukaemia (AML) who lack a matched sibling or unrelated donor commonly undergo transplantation from a donor matched at 9/10 HLA-A, -B, -C, -DRB1, -DQB1 alleles, and it is unclear if a specific locus mismatch is preferable to any other. We therefore studied 937 patients with AML in complete remission transplanted using a reduced intensity conditioning regimen from an unrelated donor mismatched at a single allele. In a multivariate analysis, patient age, adverse karyotype and patient cytomegalovirus (CMV) seropositivity were correlated with decreased leukaemia free survival (LFS) and overall survival (OS). There was no significant difference in LFS or OS between patients transplanted from donors mismatched at HLA-A, -B, -C or -DRB1 in comparison to a HLA-DQB1 mismatched transplant. In a multivariate analysis, patients transplanted with a HLA-A mismatched donor had higher rates of acute graft-versus-host disease (GVHD) and non-relapse mortality (NRM) than patients transplanted with a HLA-DQB1 mismatched donor. Patient CMV seropositivity was associated with an increase in NRM and acute GVHD and reduced LFS and OS, regardless of donor CMV status. For CMV seropositive patients lacking a fully matched donor, alternative GVHD and CMV prophylaxis strategies should be considered.

Introduction

The most effective form of consolidation for patients with high risk acute myeloid leukaemia (AML) is an allogeneic stem cell transplant (allo-SCT) [1–5]. The use of reduced intensity conditioning (RIC) regimens for AML has resulted

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in the safe delivery of allo-SCT to older patients and those with co-morbidities [6–8] and has resulted in AML becoming the leading indication for allo-SCT [9], thus, optimal donor selection is a critical part of the management of these patients.

Studies have shown outcomes for patients transplanted with a matched sibling donor are similar to those transplanted with a 10/10 HLA matched unrelated donor (MUD) [10]. Using large international registers of potential donors, a 10/10 HLA MUD could be found in ~75% of patients of European ethnic descent [11]. For the remainder of patients an alternative donor source has to be found, and a commonly used donor source is a 9/10 HLA MUD. A full 10/10 donor match remains the preferred option to a 9/10 match in terms of acute graft-versus-host disease (aGVHD), non-relapse mortality (NRM) and overall survival (OS) [12–14].

However, it is unclear whether for patients with only a 9/10 match, a mismatch at a particular locus is preferable to any others. For example, one study suggest that HLA-A, -B and -C mismatches were associated with an increased mortality compared to mismatches at HLA-DRB1/DQB1 [15], while in another, single mismatches at HLA-B or HLA-C appear better tolerated than mismatches at HLA-A or HLA-DRB1 [16].

The use of in vivo T-cell depletion (TCD) has reduced the rate of GVHD and allowed tolerable rates of NRM in HLA mismatched RIC allo-SCT [17] but there are concerns that this results in an increase in relapse rates and in infective complications, notably that of cytomegalovirus (CMV) [18]. CMV seropositivity is known to be a poor risk factor in patients with mismatched HLA donors [14, 19], but previous studies have analysed very heterogeneous cohorts of patients in terms of both underlying disease and conditioning intensity [14, 19]. There is a paucity of data regarding the interaction of donor: recipient HLA mismatch with these other factors outlined above in this treatment setting.

To resolve these questions, we interrogated the multicentre European Society for Blood and Marrow Transplantation (EBMT) registry to analyse the outcomes of patients who received a RIC allo-SCT with a 9/10 HLA MUD for AML, and compared the outcomes of patients transplanted with donors mismatched at different loci.

Materials and methods

Study design and data collection

We retrospectively investigated the outcomes of patients with AML in CR1 or CR2 who received a RIC allo-SCT between 2001 and 2015 from an unrelated donor who was reported as 9/10 HLA match using high-resolution typing performed at HLA -A, -B, -C, -DRB1 and -DQB1. Any difference in HLA typing (at either antigen or allelic level) between patients and donor was considered a mismatch. Data were provided and approved for this study by the review committee of the Acute Leukemia Working Party of the EBMT group registry. The latter is a voluntary working group of more than 600 transplant centres that are required to report all consecutive stem cell transplantations and follow-ups once a year (Supplementary Table 1). Patients participating in the data collection provided informed consent for the use of their personal information for research purposes.

Statistical analysis

Patient, disease and transplant-related characteristics for the five cohorts (HLA-A -B -C -DQ or -DR mismatch) were compared by using χ^2 statistics for categorical variables and the Kruskal–Wallis test for continuous variables.

Acute and chronic GVHD was graded using previous descriptions [20, 21]. GVHD-free, relapse-free survival (GRFS) was calculated as described previously [22]. Relapse was defined as the emergence of ≥5% blasts, and NRM was defined as death in the absence of relapse or progression. Survival (OS/LFS) was measured from the time of transplant to the event. Cumulative incidence was used to estimate the endpoints of NRM, relapse incidence (RI), acute and chronic GVHD to accommodate for competing risks. To study acute and chronic GVHD, we considered relapse and death to be competing events. The Kaplan–Meier estimate was used to calculate the probabilities of GRFS, LFS and OS [23, 24]. Univariate analyses were performed using Gray's test for cumulative incidence functions and the log-rank test for OS, GRFS and LFS. A Cox proportional-hazards model was used to assess the impact of different variables including patient, disease and transplant characteristics on survival outcomes. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). All tests were two-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed using R 3.4.0 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Results

Patient and transplant characteristics

Nine hundred and thirty-seven patients were included with a median follow-up period of 24 months. The median

Table 1 Patient and transplant characteristics.

HLA mismatch	A	B	C	DQ	DR	Test p value	Total
Number	264	127	292	180	74	(Global)	937
Median follow-up (range)	16.39 (1.02–139.08)	23.64 (0.79–114.43)	25.67 (0.82–123.51)	29.61 (2.52–90.56)	24.33 (1.41–97.05)		23.95 (0.79–139.08)
Median age of patient at transplant (range)	57.7 (18.5–75.4)	56.8 (20.9–72)	59.2 (18.1–74.7)	58 (19.3–75.3)	57.8 (18.8–71.5)	0.17	57.92 (18.15–75.43)
Disease status at transplant							
CR1	170 (64.39%)	83 (65.35%)	205 (70.21%)	127 (70.56%)	55 (74.32%)	0.34	640 (68.3)
CR2	94 (35.61%)	44 (34.65%)	87 (29.79%)	53 (29.44%)	19 (25.68%)		297 (31.7)
De novo AML	199 (75.38%)	101 (79.53%)	248 (84.93%)	146 (81.11%)	57 (77.03%)	0.073	751 (80.15)
Secondary AML	65 (24.62%)	26 (20.47%)	44 (15.07%)	34 (18.89%)	17 (22.97%)		186 (19.85)
Donor/recipient CMV serostatus							
D−/R−	62 (24.12%)	26 (21.67%)	62 (21.53%)	43 (24.29%)	16 (22.22%)	0.32	209 (22.87)
D+/R−	23 (8.95%)	16 (13.33%)	26 (9.03%)	7 (3.95%)	11 (15.28%)		83 (9.08)
D−/R+	76 (29.57%)	39 (32.5%)	95 (32.99%)	64 (36.16%)	23 (31.94%)		297 (32.49)
D+/R+	96 (37.35%)	39 (32.5%)	105 (36.46%)	63 (35.59%)	22 (30.56%)		325 (35.56)
Missing	7	7	4	3	2		23
No in vivo TCD	37 (14.07%)	18 (14.29%)	50 (17.24%)	42 (23.46%)	20 (27.03%)	0.019	167 (17.92)
In vivo TCD	226 (85.93%)	108 (85.71%)	240 (82.76%)	137 (76.54%)	54 (72.97%)		765 (82.08)
Missing	1	1	2	1	0		5
No acute GVHD II–IV	164 (64.31%)	88 (70.4%)	209 (72.07%)	132 (75%)	53 (74.65%)	0.12	646 (70.45)
Acute GVHD II–IV	91 (35.69%)	37 (29.6%)	81 (27.93%)	44 (25%)	18 (25.35%)		271 (29.55)
Missing	9	2	2	4	3		20
No chronic GVHD	169 (69.26%)	83 (69.75%)	193 (71.22%)	116 (69.88%)	43 (63.24%)	0.80	604 (69.59)
Chronic GVHD	75 (30.74%)	36 (30.25%)	78 (28.78%)	50 (30.12%)	25 (36.76%)		264 (30.41)
Missing	20	8	21	14	6		69

age of the entire cohort of patients was 58 years. Sixty-eight percent of patients were transplanted in CR1 and 80% had de novo AML. The patient, transplant and disease characteristics are described in Table 1, according to the locus of mismatch. All patients were transplanted using a RIC regimen as defined previously [6], and included patients transplanted with non-myeloablative conditioning regimens. Ninety-one percent of patients received a peripheral blood stem cell source, with 9% of patients receiving stem cells from a bone marrow source. In vivo TCD was used in the majority of patients, 62% received antithymocyte globulin (ATG) and 19.7% received alemtuzumab.

Transplant outcomes

LFS, OS and RI at 2 years were 45% (95% CI: 41.5–48.5%), 49.6% (95% CI: 46–53.2%) and 28.6% (95% CI: 25.5–31.8%), respectively (Table 2). The 2-year NRM for the whole cohort was 26.4% (95% CI: 23.4–29.5%), and GRFS was 34.3% (95% CI: 30.9–37.7%). The incidence of acute GVHD II–IV was 29.9% (95% CI: 26.9–32.9%), and extensive chronic GVHD was 14.2% (95% CI: 11.8–16.9%).

Table 2 Survival, GVHD and relapse rate for the entire cohort.

LFS	45% (95% CI: 41.5–48.5)
OS	49.6% (95% CI: 46–53.2)
RI	28.6% (95% CI: 25.5–31.8)
NRM	26.4% (95% CI: 23.4–29.5)
GRFS	34.3% (95% CI: 30.9–37.7)
Acute GVHD II–IV	29.9% (95% CI: 26.9–32.9)
Acute GVHD III–IV	12.2% (95% CI: 10.1–14.4)
Chronic GVHD	34.5% (95% CI: 31.1–37.9)
Ext. Chronic GVHD	14.2% (95% CI: 11.8–16.9)

In a Cox multivariate analysis (Table 3), age and adverse risk cytogenetics had a significant impact on RI, LFS and OS. It was notable that recipient CMV seropositivity had a significant detrimental effect on OS: HR 1.3 (95% CI 1.05–1.61, $p = 0.016$). Year of transplant (2001–2009 versus 2010–2015) had no impact on OS or LFS by univariate or multivariate analysis (Table 3 and Supplementary

Table 3 Cox multivariate analysis of the impact of HLA mismatch at different loci alongside other patient, transplant and disease characteristics.

	RELAPSE		NRM		LFS		OS		GRFS		Acute GVHD II–IV		chronic GVHD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	p value
Patient age (per 10 years)	1.16 (1.03–1.31)	0.015	1.27 (1.11–1.45)	0.0006	1.21 (1.1–1.32)	<0.0001	1.21 (1.1–1.33)	<0.0001	1.11 (1.02–1.2)	0.012	1.04 (0.93–1.17)	0.47	1.07 (0.95–1.19)	0.26
Poor cytogenetics vs. other	1.72 (1.2–2.47)	0.003	1.25 (0.79–1.97)	0.34	1.5 (1.13–1.98)	0.005	1.44 (1.07–1.94)	0.016	1.29 (0.98–1.69)	0.072	1.14 (0.75–1.74)	0.54	0.98 (0.61–1.55)	0.92
Year of transplant (2010–2015) vs. (2001–2009)	0.97 (0.74–1.27)	0.84	1 (0.74–1.36)	0.99	0.98 (0.8–1.2)	0.87	0.98 (0.79–1.21)	0.85	0.97 (0.81–1.18)	0.78	0.71 (0.54–0.92)	0.011	1.04 (0.79–1.38)	0.76
Patient CMV positive	1.03 (0.79–1.35)	0.82	1.67 (1.21–2.3)	0.002	1.28 (1.04–1.57)	0.019	1.3 (1.05–1.61)	0.016	1.27 (1.05–1.54)	0.012	1.33 (1–1.75)	0.046	1.07 (0.81–1.41)	0.63
Donor CMV positive	1.02 (0.79–1.31)	0.89	0.93 (0.71–1.22)	0.61	0.97 (0.81–1.17)	0.76	0.96 (0.79–1.16)	0.65	1.03 (0.87–1.22)	0.74	0.78 (0.61–1.01)	0.06	1.21 (0.94–1.56)	0.14
In vivo TCD	1.39 (0.96–2.03)	0.081	1.11 (0.77–1.61)	0.57	1.24 (0.96–1.62)	0.1	1.11 (0.85–1.46)	0.45	0.96 (0.76–1.21)	0.73	0.67 (0.5–0.9)	0.009	0.62 (0.45–0.84)	0.002
Mismatch at HLA-DQ (reference)	1		1		1		1				1		1	
Mismatch at HLA-A	0.76 (0.53–1.09)	0.14	1.75 (1.14–2.67)	0.01	1.11 (0.85–1.46)	0.45	1.23 (0.92–1.65)	0.16	1.19 (0.92–1.53)	0.18	1.79 (1.24–2.6)	0.002	1.26 (0.86–1.83)	0.23
Mismatch at HLA-B	0.65 (0.41–1.04)	0.074	1.46 (0.88–2.43)	0.15	0.93 (0.66–1.31)	0.69	0.98 (0.69–1.41)	0.92	1.05 (0.77–1.44)	0.75	1.45 (0.92–2.28)	0.11	1.27 (0.81–1.99)	0.29
Mismatch at HLA-C	0.96 (0.69–1.35)	0.83	1.43 (0.93–2.19)	0.1	1.13 (0.87–1.47)	0.35	1.21 (0.91–1.59)	0.18	1.16 (0.91–1.48)	0.24	1.19 (0.82–1.75)	0.36	1.11 (0.77–1.61)	0.57
Mismatch at HLA-DR	0.83 (0.5–1.38)	0.48	1.18 (0.63–2.2)	0.6	0.96 (0.65–1.42)	0.83	1.05 (0.7–1.57)	0.81	0.91 (0.63–1.32)	0.63	1.14 (0.65–1.98)	0.65	1.13 (0.69–1.85)	0.63

Table 2). More recent transplants (2010–2015) appear to be associated with a reduced risk of acute GVHD on multivariate analysis (HR 0.71, 95% CI (0.54 = 0.92), $p = 0.011$) but had no impact on NRM.

Impact of specific HLA mismatch on transplant outcome

The effect of HLA mismatch on transplant outcome was first examined by performing a univariate analysis, results of which are shown in Supplementary Table 2. Mismatch at HLA-A resulted in higher rates of NRM because of an increase in acute GVHD (Supplementary Table 2 and Supplementary Figs. 1, 2). In contrast, in this cohort of 9/10 HLA matched donor allo-SCT patients, HLA-DQB1 mismatch was better than mismatch at other loci in terms of NRM (Supplementary Table 2).

We wished to answer the question of whether a mismatch at a particular HLA locus was preferable than a mismatch at any other. To account for other confounding factors, we used a Cox proportional-hazards regression model to determine the relative impact of mismatch at different HLA loci alongside the presence of different patient and transplant characteristics (Table 3) on rates of RI, GVHD, NRM, LFS and OS. HLA-DQB1 mismatch was used as the reference to compare the relative impact of mismatch at the other HLA loci. There was no significant difference in HLA mismatch at any loci as compared to each other, on LFS, OS, RI and GRFS (Table 3 and Supplementary Fig. 1). However, mismatch at HLA-A, as compared to HLA- DQB1 mismatch, was associated with a higher NRM (HR = 1.75; 95% CI: 1.14–2.67; $p = 0.01$) likely due to a higher likelihood of aGVHD (HR = 1.79; 95% CI: 1.24–2.6; $p = 0.002$) (Table 3 and Supplementary Figs. 1, 2).

Patient CMV seropositivity is a critical determinant of transplant outcome in HLA 9/10 matched RIC allo-SCT in AML

In the univariate analysis, CMV seropositive recipients had a higher rate of acute GVHD than did CMV seronegative recipients, which resulted in an inferior OS ($p = 0.01$) (Supplementary Table 2). Donor CMV serology did not impact survival rates and there was no significant association between patient and donor CMV serostatus.

These results were also evident in the multivariate analysis, where patient CMV seropositivity increased NRM (HR 1.67; 95% CI: 1.21–2.30) but donor CMV seropositivity had no significant effect on NRM. Patient CMV seropositivity appeared to increase the risk of acute GVHD (HR 1.33; 95% CI 1–1.75, $p = 0.046$), whilst interestingly, donor CMV seropositivity appeared to decrease this risk, (HR 0.78; 95% CI 0.61–1.01, $p = 0.06$). CMV serostatus had no impact on risk of chronic GVHD.

Although patient CMV seropositivity increased the risk of acute GVHD, there was no concomitant reduction in relapse rates and hence recipient CMV seropositivity was associated with a decrease in LFS and OS. Thus, recipient serostatus appears to be a particularly important prognostic factor in HLA mismatched transplant patients.

In vivo TCD appears to reduce the risk of both acute GVHD (HR 0.67; 95% CI 0.5–0.9, $p = 0.009$) and chronic GVHD (HR 0.62; 95% CI 0.45–0.84, $p = 0.002$), but did not affect relapse risk, emphasising the importance of TCD in the setting of HLA mismatched allo-SCT. To understand if our observations above were affected by the presence of in vivo TCD, we repeated the multivariate analysis with data only from the 765 patients who had received in vivo TCD allo-SCT. This did not significantly impact our findings described above, with the patients receiving an allo-SCT with a HLA-A mismatch having a higher rate of acute GVHD and NRM, and patient CMV seropositivity resulting in a higher rate of acute GVHD, NRM and reduction in OS (Supplementary Table 3).

Discussion

Previous studies have established the benefits of a 10/10 HLA matched transplant over a 9/10 HLA matched donor allo-SCT, alongside the detrimental effect of >1 HLA mismatched locus [14, 19, 25, 26]. In this large retrospective analysis, we have addressed the important question of whether, in patients transplanted using a 9/10 HLA MUD, there is a specific HLA locus that is preferential to be mismatched to, in comparison to other loci. Although we identified a significant impact on OS by age, adverse risk cytogenetics and recipient CMV seropositivity, there was no HLA mismatch that was superior to any others in terms of OS. However, HLA-A mismatch increased acute GVHD risk resulting in an increase in NRM, as compared to a HLA-DQB1 mismatch. This appears to be the case, irrespective of the use of in vivo TCD depletion, which occurred in the majority of patients. This bears some similarities to data from Switzerland, which compared allo-SCTs that included 9/10 and 10/10 matched donors and showed that HLA-A, -B and -C mismatches had inferior outcomes to others but this was not significant with single MHC class II mismatch (DRB1 or DQB1) [15]. Similarly, an analysis of single mismatches in a large German retrospective study showed detrimental effects of HLA class I (-A, -B, -C) and HLA- DRB1 mismatch on OS but this did not extend to HLA-DQB1 mismatch [27]. A recent analysis of a large cohort of 11,872 patients who received an allograft from a 9/10 HLA matched donor, demonstrated inferior OS and increased risk of GVHD in patients transplanted with a donor mismatched at either HLA-A, -B, -C

as compared to -DQB1 [26]. However, this large international cooperative study included a more heterogeneous population in terms of patient selection and transplant methodology (e.g., greater proportion of patients transplanted with bone marrow as source of cells). These studies taken together supports the alternative matching algorithm of the NMDP/CIBMTR to prioritise HLA-A, -B, -C and -DRB1 compatible donors, and to consider loci including HLA-DQB1 when multiple 8/8 HLA MUDs are available [28]. The strength of this current study is the homogeneous nature of the patient disease background as this is known to have a strong influence on subsequent outcome. For example, higher risk disease may be associated with a reduction in risk incurred by a HLA mismatched donor [29]. Furthermore, our analysis is centred on a cohort of patients transplanted with a 9/10 HLA matched volunteer unrelated donor, thereby maximising the statistical power of the comparisons of outcomes in patients with a single HLA mismatch.

An association between increased acute GVHD and recipient CMV seropositivity has been previously observed but specifically in HLA matched sibling myeloablative allo-SCT, using ATG as partial TCD [30]. This study extends this observation by showing that patients who are CMV seropositive, and receiving a RIC allo-SCT for AML with a 9/10 MUD, have an inferior OS as a result of an increased rate of acute GVHD and NRM.

Why might recipient CMV seropositivity result in increased acute GVHD and impaired OS? In this registry data, we lack CMV replication data, but this mechanism is the most likely explanation behind the profound detrimental effect of recipient CMV seropositivity. There is an increased risk of CMV infection in patients receiving a mismatched donor source as compared to a 10/10 HLA matched donor [17], and risk of acute GVHD increases during phases of CMV replication [31]. Possible mechanisms have been postulated such as HLA class II upregulation during an acute viral infection promoting acute GVHD [32]. Interestingly, the poor prognosis of recipients who are CMV seropositive was not ameliorated by the presence of donor CMV seropositivity, despite data from other groups suggesting otherwise [19]. This may be due to the heterogeneity of in vivo TCD techniques used in our cohort.

This data suggests that for CMV seropositive patients who lack a sibling or 10/10 matched MUD, alternative CMV and GHVD prophylaxis strategies should be considered. This is especially, as we demonstrate that donor CMV seropositivity does not overcome the adverse risk experienced by recipients who are CMV seropositive.

Interestingly, recent data have suggested further factors involved in the outcomes of patients undergoing HLA mismatched allo-SCT, which was not collected in our registry study. For example, in HLA-C mismatched allo-SCTs, a factor in consideration is the expression level of the HLA-C allotype. Increasing expression levels of the recipient HLA-C mismatched allotype are associated with increase in GVHD and mortality [33]. Similarly, a recent paper has illustrated the importance of exon 1 in HLA-B, which is not routinely considered in clinical practice, and is not directly involved in antigen binding, but may differentially affect NK and T-cell responses. Disparities in this sequence appears to affect patients' risk of GVHD in patients undergoing HLA-B mismatch allo-SCT [26]. HLA-DP typing results were only available in 357/937 (38%) of patients, limiting use of this factor in our analysis. Previous studies have recognised the importance of T-cell epitope matching in HLA-DP in the setting of HLA mismatched allo-SCT [34].

Overall, the 2-year outcomes (Table 2) confirm the utility of 9/10 HLA matched donor as a stem cell source in patients with AML undergoing a RIC allo-SCT without either a sibling or 10/10 HLA matched donor [35]. This is the first study, in this setting, to demonstrate inferior OS of CMV seropositive recipients subsequent to increased acute GVHD. CMV seropositive recipients were 30% more likely to die than CMV seronegative patients. This data set has the potential to inform optimal donor selection in those patients lacking a 10/10 HLA matched donor, and will be challenged in the era of emerging technologies such as improved CMV prophylaxis and treatment with letermovir and the adoption of post-transplant cyclophosphamide outside of the haploidential donor transplant setting [36, 37].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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