Allogeneic haemopoietic transplantation for acute myeloid leukaemia in second complete remission: A registry report by the Acute Leukaemia Working Party of the EBMT

Running title: Allograft in second remission acute myeloid leukaemia

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Abstract

Allogeneic haemopoietic cell transplant (allo-HCT) may be curative in acute myeloid leukaemia (AML) in second complete remission (CR2) but the impact of reduced intensity (RIC) versus myeloablative conditioning (MAC) is uncertain. The Acute Leukaemia Working Party of the European Society for Blood and Bone Marrow Transplantation Registry studied an AML CR2 cohort characterised by age ≥18y, first allo-HCT 2007-2016, available cytogenetic profile at diagnosis, donors who were matched family, volunteer unrelated with HLA antigen match 10/10 or 9/10 or haplo-identical. The 1879 eligible patients included 1010 (54%) MAC allo-HCT recipients.

In patients <50 years (y), two year outcomes for MAC vs RIC allo-HCT were equivalent with leukaemia free survival (LFS) 54% for each, overall survival (OS), 61 vs 62%, non-relapse mortality (NRM) 18 vs 15% and graft versus host disease relapse free survival (GRFS) 38 vs 42%. In patients ≥50y, 2y outcomes for MAC vs RIC allo-HCT were equivalent for LFS 52 vs 49%, OS 58 vs 55% and GRFS 42.4 vs 36%. However, NRM was significantly inferior after MAC allo-HCT, 27 vs 19% (P=0.01) despite worse cGVHD after RIC-allo (32 vs 39%). These data

support the need for ongoing prospective study of conditioning intensity and GVHD mitigation in AML.

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Introduction

Acute myeloid leukaemia (AML) is grouped into good, intermediate and adverse genetic risk categories that may be combined with response rates to induction therapy to predict survival outcomes (1–3). Integration of relapse rates, procedural mortality of allogeneic haemopoietic cell transplant (allo-HCT) and projected success rates of salvage regimens permits an estimate of the potential benefit and optimal timing of an allo-HCT as consolidation therapy (4–6,1). Consequently, for patients achieving first complete remission (CR1) it is conventional to offer allo-HCT in adverse and intermediate risk disease where the relapse risk is more than 45% and there are clear benefits to transplantation (7,8). Allo-HCT is deferred to CR2 for patients with good risk disease despite a relapse risk of up to 35%, since

many will be cured without the hazards of allo-HCT (5). However, management of an individual patient requires a personalised amalgamation of risk of relapse, transplant related mortality and access to a suitable donor (1,6,9,10). Thus, patients with high HCT comorbidity index scores and a mismatched volunteer donor may wish to defer allo-HCT (11,12).

While it is often assumed that those patients who relapse subsequent to a first CR may be duly salvaged and offered allo-HCT in CR2, this does not square with reality (13–16). Breems *et al* studied a cohort of 1540 patients with newly diagnosed AML enrolled on clinical trials between 1987 and 2001 and established that the duration of CR1, age at relapse, cytogenetic risk factor at diagnosis and a prior allo-HCT could be used to predict the likelihood of CR2 (4). Those patients who did achieve CR2 were shown to have a survival benefit from allo-HCT compared to alternative therapies. Subsequent studies have largely confirmed these findings (Table 1) (17–21).

Since no other large series address the impact of conditioning regimen intensity on the outcomes of HCT in patients with AML CR2, we have analysed an eligible cohort of patients for whom data had been deposited in

the registry of the European Society for Blood and Marrow Transplantation (EBMT).

Methods

Study design and data collection

This was a multicentre, retrospective registry study by the Acute Leukaemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary group that represents more than 600 transplant centers, predominantly European, which are required to report all consecutive HCT and follow-up once a year. EBMT Med A/B standardized data collection forms are completed and submitted to the registry by transplant center personnel following written informed consent from patients in accordance with center ethical research guidelines (22). Accuracy of data is assured by the individual transplant centers and by quality control measures such as regular internal and external audits. Since January 1, 2003, all transplant centers have been required to obtain written informed consent prior to data registration with the EBMT, following the Helsinki Declaration of 1975.The study was approved by the ALWP.

Eligibility criteria

Eligibility criteria were: age ≥18y, first allo-HCT 2007-2016, diagnosis of AML CR2, availability of cytogenetic profile at diagnosis.

Cytogenetic status was classified using MRC UK criteria while any identified molecular markers at diagnosis were also noted (23). Donors were restricted to a human leukocyte antigen (HLA) matched family donor (MFD), volunteer unrelated donor with HLA match 10/10 (VUD) or 9/10 match (MMVUD) or haplo-identical (Haplo ID) donor. Graft source included peripheral blood stem cells (PBSC) or bone marrow (BM) grafts. Engraftment was assessed by conventional EBMT standards (22).

Intensity of conditioning was classified in accordance with published criteria while the more recently adopted regimens Treosulfan/Fludarabine (TF) and Thiotepa/Busulfan/Fludarabine (TBF) were considered as myeloablative when the busulfan dose was at least 9.6 mg/kg (24–26).

Statistical analysis

Patient, disease, and transplant-related characteristics for the two cohorts (MAC or RIC) were compared by using χ^2 statistics for categorical variables and the Mann-Whitney test for continuous variables. The primary endpoint was

leukemia-free survival (LFS). Secondary endpoints were relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS), acute graft-versus-host disease (aGVHD), chronic graft-versus-host-disease (cGVHD) and GVHD-free/relapse-free survival (GRFS). LFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the presence of 5% BM blasts and/or reappearance of the underlying disease. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from allo-HCT to death, regardless of the cause. GRFS was defined as events excluding grade 3-4 acute GVHD, extensive chronic GVHD, relapse, or death in the first post-HCT year (27–29).

Cumulative incidence was used to estimate the endpoints of NRM, 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. Probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier method. Univariate analyses were done using the Gray's test for cumulative incidence functions and the log rank test for OS, GRFS, and LFS. Cox proportional hazards model was used for multivariate regression. All variables differing significantly

between the 2 groups or factors associated with one outcome in univariate analysis were included in the Cox model. In order to test for a centre effect, we introduced a random effect or frailty for each center into the model (30,31). We studied 2 different Cox models in patients aged under 50 or 50 years and above at the time of allo-HCT. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). Proportional hazards assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests were 2-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Analyses were stratified by age at allo-HCT (less or ≥50 years) and declared measurable residual disease (MRD) status at HCT. Statistical analyses were performed with SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and R 3.4.0 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna; Austria. https://www.R-project.org/.)

Results

Patient, disease and transplant characteristics

A total of 1879 patients, 1013 male, from 230 transplant centers were eligible. Patient, disease, donor and

transplant characteristics are detailed in Supplementary Table 1 (Table S1).

Median follow-up of surviving patients was 26.16 months (m) (0.49 - 124.63). Approximately 95% of patients in each group had *de novo* AML at initial diagnosis.

MAC regimens were used in 1010 while 869 received RIC allo-HCT. Time from diagnosis to transplant was marginally longer in RIC allo-HCT recipients at a median of 18.5 m (range 0.8-222.9) vs 17.7m (1.2-239.1) (P=0.017) in MAC recipients.

Recipients of RIC allo-HCT compared to MAC allo-HCT recipients were older (median age 57.3y (18.2-75.3) vs 42.8y, (18-72y) P<0.001), had a worse Karnofsky performance status (P<0.001) and had a higher proportion of adverse or intermediate cytogenetics at diagnosis (P $<10^{-3}$) (Table S1).

Family donors, whether MFD or Haplo-ID, were more commonly available for MAC allo-HCT than RIC allo-HCT recipients and accounted for half of the donors in the MAC allo-HCT group. Conversely, unrelated donors, particularly HLA 10/10 VUDs were more likely than family donors to be used in the RIC allo-HCT setting (P<0.0 01). While PBSC was the preferred source of stem cells in both conditioning groups, this was more pronounced in

the RIC allo-HCT group with only 7.59% cases using BM vs 24.78% in the MAC HCT group (P<0.001). A preference for male donors was seen in both groups and particularly so in RIC allo-HCT (P=0.005) (Table S1).

Transplant characteristics are shown in Table S1. T cell depletion, whether with anti-thymocyte globulin or alemtuzumab was applied in 47.01% MAC HCT and 70.59% RIC/NMA HCT (P <0.001).

Regimens used for GVHD prophylaxis favoured cyclosporine based approaches rather than tacrolimus or post-transplant cyclophosphamide. Cyclosporine was most often used in combination with methotrexate in MAC HCT and alone or with mycophenolate mofetil in RIC/NMA HCT (P<0.001).

Outcomes of transplantation

At 2y, the overall outcomes were LFS 52% (CI: 49.5 - 54.5), OS 58.7% (CI: 56.2 - 61.2), RI 28.9% (CI: 26.7 - 31.2), NRM 19% (CI: 17.2 - 21), GRFS 38.7% (CI: 36.2 - 41.1), cGVHD 37.2% (CI: 34.7 - 39.7) and extensive cGVHD 15.9% (CI: 14.1 - 17.8) (Tables S2 and S3) Non-relapse deaths were predominantly due to GVHD or sepsis (Table S2).

Multivariate analysis was performed to examine the impact of conditioning intensity as well as other parameters believed to determine transplant outcomes. Table S4 summarises the MVA for all patients. In this cohort, no transplant outcome differed significantly by conditioning intensity with the notable exception of NRM which favoured RIC Allo-HCT, (HR 0.65 95% CI 0.50-0.84 P=0.001). However, when patients were divided by age range <50y vs ≥50y this advantage to RIC ALLO-HCT retained significance only in patients ≥50y (HR 0.54 CI 0.38-0.76 P <0.001) (Tables 2 and 3). Thus, even in patients selected as being fit for MAC Allo-HCT by their transplant team, we found excess NRM in older patients. This is supported by the increase in NRM that is seen with increasing age in the <50y (HR 1.25 CI 1.01-1.53 P=0.034) as well as the ≥50y (HR 1.6 CI: 1.21-2.03 P=0.001) (Tables 2 and 3).

The other striking association with conditioning intensity was also seen in patients ≥50y, but not in younger patients, and this was an excess of cGVHD in those undergoing RIC allo-HCT (HR 1.38 CI 1.03-1.85; P=0.03) although this difference did not extend to extensive GVHD (Table 3).

A decision to use reduced intensity rather than myeloablative conditioning may be influenced by the age, comorbidity and performance status of the patient (32–34). As well as the impact of increasing age as a continuous variable on NRM, we also found an adverse effect on GRFS which reached significance in patients <50y (HR 1.13 CI 1.01-1.26 P=0.03) while remaining a trend in older patients. Overall, older patients also had worse LFS and OS (31–(32–34)33) (Table S4 and Table 3).

Karnofsky Performance Scores (KPS) >80% were predictive of lower NRM in both age-groups. Additionally, in patients ≥50y, KPS >80 predicted lower rates of aGVHD and superior OS, LFS and GRFS (Table 3).
In accordance with other large studies of patients transplanted in AML CR2 that have found better transplant outcomes in those patients with longer duration CR1, probably reflecting the innate aggressiveness of disease, (17–20), we found that patients with longer intervals from diagnosis to allo-HCT had superior RI, LFS, OS and GRFS. (Table S4).

The distribution of cytogenetic risk groups at diagnosis resembled the MRC and Japanese cohorts (17,18).

Patients with good risk cytogenetics at diagnosis fare better after transplant than those with intermediate and adverse risk cytogenetics (17–20) and our results are confirmatory in a different data set and across all age groups. (Supplementary Tables 4 and 5).

At 2y, OS following allo-HCT was 67.4, 56.8 and 37.9% in good, intermediate and adverse risk cytogenetic groups respectively. Overall, this compares favourably with the 5y OS of 35, 47 and 34% reported by Burnett in which survival curves flattened between 2 and 3 years from transplant, but emphasises the persistently poor outcome due to relapse for patients with adverse karyotypes (17,32,35,36).

Donor selection has historically had a major impact on the outcomes of transplant, although the increasing use of high resolution HLA typing and novel GVHD prophylaxis strategies may be eroding the differences in outcomes associated with unrelated versus matched or haploidentical family donors (37–40). In this study we found that donor characteristics retained a significant impact upon transplant outcomes (Tables 2 and 3). MMVUD and Haplo-ID donors were associated with increased rates of NRM and aGVHD II-IV and the use of

female donors was associated with higher rates of extensive cGVHD.

In general in modern transplant practice PBSC is the preferred stem cell source although faster engraftment may be offset by increased risks of GVHD (41). We found that the use of PBSC was associated with significantly increased rates of cGVHD in both the <50y and the ≥50y (HR 1.784 CI 1.253-2.539, HR 1.683 CI 1.08-2.624) but no improvements in OS or LFS in either group (Tables 2 and 3). Similar to our earlier study in AML CR1, (42), TCD led to beneficial effects on GRFS, aGVHD and cGVHD in <50y and to improvements in GRFS and cGVHD in the ≥50y without detriment to RI, OS or LFS suggesting that TCD reduces GVHD without increasing relapse risks (Tables 2 and 3).

Finally, we looked for the impact of centre and year of transplant but found no significant effect on transplant outcomes (Tables 3 and 4).

Discussion

This large registry study tracked the effect of allo-HCT on the post-transplant survival characteristics of 1879 patients with AML in CR2 in the modern era (2007-2016) and investigated the impact of conditioning intensity on

outcomes in patients aged <50y or ≥50y. OS, LFS and GRFS at 2y were 58.7%, 52% and 38.7%.

We established that in patients aged <50y, 2y OS was 61.1% vs 61.8% for MAC vs RIC allo-HCT (P=0.7) while LFS was 53.9% vs 54.1% (P=0.61). Similarly, in patients aged 50y or more at HCT, MAC allo-HCT and RIC allo-HCT were equivalent with 2y OS of 58.3% vs 55.1% (P=0.3) and LFS of 51.5% vs 49.3% (P=0.7). Multivariate analysis confirmed that in patients <50y and ≥50y, intensity of conditioning made no significant difference to OS, LFS or RI. However, in ≥50y, NRM rates were significantly reduced following RIC allo-HCT and while there was an increased risk of cGVHD this did not manifest as extensive cGVHD. These observations suggest overall equivalence of MAC and RIC regimens and a rationale for further prospective study. This is in keeping with our previous observations in AML CR1 but contrasts with the outcomes of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901 prospective study of 272 patients with AML or myelodysplasia in which high relapse rates in patients receiving RIC Allo-HCT compared to MAC Allo-HCT led to premature study closure (42,43). Despite the caveat that our current study is retrospective, it is a larger one, encompassing a wider range of regimens and with longer

follow-up. Additionally, the outcomes of patients with AML CR2 in the BMT CTN study are not specified.

Similar to earlier studies, we found that adverse factors included increasing age, cytogenetics other than good risk, poor performance status, shorter time intervals from initial diagnosis to transplant and mismatched donor allo-HCT (4,17,20).

Given the high rates of relapse, with overall 2y RI of 28.9%, there is a grave need for more active leukaemia therapy. This might be addressed by sequential chemotherapy approaches such as the FLAMSA based regimens or by combining alkylating agents in the conditioning regimen (26,44–46). Additionally, new agents hold out the promise of higher CR rates and prospects for maintenance therapies which may potentially be used in conjunction with allo-HCT to improve survival in AML(47–50). Immunotherapy approaches, while less advanced than for lymphoid malignancies also hold potential (51).

Our study is limited since it can only address the outcomes of those patients who achieved CR2 and were transplanted, thus not addressing the larger problem of management of relapse after CR1. Likewise, we may only

speculate as to the reasons why allo-HCT was deferred to CR2. We had insufficient data to draw conclusions about the impact of comorbidity, MRD or molecular sub-groups such as FLT3 ITD with or without NPM1 mutations (34,52–54). While MRD status was available in 67% patients, equally distributed across conditioning groups, it had no confounding influence on the relationship between conditioning intensity and transplant outcomes.

However, we show improving survival outcomes after allo-HCT in a large cohort of patients with AML CR2 treated in a recent time-frame while confirming that existing prognostic indicators retain their value. These data also provide fresh impetus for the prospective comparison of the impact of conditioning intensity on allo-HCT outcomes in AML CR2.

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Competing interests statement

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Legends

Main text tables

Table 1 Large Studies of outcome of haemopoietic cell transplant in second complete remission

Table 2 Multivariate analysis of outcomes of haemopoietic cell transplant in patients aged under 50 years.

aGVHD acute graft versus host disease
Allo-HCT allogeneic hematopoietic cell transplant
AML acute myeloid leukemia
cGVHD chronic graft versus host disease
CI confidence interval
GRFS graft versus host disease and relapse free survival
Haplo haploidentical
HR hazard ratio
KPS Karnofsky performance status
LFS Leukaemia free survival
MFD matched family donor
MMVUD mismatched volunteer unrelated donor
NRM Non-relapse mortality
OS Overall survival
PBSC peripheral blood stem cells
RI relapse incidence
TCD T cell depletion
VUD volunteer unrelated donor

Table 3 Multivariate analysis of outcomes of haemopoietic cell transplant in patients aged 50 years or above.

aGVHD acute graft versus host disease
Allo-HCT allogeneic hematopoietic cell transplant
AML acute myeloid leukemia
cGVHD chronic graft versus host disease
CI confidence interval
GRFS graft versus host disease and relapse free survival
Haplo haploidentical
HR hazard ratio
KPS Karnofsky performance status
LFS Leukaemia free survival
MFD matched family donor
MMVUD mismatched volunteer unrelated donor
NRM Non-relapse mortality
OS Overall survival
PBSC peripheral blood stem cells
RI relapse incidence
TCD T cell depletion
VUD volunteer unrelated donor

812
813 Figure 1
814 Outcomes of reduced intensity conditioning (RIC) versus
815 myeloablative conditioning (MAC) allogeneic
816 haemopoietic cell transplant in patients aged 50 or older.
817 (a) Non-relapse mortality (NRM)
818 (b) Relapse incidence
819 (c) Chronic Graft versus Host disease
820 (d) Overall survival (OS)
821 (e) Leukaemia-free survival (LFS)
822 (f) Graft versus host and relapse free survival (GRFS)
823

Table 1

Author, Group & Study type	Study population	Outcomes	Conclusions and limitations
Burnet et al (reference 17) UK Medical Research Council	n=1160 Age 16-49y AML patients in first relapse (excluding APL and any prior transplant) Risk stratification by MRC criteria (Grimwade et al 2001 reference 23) Era: 1988-2009	642 (55%) achieved CR2. 314 (27%) had allo-HCT Allo-HCT 5Y OS from CR2 by MRC risk category: Good: 35% overall, t(8;21) 29% and inv16 39% Intermediate: 47% Adverse: 34% Unknown: 53%	Post-trial analysis with centre defined relapse and reinduction. The benefits of allo-HCT were seen only in those with intermediate or adverse cytogenetic risk groups at diagnosis. Multivariate analysis found that only CR1 duration was significantly associated with survival. Conditioning intensity did not determine outcome. Era coincides with significant changes in HCT practice such as the introduction of reduced intensity conditioning and improvements in supportive care and high resolution HLA typing.
Kurosawa et al(reference 18) Japan retrospectivenational study,	n=931 Age 16-70y AML patients in first relapse (excluding APL and any with prior transplant) Risk stratification by South-West Oncology Group (SWOG) criteria(reference 21). Era 1994-2006	463 (50%) achieved CR2 242 (26%) had allo-HCT in CR2 Allo-HCT 3Y OS from relapse by SWOG cytogenetic risk criteria Overall: 59% Good: t(8;21) 64% and inv16 70% Intermediate: 58% Adverse:67%	The benefits of allo-HCT were only seen in those with intermediate or adverse risk cytogenetic risk groups at diagnosis. Multivariate analysis found that CR1 duration ≥1y, cytogenetic risk group at diagnosis, white cell count at diagnosis ≤20 x10^9/L and CR1 status achieved with first cycle of inducton therapy all predicted survival after relapse. Era coincides with significant changes in HCT practice such as the introduction of reduced intensity conditioning and improvements in supportive care and high resolution HLA typing.
Hospital et al,(reference 19) French AML Intergroup retrospective study	n=145 Age 16-76y AML patients with core-binding factor mutations in first relapse (excluding any with prior transplant). Era 1994-2011	127 (88%) achieved CR2 77 (53%) had allo-HCT in CR2 Allo-HCT 5Y OS 59% and DFS 57% from relapse Incorporation of gemtuzumab ozogamycin (GO) into salvage regimen yielded superior 5Y OS of 82 vs 48% and DFS of 83 vs 44%.	Multivariate analysis found that the benefits of allo-HCT were greater in younger patients, those with inv16/t(16;16), longer duration CR1 and use of GO as part of salvage therapy at relapse. Era spans 17 years during which confounders such as experience of RIC-Allo-HCT, supportive care and resolution of HLA matching made significant advances. Residual disease status by molecular and/or immunophenotype was unavailable.
Weisdorf et al(reference 20) Center for International Blood Marrow Transplant Research retrospective study	n=4682 Age ≥ 18y AML patients with disease status primary induction failure (PIF) n=1440, median age 52y, relapse failing ≥1 reinduction cycle (RI) n =1256, median age 49y and CR2 n = 1986,median age 47y. All patients received an allo-HCT Era 2000-2013	Allo-HCT 5Y OS: PIF 21%, RI 18% CR2 39%	Multivariate analysis found that the superior outcomes of allo-HCT in AML CR2 were associated with better performance scores (≥90), longer duration CR1 (>12 months), a history of *de novo* AML and non-adverse cytogenetics (SWOG criteria). Era spans 13 years during which confounders such as experience of RIC-Allo-HCT, supportive care and resolution of HLA matching made significant advances. Residual disease status by molecular and/or immunophenotype was unavailable.

Table 2

Age <50y	Relapse HR	Relapse CI	Relapse p	NRM HR	NRM CI	NRM p	LFS HR	LFS CI	LFS p
RIC vs MAC	1.00	0.724 - 1.38	1.00	0.779	0.513 - 1.182	0.24	0.903	0.7 - 1.166	0.43
Age (per 10 y)	1.05	0.898 - 1.219	0.56	1.245	1.014 - 1.529	0.04	1.114	0.986 - 1.259	0.08
Time Diagnosis to allo-HCT (m)	0.96	0.948 - 0.975	<10-5	0.999	0.991 - 1.007	0.78	0.982	0.974 - 0.99	10-5
Cytogenetics									
Good risk group (reference data	1.00			1.00			1.00		
Intermediate	1.52	1.115 - 2.071	0.01	0.922	0.638 - 1.331	0.66	1.266	1.001 - 1.603	0.05
Adverse	3.347	2.26 - 4.958	<10-5	0.917	0.463 - 1.816	0.80	2.326	1.675 - 3.23	<10-5
Donor									
MFD (reference data)	1.00			1.00			1.00		
VUD 10/10	0.809	0.578 - 1.131	0.21	1.271	0.802 - 2.014	0.31	0.97	0.74 - 1.27	0.82
MMUD 9/10	0.842	0.546 - 1.3	0.44	1.986	1.168 - 3.377	0.01	1.189	0.854 - 1.657	0.31
Haplo	0.576	0.312 - 1.065	0.08	2.096	1.097 - 4.002	0.02	0.944	0.61 - 1.462	0.80
KPS>80%	1.084	0.497 - 2.362	0.84	0.447	0.219 - 0.914	0.03	0.716	0.424 - 1.207	0.21
PBSC vs BM	0.714	0.51 - 0.999	0.05	1.599	0.97 - 2.636	0.07	0.957	0.725 - 1.264	0.76
Year of allo-HCT	1.005	0.953 - 1.06	0.86	0.987	0.922 - 1.057	0.72	1.002	0.961 - 1.045	0.93
Patient female	0.865	0.659 - 1.135	0.29	0.981	0.693 - 1.389	0.92	0.894	0.723 - 1.107	0.31
Donor female	0.76	0.574 - 1.006	0.06	1.089	0.77 - 1.539	0.63	0.87	0.701 - 1.081	0.21
in vivo TCD	1.064	0.767 - 1.475	0.71	0.853	0.564 - 1.289	0.45	0.972	0.752 - 1.256	0.83
centre			0.25			0.25			0.18

Age <50y	OS HR	OS CI	OS p	GRFS HR	GRFS CI	GRFS p	acute GVHD II-IV HR	acute GVHD II-IV CI	acute GVHD II-IV p
RIC vs MAC	0.914	0.7 - 1.192	0.507	0.863	0.683 - 1.091	0.217	0.863	0.62 - 1.201	0.381
Age (per 10 y)	1	0.965 - 1.25	0.155	1.129	1.012 - 1.259	0.030	1.017	0.869 - 1.189	0.838
Time Diagnosis to allo-HCT (m)	0.982	0.974 - 0.991	<10-4	0.991	0.985 - 0.997	0.003	0.999	0.992 - 1.006	0.763
Cytogenetics									
Good risk group (reference data	1			1			1		
Intermediate	1.318	1.026 - 1.692	0.031	1.14	0.926 - 1.403	0.217	0.91	0.678 - 1.222	0.531
Adverse	2.417	1.708 - 3.421	<10-5	1.822	1.344 - 2.471	<10-3	0.804	0.484 - 1.337	0.401
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.044	0.784 - 1.389	0.770	1.049	0.825 - 1.334	0.698	2.057	1.439 - 2.939	<10-4
MMUD 9/10	1.406	0.997 - 1.983	0.052	1.195	0.881 - 1.622	0.252	2.679	1.721 - 4.17	<10-4
Haplo	1.217	0.776 - 1.908	0.393	0.692	0.46 - 1.039	0.076	1.595	0.949 - 2.683	0.078
KPS>80%	0.62	0.371 - 1.035	0.067	0.955	0.574 - 1.588	0.859	0.701	0.356 - 1.378	0.303
PBSC vs BM	1.087	0.809 - 1.46	0.581	1.252	0.97 - 1.615	0.084	1.203	0.849 - 1.705	0.298
Year of allo-HCT	0.989	0.946 - 1.035	0.643	1.021	0.983 - 1.06	0.288	0.974	0.927 - 1.023	0.291
Patient female	0.838	0.667 - 1.053	0.129	0.917	0.758 - 1.109	0.371	0.88	0.668 - 1.161	0.367
Donor female	0.941	0.749 - 1.183	0.603	0.953	0.787 - 1.154	0.623	0.811	0.613 - 1.074	0.144
in vivo TCD	0.901	0.692 - 1.173	0.439	0.622	0.492 - 0.786	<10-4	0.479	0.346 - 0.663	<10-4
centre			0.291			0.090			0.912

Age <50y	acute GVHD III-IV HR	acute GVHD III-IV CI	acute GVHD III-IV p	chronic GVHD HR	chronic GVHD CI	chronic GVHD p	ext. chronic GVHD HR	ext. chronic GVHD CI	ext. chronic GVHD p
RIC vs MAC	0.773	0.414 - 1.443	0.418	0.959	0.698 - 1.317	0.795	1.024	0.638 - 1.644	0.922
Age (per 10 y)	1.129	0.841 - 1.515	0.418	1.049	0.907 - 1.213	0.519	0.999	0.803 - 1.242	0.993
Time Diagnosis to allo-HCT (m)	1.004	0.993 - 1.014	0.499	1.005	1 - 1.011	0.067	0.997	0.988 - 1.007	0.564
Cytogenetics									
Good risk group (reference data	1			1			1		
Intermediate	1.011	0.589 - 1.735	0.969	1.011	0.77 - 1.328	0.936	0.904	0.604 - 1.351	0.621
Adverse	1.03	0.423 - 2.506	0.949	1.354	0.846 - 2.167	0.206	1.187	0.564 - 2.495	0.652
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.844	1.002 - 3.395	0.049	1.205	0.879 - 1.652	0.247	1.27	0.816 - 1.977	0.290
MMUD 9/10	1.529	0.657 - 3.559	0.324	1.072	0.689 - 1.669	0.758	0.963	0.481 - 1.926	0.914
Haplo	0.881	0.29 - 2.672	0.823	0.771	0.446 - 1.332	0.351	0.501	0.199 - 1.264	0.143
KPS>80%	0.477	0.169 - 1.345	0.162	1.608	0.633 - 4.083	0.318	4.276	0.563 - 32.455	0.160
PBSC vs BM	1.504	0.765 - 2.958	0.237	1.784	1.253 - 2.539	0.001	3.131	1.738 - 5.64	<10-3
Year of allo-HCT	0.971	0.886 - 1.064	0.528	0.974	0.924 - 1.026	0.315	1.052	0.971 - 1.14	0.213
Patient female	0.821	0.492 - 1.369	0.450	1.04	0.802 - 1.348	0.768	0.849	0.578 - 1.247	0.404
Donor female	0.825	0.493 - 1.381	0.465	1.719	1.331 - 2.22	<10-4	1.515	1.047 - 2.194	0.028
in vivo TCD	0.429	0.24 - 0.769	0.004	0.562	0.411 - 0.77	<10-3	0.27	0.167 - 0.435	<10-5
centre			0.779			0.076			0.016

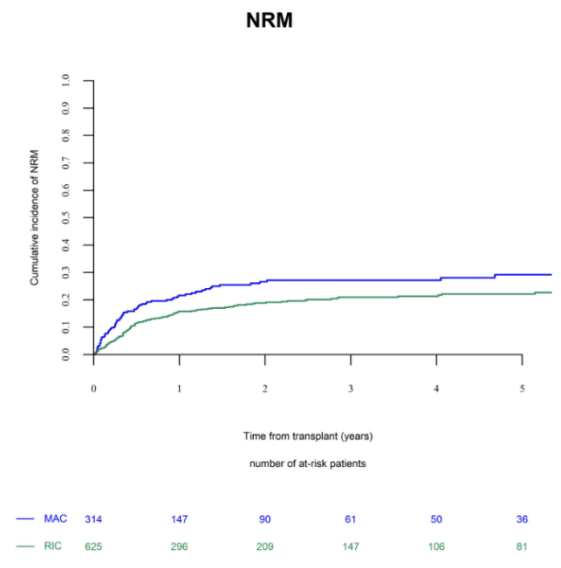
Table 3

Age ≥50y	Relapse HR	Relapse CI	Relapse p	NRM HR	NRM CI	NRM p	LFS HR	LFS CI	LFS p
RIC vs MAC	1.261	0.912 - 1.743	0.161	0.535	0.378 - 0.758	<10-3	0.883	0.695 - 1.122	0.310
Age (per 10 y)	0.981	0.781 - 1.232	0.868	1.567	1.211 - 2.027	0.001	1.205	1.013 - 1.432	0.035
Secondary AML	0.857	0.521 - 1.41	0.543	0.99	0.564 - 1.737	0.971	0.916	0.63 - 1.333	0.647
Time Diagnosis to allo-HCT (m)	0.974	0.963 - 0.986	10-5	1.001	0.992 - 1.01	0.786	0.987	0.98 - 0.995	0.001
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.436	1.006 - 2.049	0.046	0.869	0.585 - 1.292	0.488	1.163	0.892 - 1.518	0.265
Adverse	1.79	1.035 - 3.096	0.037	1.108	0.579 - 2.121	0.756	1.465	0.961 - 2.234	0.076
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.097	0.805 - 1.495	0.558	1.237	0.822 - 1.859	0.308	1.146	0.894 - 1.469	0.281
MMUD 9/10	0.93	0.614 - 1.409	0.733	2.241	1.419 - 3.539	0.001	1.338	0.987 - 1.814	0.061
Haplo	0.577	0.298 - 1.117	0.103	1.948	1.069 - 3.552	0.029	1.017	0.657 - 1.574	0.941
KPS >80%	0.867	0.472 - 1.592	0.646	0.265	0.162 - 0.435	<10-5	0.486	0.331 - 0.715	<10-3
PBSC vs BM	0.998	0.635 - 1.568	0.992	1.325	0.825 - 2.128	0.244	1.117	0.804 - 1.553	0.509
Year of allo-HCT	0.985	0.935 - 1.037	0.556	0.943	0.889 - 1.001	0.054	0.968	0.93 - 1.007	0.104
Patient female	0.747	0.575 - 0.971	0.029	0.825	0.608 - 1.12	0.218	0.774	0.633 - 0.945	0.012
Donor female	0.909	0.687 - 1.203	0.505	1.027	0.745 - 1.415	0.869	0.95	0.768 - 1.174	0.634
in vivo TCD	1.028	0.761 - 1.389	0.859	1.047	0.746 - 1.468	0.792	1.042	0.826 - 1.315	0.727
centre			0.228			0.256			0.188

Age ≥50y	OS HR	OS CI	OS p	GRFS HR	GRFS CI	GRFS p	acute GVHD II-IV HR	acute GVHD II-IV CI	acute GVHD II-IV p
RIC vs MAC	0.915	0.713 - 1.175	0.489	1.04	0.832 - 1.299	0.733	0.921	0.648 - 1.307	0.644
Age (per 10 y)	1.265	1.056 - 1.516	0.011	1.017	0.865 - 1.196	0.840	0.927	0.717 - 1.197	0.559
Secondary AML	0.955	0.646 - 1.412	0.819	1.061	0.755 - 1.491	0.734	1.506	0.92 - 2.467	0.104
Time Diagnosis to allo-HCT (m)	0.988	0.98 - 0.996	0.002	0.993	0.986 - 1	0.037	1.004	0.996 - 1.012	0.357
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.202	0.903 - 1.6	0.206	1.192	0.934 - 1.521	0.159	1.031	0.685 - 1.552	0.883
Adverse	1.607	1.042 - 2.479	0.032	1.31	0.879 - 1.954	0.185	0.833	0.403 - 1.724	0.623
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.183	0.909 - 1.54	0.210	1.137	0.906 - 1.426	0.267	1.68	1.118 - 2.525	0.013
MMUD 9/10	1.511	1.098 - 2.081	0.011	1.516	1.146 - 2.004	0.004	2.685	1.692 - 4.26	<10-4
Haplo	1.321	0.842 - 2.074	0.226	1.016	0.681 - 1.517	0.937	2.434	1.341 - 4.417	0.003
KPS >80%	0.437	0.297 - 0.645	<10-4	0.363	0.254 - 0.518	0.000	0.562	0.322 - 0.982	0.043
PBSC vs BM	1.167	0.827 - 1.649	0.379	1.172	0.863 - 1.593	0.309	1.331	0.809 - 2.191	0.260
Year of allo-HCT	0.968	0.927 - 1.01	0.133	0.97	0.936 - 1.007	0.108	0.986	0.932 - 1.043	0.622
Patient female	0.828	0.672 - 1.022	0.078	0.884	0.735 - 1.062	0.188	1.044	0.779 - 1.4	0.771
Donor female	1.008	0.808 - 1.259	0.941	1.065	0.88 - 1.29	0.516	0.919	0.669 - 1.261	0.599
in vivo TCD	1.082	0.853 - 1.371	0.516	0.764	0.617 - 0.945	0.013	0.93	0.659 - 1.312	0.679
centre			0.312			0.120			0.263

Age ≥50y	acute GVHD III-IV HR	acute GVHD III-IV CI	acute GVHD III-IV p	chronic GVHD HR	chronic GVHD CI	chronic GVHD p	ext. chronic GVHD HR	ext. chronic GVHD CI	ext. chronic GVHD p
RIC vs MAC	0.729	0.428 - 1.242	0.245	1.377	1.027 - 1.845	0.032	1.352	0.869 - 2.102	0.181
Age (per 10 y)	0.71	0.469 - 1.075	0.106	0.863	0.698 - 1.067	0.173	0.79	0.571 - 1.093	0.155
Secondary AML	1.669	0.78 - 3.573	0.187	0.933	0.57 - 1.527	0.782	1.45	0.741 - 2.838	0.279
Time Diagnosis to allo-HCT (m)	1.008	0.997 - 1.02	0.143	0.996	0.988 - 1.003	0.249	1.005	0.995 - 1.015	0.316
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.082	0.574 - 2.043	0.807	1.161	0.843 - 1.599	0.359	1.064	0.667 - 1.7	0.794
Adverse	0.357	0.079 - 1.614	0.181	1.583	0.917 - 2.732	0.099	1.071	0.435 - 2.639	0.881
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.293	0.669 - 2.5	0.445	0.983	0.738 - 1.311	0.909	1.388	0.892 - 2.159	0.146
MMUD 9/10	4.167	2.125 - 8.173	<10-4	1.006	0.678 - 1.493	0.975	1.741	0.992 - 3.056	0.054
Haplo	1.811	0.717 - 4.572	0.209	0.86	0.508 - 1.455	0.575	0.585	0.234 - 1.464	0.252
KPS >80%	0.338	0.152 - 0.748	0.007	0.758	0.432 - 1.33	0.333	0.66	0.261 - 1.671	0.381
PBSC vs BM	1.441	0.679 - 3.06	0.341	1.683	1.08 - 2.624	0.021	1.599	0.814 - 3.144	0.173
Year of allo-HCT	0.994	0.909 - 1.086	0.886	0.985	0.939 - 1.034	0.543	1.004	0.933 - 1.081	0.905
Patient female	1.114	0.704 - 1.762	0.644	1.137	0.886 - 1.458	0.313	1.08	0.743 - 1.571	0.686
Donor female	1.107	0.686 - 1.787	0.676	1.034	0.795 - 1.344	0.804	1.558	1.065 - 2.28	0.022
in vivo TCD	0.747	0.44 - 1.269	0.281	0.484	0.373 - 0.627	0.000	0.266	0.18 - 0.393	<10-5
centre			0.283			0.271			0.921

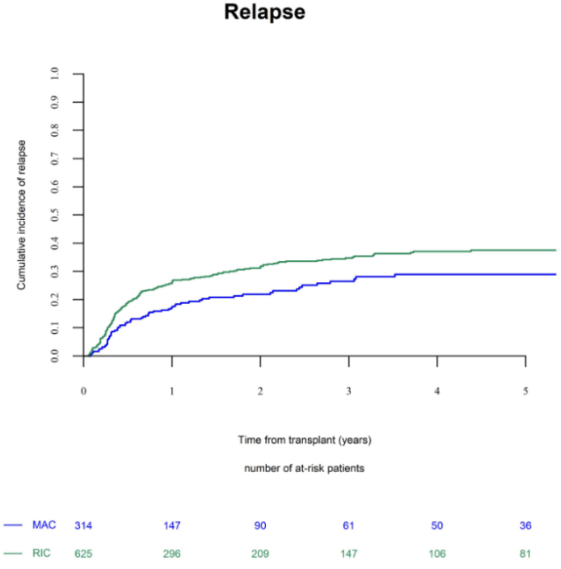
A



number of at-risk patients

MAC	314	147	90	61	50	36
RIC	625	296	209	147	106	81

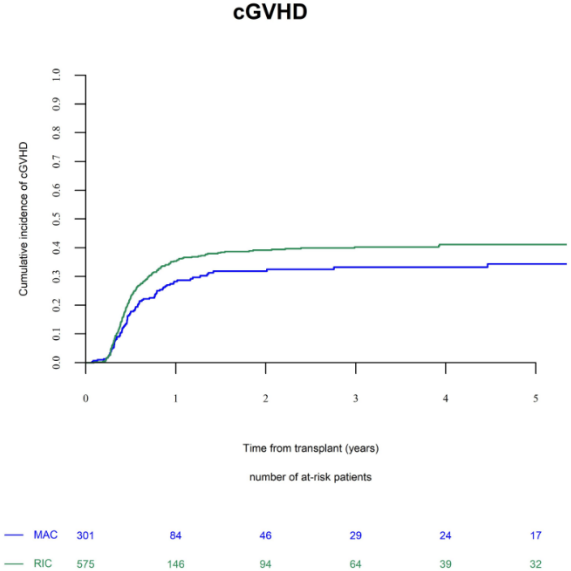
B



number of at-risk patients

MAC	314	147	90	61	50	36
RIC	625	296	209	147	106	81

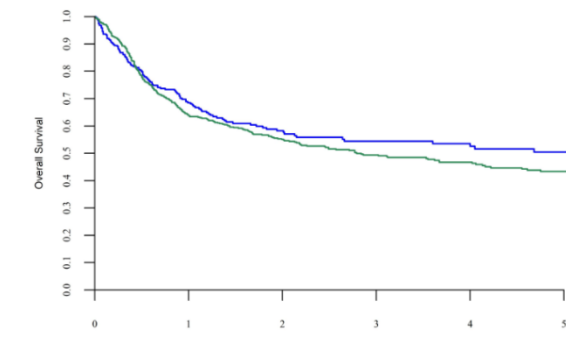
C



number of at-risk patients

MAC	301	84	46	29	24	17
RIC	575	146	94	64	39	32

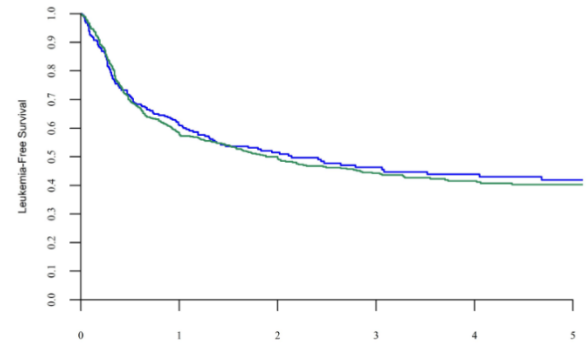
D



number of at-risk patients

MAC	314	147	90	61	50	3(
RIC	625	296	209	147	106	8'

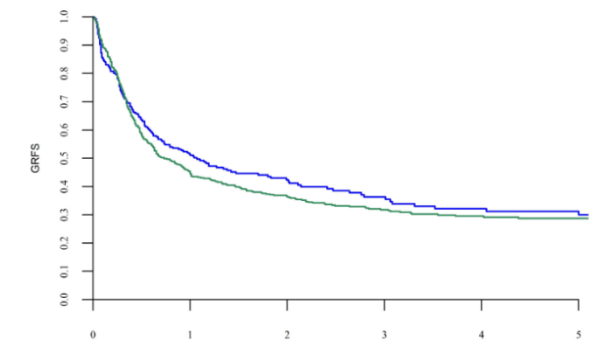
E



number of at-risk patients

MAC	314	147	90	61	50	36
RIC	625	296	209	147	106	81

F



number of at-risk patients

MAC	308	119	71	46	35	25
RIC	600	223	154	108	78	57