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Fludarabine/busulfan versus fludarabine/total-body-irradiation (2 Gy) as conditioning prior to allogeneic stem cell transplantation in patients (≥ 60 years) with acute myelogenous leukemia: a study of the acute leukemia working party of the EBMT

Thomas Heinicke¹ · Myriam Labopin² · Emmanuelle Polge² · Dietger Niederwieser³ · Uwe Platzbecker³ · Henrik Sengelov⁴ · Goda Choi⁵ · Jan Cornelissen⁶ · Didier Blaise⁷ · Jürgen Kuball⁸ · Gwendolyn van Gorkom⁹ · Nicolaas Schaap¹⁰ · Victoria Potter¹¹ · Franciane Paul¹² · Bipin N. Savani¹³ · Arnon Nagler^{14,15} · Mohamad Mohty²

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Abstract

Nonmyeloablative (NMA) conditioning regimens facilitate allogeneic stem cell transplantation (alloSCT) in elderly patients and/or in those with comorbidities. The acute leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) compared the outcomes of patients ≥ 60 years with AML in first complete remission (CR1), that had received an alloSCT following NMA conditioning, i.e. either fludarabine/busulfan (FB2) or fludarabine/total-body-irradiation-2Gy (FluTBI2Gy). A total of 1088 patients were included (median age 65 years). Donors were matched siblings (MSD) and matched unrelated donors (MUD) in 47% and 53%, respectively. In vivo T-cell depletion (TCD) was applied to 79% and none (0%) of patients in the FB2 and FluTBI2Gy groups, respectively. In the MSD group we found a trend for less extensive cGVHD in patients receiving FB2 with in vivo TCD, HR: 0.49, $p = 0.08$, and in those without worse NRM, HR: 2.14, $p = 0.04$, and a trend for more total cGVHD, HR: 1.61, $p = 0.09$. Patients transplanted from MUDs had a significantly higher incidence of total cGVHD, extensive cGVHD and a worse GRFS with FluTBI2Gy in comparison to FB2, HR: 2.44; $p < 0.0001$; HR 4.59; $p < 0.00001$ and HR: 1.35; $p = 0.03$, respectively. No differences were observed with respect to LFS, OS, RI, NRM, and aGVHD.

Introduction

Allogeneic stem cell transplantation (alloSCT) remains the only curative treatment option for many patients with acute myelogenous leukemia (AML). However, given the median age of AML patients of more than 70 years and the fact that this age group often present with significant comorbidities, alloSCT after myeloablative conditioning (MAC) is associated with high-treatment-related morbidity and mortality [1].

Reduced intensity conditioning (RIC) regimens were developed in order to facilitate alloSCT in otherwise ineligible patients due to age and/or comorbidities [2]. Furthermore, even less toxic, nonmyeloablative (NMA) regimens characterised by a markedly reduced intensity of drugs or applied irradiation were developed. More importantly, these regimens can safely be administered to patients older than 70 years and to those with specific comorbidities [3–11]. The concept of NMA conditioning relies more on the graft-versus-leukemia (GVL) effect than on the antileukemic activity of the conditioning regimen [8].

Two major NMA protocols have been developed and were generally applied in many studies. The NMA regimen based on low doses of chemotherapy i.e. the FB2 regimen, and the one based on low-dose irradiation i.e. the FluTBI2Gy protocol [9–11].

The original FB2 regimen has been developed further and many groups use fludarabine at a dose of 30 mg/m²

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✉ Thomas Heinicke
thomas.heinicke@med.ovgu.de

Extended author information available on the last page of the article

for 5 consecutive days combined with i.v. busulfan at a dose of 3.2 mg/kg b.w. daily on 2 consecutive days [12]. Antithymocyte globulin (thymoglobulin or ATG Fresenius/Grafalon) or alemtuzumab are often used for in vivo T-cell depletion according to the policy in individual centers [13–16].

The FluTBI2Gy regimen was developed by Storb et al. after preclinical experiments in outbred dogs using low-dose TBI only [17]. The combination of cyclosporine and mycophenolate mofetil for post-grafting immunosuppression was most effective in preventing graft rejection and GVHD compared to cyclosporine alone or cyclosporine combined with methotrexate [17]. Later this approach was tested clinically [10]. In addition, fludarabine was added to low-dose TBI in order to prevent graft rejection [11, 18–21].

A randomized comparison of the FB2 and FluTBI2Gy regimens was conducted by Blaise et al. in 139 patients with various malignant hematologic diseases including 21 patients with AML [22]. FB2 resulted in improved disease control that did not translate into a difference in overall or disease-free survival. In the present study therefore, we retrospectively compared outcomes of alloSCT after FB2 and FluTBI2Gy conditioning in a large population of AML patients ≥ 60 years of age in CR1.

Patients and Methods

Study design

This is a retrospective registry-based analysis on behalf of the ALWP of the EBMT. The EBMT is a nonprofit, scientific society representing more than 600 transplant centers mainly in Europe that are required to report all consecutive stem cell transplantations and follow-ups once a year. Data are entered, managed and maintained in a central database in which each EBMT center is represented. Audits are routinely performed to determine the accuracy of the data. Patients provide informed consent authorizing the use of their personal information for research purposes. Patients were eligible for the study if they had received a first alloSCT for AML in CR1 after one of the following conditioning regimens: (a) FB2, i.e. fludarabine 5×30 mg/m², busulfan 8×0.8 mg/kg b.w. i.v. with or without in vivo TCD or (b) FluTBI2Gy, i.e. fludarabine 3×30 mg/m² combined with TBI at a single dose of 200 cGy. In the latter group no use of in vivo TCD was allowed. Only matched sibling (MSD) or unrelated donors (MUD) were acceptable. Only patients who had received peripheral blood stem cell grafts were included. Cytogenetic abnormalities were classified according to the Medical Research Council classification system [23].

Transplants were done in 134 centers between January 2003 and June 2017. Data were taken from the EBMT registry.

Endpoints and definitions

The primary endpoint was leukemia-free survival (LFS). Secondary endpoints were relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS), refined graft-versus-host disease-free, relapse-free survival (GRFS) [24], neutrophil engraftment, acute (a)GVHD and chronic (c)GVHD. Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $>0.5 \times 10^9$ /l. Relapse was defined according to standard hematologic criteria. NRM was defined as death from any cause in the absence of prior disease recurrence. LFS was defined as the time to either relapse or death in remission. OS was defined as the time to death from all causes. aGVHD was graded according to the modified Glucksberg criteria [25] and cGVHD according to the revised Seattle criteria [26]. GRFS events have been defined as grade III–IV aGVHD, severe cGVHD, disease relapse, or death from any cause after alloSCT [24]. All time-to-event outcomes were calculated from the date of alloSCT. Patients with no event were censored at last contact.

Statistical analysis

The two regimen groups were compared using the Mann–Whitney *U* test for quantitative variables and the chi-square test or Fisher's exact test for categorical variables. Cumulative incidence was used to estimate the endpoints of NRM, RI and 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. A Cox proportional hazards model was used for multivariate regression. All variables differing significantly between the two groups or factors associated with one outcome in univariate analysis were included in the Cox model. In order to account for differences in rates of missing data on pretransplant molecular markers which may have an impact on outcome (FLT3-ITD and NPM1-mutations) we introduced a missing category for these variables and included this into the multivariate analyses. In order to test for a centre effect, we introduced a random effect or frailty for each center into the model [27, 28]. Results were expressed as a 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 two-sided. The type I error rate was fixed at 0.05 for the determination of factors associated with time-to-event outcomes. As planned in the protocol, further analyses were stratified by donor type (MSD or MUD). Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R 3.4.0 [29].

Results

A total of 1088 patients met the inclusion criteria for the study, 553 patients in the FB2 group and 535 in the FluTBI2Gy group. Median follow-up was 35.7 months (interquartile range (IQR) 14.0–64.4) and was 26.7 (IQR 12.3–51.1) months and 47.7 (IQR 20.2–74.5) months for the FB2 and FluTBI2Gy group, respectively, $p < 0.001$. Treatment groups were compared with respect to patient characteristics (Table 1) and some differences were observed. Patients in the FB2 group more often had a Karnofsky performance score of $\geq 90\%$, 74.1% vs. 66.4%, $p = 0.009$. Seventy-nine percent of patients in the FB2 group received in vivo TCD whereas none of the patients in the FluTBI2Gy group received this, $p < 0.0001$. Other differences were observed in terms of follow-up, age at transplant, time from diagnosis to transplant, year of transplant and GVHD prophylaxis (Table 1). Furthermore, data on some patient characteristics were missing in parts of patients in both treatment groups (Table 1). In addition, information on measurable residual disease at the time of transplant was available only in 251 patients. Out of them, 196 (78%) were reported as being in molecular remission at the time of HSCT (75% in the FB2 group and 83% in the FluTBI group, $p = 0.10$). Twenty-six of the centers used both conditioning regimens, whereas 32 centers used FluTBI2Gy only and 76 centers used FB2 only.

Engraftment and GVHD

Engraftment was comparable between the FB2 and FluTBI2Gy groups with 99.3% and 98.5%, respectively. Acute GVHD II–IV and aGVHD III–IV at day 100 were not significantly different with 22.7% and 7.6% for the FB2 group and 22.3% and 7.6% for the FluTBI2Gy group, respectively. The 2-year cGVHD and extensive cGVHD were significantly lower in the FB2 group with 33.4% and 14.6%, respectively, vs. 50.0% and 29.8% in the FluTBI2Gy group, respectively, $p < 0.001$. This was confirmed by multivariate analysis (HR: 1.61; 95% CI: 1.15–2.24; $p = 0.005$ and HR = 2.46; 95% CI:

1.50–4.06; $p = 0.0004$) for cGVHD and extensive cGVHD, respectively.

RI, NRM, LFS, OS and GRFS

At 2 years, there was no difference in RI between the FB2 and FluTBI2Gy conditioning groups with 33.6% vs. 31.7%, respectively, or in NRM between the two groups, 19.7% vs. 18.4%, respectively. There was no difference in the 2-year LFS (46.8% vs. 49.9% respectively) or the 2-year OS (52.3% vs. 52.7% respectively). However, GRFS at 2 years in FB2 patients compared to those in the FluTBI2Gy group was significantly different on multivariate analysis (HR: 1.19; 95% CI: 1.00–1.43; $p = 0.048$).

Transplants from matched sibling donors

We further investigated the effect of the two conditioning regimens separately in MSD and MUD, looking also at the potential impact of in vivo TCD in the FB2 group. In patients transplanted from MSD, multivariate analysis did not reveal any significant difference between FB2 and FluTBI2Gy groups in terms of LFS, OS, RI, and NRM (Table 2 and Fig. 1a). In addition, no differences were observed in aGVHD II–IV, aGVHD III–IV, cGVHD, ext. cGVHD, or GRFS (Table 2 and Fig. 1a).

Ninety-eight out of 270 patients in the FB2 MSD group had not received in vivo TCD. In order to investigate the role of in vivo TCD in this group we separately compared FB2 MSD patients with or without in vivo TCD to FluTBI2Gy patients (all without in vivo TCD). In univariate analysis no differences were observed in LFS, OS, RI, NRM, aGVHD and aGVHD III–IV. In contrast, rates of cGVHD were 43.6% (95% CI: 36.8–50.3), 30.5% (95% CI: 22.9–38.4) and 43.4% (95% CI: 30.8–55.3) for FluTBI2Gy, FB2 with TCD, and FB2 without TCD, respectively, $p = 0.01$. Rates of extensive cGVHD were 25.1% (95% CI: 19.3–31.3), 13.7% (95% CI: 8.4–20.4) and 24.6% (95% CI: 14.9–35.5) for FluTBI2Gy, FB2 with TCD, and FB2 without TCD, respectively, $p = 0.007$. GRFS was 31.4% (95% CI: 25.2–37.6), 35.2% (95% CI: 27–43.4) and 25.8% (95% CI: 15.6–36) for FluTBI2Gy, FB2 with TCD, and FB2 without TCD, respectively, $p = 0.07$. On multivariate analysis NRM was significantly higher in FB2 patients that had not received in vivo TCD, HR: 2.14; 95% CI: 1.04–4.39; $p = 0.04$, compared to FluTBI2Gy-treated patients (Table S1). In addition, a trend for more total cGVHD was observed in this subgroup, HR: 1.61; 95% CI: 0.93–2.79; $p = 0.09$. Furthermore, a trend for a lower rate of extensive cGVHD was observed in FB2 with in vivo TCD, compared to FluTBI2Gy, HR: 0.49; 95% CI: 0.23–1.08; $p = 0.08$. All other endpoints did not differ significantly between the groups (Table S1).

Table 1 Patients and disease characteristics

		FB2	FluTBI2Gy	Test <i>p</i> value
<i>N</i>		553	535	
Follow-up (reverse KM) (mo)	Median (IQR)	26.72 (12.3–51.1)	47.7 (20.2–74.5)	<0.001
Age at HSCT (yrs)	Median (IQR)	64.8 (62.2–67.2)	65.3 (62.7–68.2)	0.0023
Time diag-HSCT (mo)	Median (IQR)	5.4 (4.4–6.9)	4.6 (3.6–5.8)	<0.0001
Year of Tx	Median (IQR)	2014 (2005–2017)	2012 (2003–2017)	<0.0001
Donor age (yrs)	Median (IQR)	47.8 (30.7–59.3)	49.4 (29.7–61.7)	0.44
	Missing	103 (18.62%)	206 (38.5%)	<0.0001*
Diagnosis	De novo	408 (73.78%)	417 (77.94%)	0.11
	secAML	145 (26.22%)	118 (22.06%)	
Cytogenetics	Good	12 (2.17%)	7 (1.31%)	0.59
	Interm	291 (52.62%)	223 (41.68%)	
	Poor	119 (21.52%)	78 (14.58%)	
	NA/failed	131 (23.69%)	227 (42.43%)	<0.0001*
KPS	<90	130 (23.51%)	161 (30.09%)	0.01
	≥90	371 (67.09%)	318 (59.44%)	
	Missing	52 (9.40%)	56 (10.47%)	0.56*
Donor type	MSD	270 (48.82%)	240 (44.86%)	0.19
	MUD 10/10	283 (51.18%)	295 (55.14%)	
FLT3-ITD	FLT3 neg	151 (27.31%)	93 (17.38%)	0.60
	FLT3 pos	63 (11.39%)	34 (6.36%)	
	Missing	339 (61.30%)	408 (76.26%)	<0.0001*
NPM1	NPM1 neg	147 (26.58%)	77 (14.39%)	0.62
	NPM1 pos	66 (11.93%)	39 (7.29%)	
	Missing	340 (61.48%)	419 (78.32%)	<0.0001*
Patient sex	Male	325 (58.77%)	311 (58.13%)	0.80
	Female	227 (41.05%)	224 (41.87%)	
	Missing	1 (0.18%)	0 (0%)	1*
Donor sex	Donor male	337 (60.94%)	321 (60.00%)	0.70
	Donor female	213 (38.52%)	213 (39.81%)	
	Missing	3 (0.54%)	1 (0.19%)	0.62*
Sex matching	No F- > M	436 (78.84%)	439 (82.06%)	0.27
	F- > M	113 (20.43%)	96 (17.94%)	
	Missing	4 (0.72%)	0 (0%)	0.12*
Patient CMV	Pat. CMV neg.	171 (30.92%)	184 (34.39%)	0.20
	Pat. CMV pos	378 (68.35%)	344 (64.30%)	
	Missing	4 (0.72%)*	7 (1.31%)*	0.33*
Donor CMV	Don. CMV neg.	253 (45.75%)	263 (49.16%)	0.28
	Don. CMV pos	293 (52.98%)	267 (49.91%)	
	Missing	7 (1.27%)	5 (0.93%)	0.60*
CMV D- > R	Neg to neg	125 (22.60%)	135 (25.23%)	0.59
	Pos to neg	46 (8.32%)	48 (8.97%)	
	Neg to pos	128 (23.15%)	125 (23.36%)	
	Pos to pos	245 (44.30%)	216 (40.37%)	
	Missing	9 (1.63%)	11 (2.06%)	0.60*
HCT-CI score	HCT-CI = 1 or 2	151 (27.31%)	96 (17.94%)	0.19
	HCT-CI ≥ 3	88 (15.91%)	73 (13.64%)	
	missing	314 (56.78%)	366 (68.41%)	<0.0001*

Table 1 (continued)

		FB2	FluTBI2Gy	Test <i>p</i> value
GVHD prevention	CSA	161 (29.11%)	7 (1.31%)	<0.0001
	CSA + MTX	207 (37.43%)	6 (1.12%)	
	CSA + MMF +/-MTX	155 (28.03%)	405 (75.7%)	
	TACRO+/-Other	17 (3.07%)	112 (20.93%)	
	Other	13 (2.35%)	5 (0.93%)	
In vivo TCD	No in vivo TCD	115 (20.8%)	535 (100%)	<0.0001
	In vivo TCD	438 (79.2%)	0 (0%)	

Test *p* values are given for the comparisons of groups using available information (excluding patients with missing data)

FB2 fludarabine/busulfan, *FluTBI2Gy* fludarabine total-body-irradiation (200 cGy), *KPS* Karnofsky performance status, *FLT3-ITD* FMS-like tyrosine kinase 3 internal tandem duplication, *NPM1* nucleophosmin 1, *CMV* cytomegalovirus, *D* donor, *R* recipient, *HcT-CI score* hematopoietic cell transplantation comorbidity score, *GVHD* graft-versus-host disease, *TCD* T-cell depletion

*Test *p* values for the comparisons including missing categories

Transplants from matched unrelated donors

With respect to patients transplanted from MUD, univariate analysis showed no significant differences between the FB2 and FluTBI2Gy groups in terms of LFS, OS, RI, NRM and aGVHD. These results were confirmed on multivariate analysis (Table 3 and Fig. 1b).

In contrast, marked differences were observed in incidence of cGVHD, extensive cGVHD and GRFS between the two groups 32.7% (95% CI: 26.6–38.9) vs. 56.6% (95% CI: 49.8–62.9) $p < 0.0001$; 11.9% (95% CI: 7.9–16.7) vs. 34.2% (95% CI: 27.9–40.6), $p < 0.0001$; 42.4% (95% CI: 35.9–48.9) vs. 26% (95% CI: 20.4–31.6), $p < 0.001$; for FB2 vs. FluTBI2Gy, respectively. These differences were confirmed on multivariate analysis with cGVHD, HR: 2.44; 95% CI: 1.60–3.72; $p < 0.0001$, ext. cGVHD, HR: 4.59; 95% CI: 2.35–8.96; $p < 0.00001$, and GRFS HR: 1.35; 95% CI: 1.02–1.79; $p = 0.03$ (Table 3 and Fig. 1b).

Cause of death

Cause of death was similarly distributed between the FB2 and FluTBI2Gy groups with respect to leukemic relapse (51.72% vs. 54.09%), GVHD (20.26% vs. 19.46%), infection (19.4% vs. 15.18%), and others 8.6% vs. 11.3%, respectively.

Discussion

NMA conditioning allows alloSCT in patients of advanced age and/or in those who are medically infirm [8]. The most important advantage of NMA regimens is their remarkable tolerability. Since relapse is the main reason for failure after alloSCT, in the low intensity type of alloSCT, the GVL

effect is of even higher importance compared to transplantations following standard or intermediate intensity conditioning. Besides others [3–5] two major protocols for NMA regimens have been developed, i.e. the busulfan-based FB2 and the low-dose TBI-based FluTBI2Gy regimens [9, 10]. Both regimens have gained broad acceptance and are widely used. They have been compared in a French randomized phase II trial of 139 patients with various hematologic malignancies, of which only 21 had AML. Only sibling donors were included in this trial [22]. The incidence of aGVHD II–IV was higher after FB2 than with FluTBI2Gy conditioning (47% vs. 27%; $p = 0.01$), whereas no difference was observed in incidence of cGVHD. In addition, the FB2 group had a greater objective antileukemic response rate (65% vs 46%; $p = 0.05$) which led to a lower relapse rate (27% vs. 54%; $p < 0.01$). However, NRM was higher with FB2 compared to FluTBI2Gy (38% vs. 22%; $p = 0.027$). Finally, at 5 years, the overall and progression-free survival rates did not differ significantly between the two regimens. These results differ from those obtained in our study. However, differences in patient selection, type of busulfan formulation used, type of post-grafting immunosuppression and others limit comparability of the two studies.

We observed a significantly lower incidence of total cGVHD and extensive cGVHD which translated into an improved GRFS with the FB2 regimen in patients transplanted from MUDs. This is most probably due to the difference in use of in vivo TCD between the two groups [30–34]. In the FB2 group 64% of patients transplanted from an MSD and 94% of those transplanted from an MUD, mean 79%, received in vivo TCD whereas TCD was not part of the FluTBI2Gy protocol. In accordance with the above-mentioned studies, use of in vivo TCD in the FB2 MSD group in our study significantly improved rates of cGVHD and extensive cGVHD in univariate analysis. On

Table 2 Multivariate analysis: patients transplanted from MSD

	RELAPSE		NRM		LFS		OS		GRFS		aGVHD II-IV		aGVHD III-IV		cGVHD		Ext. cGVHD	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
FluTBI vs. FB2	0.91 (0.63–1.32)	0.61	0.66 (0.37–1.17)	0.16	0.84 (0.61–1.15)	0.28	0.91 (0.64–1.28)	0.59	0.99 (0.74–1.32)	0.93	1.18 (0.58–2.4)	0.64	2.11 (0.65–6.82)	0.21	0.99 (0.62–1.58)	0.96	1.2 (0.63–2.32)	0.58
Age (per 10y)	0.84 (0.52–1.36)	0.48	1.2 (0.57–2.55)	0.63	0.91 (0.60–1.36)	0.63	0.98 (0.64–1.52)	0.94	0.89 (0.61–1.29)	0.53	1.38 (0.63–3.02)	0.42	2.1 (0.55–7.95)	0.28	1.4 (0.8–2.47)	0.24	1.18 (0.54–2.55)	0.68
Year of Tx	1.04 (0.99–1.1)	0.12	0.94 (0.87–1.02)	0.15	1.02 (0.97–1.06)	0.49	1.01 (0.97–1.06)	0.57	1.01 (0.97–1.05)	0.73	0.94 (0.87–1.02)	0.15	0.91 (0.79–1.05)	0.19	0.97 (0.9147–1.02)	0.26	0.98 (0.91–1.07)	0.7
<i>Cytogenetics</i>																		
Good/intermediate (reference)	1		1		1		1		1		1		1		1		1	
Poor	2.25 (1.54–3.28)	<0.0001	0.66 (0.27–1.6)	0.36	1.8 (1.29–2.52)	0.001	1.85 (1.3–2.64)	0.001	1.78 (1.31–2.43)	0.0003	0.99 (0.48–2.07)	0.98	0.93 (0.23–3.7)	0.92	1.21 (0.72–2.03)	0.48	1.44 (0.73–2.81)	0.29
NA/failed	1.12 (0.74–1.7)	0.58	0.94 (0.50–1.77)	0.85	1.04 (0.74–1.47)	0.80	1.12 (0.77–1.63)	0.54	1.01 (0.73–1.38)	0.97	1.17 (0.62–2.22)	0.63	1.28 (0.43–3.77)	0.66	1.03 (0.65–1.62)	0.91	0.73 (0.38–1.43)	0.36
Pat. CMV pos	1.11 (0.77–1.59)	0.58	1.15 (0.65–2.02)	0.63	1.12 (0.82–1.52)	0.48	1.1 (0.79–1.51)	0.58	1.21 (0.92–1.6)	0.17	1.58 (0.86–2.89)	0.14	0.89 (0.32–2.47)	0.82	1.28 (0.85–1.92)	0.24	1.37 (0.79–2.37)	0.26
Don. CMV pos	1.05 (0.75–1.46)	0.80	0.63 (0.37–1.09)	0.10	0.93 (0.70–1.23)	0.59	0.94 (0.69–1.27)	0.67	0.97 (0.75–1.25)	0.81	0.72 (0.42–1.22)	0.22	1.74 (0.64–4.75)	0.28	0.98 (0.68–1.42)	0.92	0.87 (0.53–1.42)	0.58
F->M	0.78 (0.55–1.12)	0.17	2.13 (1.27–3.57)	0.004	1.03 (0.77–1.38)	0.83	1.28 (0.94–1.73)	0.11	1.33 (1.02–1.72)	0.03	1.13 (0.67–1.93)	0.64	1.64 (0.67–4.05)	0.28	1.62 (1.11–2.37)	0.01	2.06 (1.25–3.41)	0.005
Time diag to Tx (mo)	0.97 (0.92–1.03)	0.35	1.01 (0.93–1.09)	0.87	0.98 (0.94–1.03)	0.47	0.97 (0.92–1.03)	0.34	0.99 (0.96–1.03)	0.71	0.99 (0.91–1.08)	0.81	0.89 (0.70–1.13)	0.33	0.98 (0.94–1.03)	0.48	1 (0.94–1.07)	0.93
KPS ≥ 90	0.93 (0.67–1.29)	0.66	0.71 (0.41–1.22)	0.21	0.87 (0.66–1.16)	0.34	0.79 (0.58–1.06)	0.12	1.07 (0.82–1.4)	0.60	0.78 (0.45–1.35)	0.37	1 (0.36–2.76)	1.00	1.07 (0.72–1.6)	0.72	1.42 (0.82–2.46)	0.21
<i>FLT3-ITD</i>																		
Negative (reference)	1		1		1		1		1		1		1		1		1	
Positive	1.48 (0.63–3.48)	0.37	1.35 (0.42–4.31)	0.61	1.45 (0.73–2.9)	0.29	1.5 (0.72–3.11)	0.28	1.09 (0.59–2.01)	0.77	2.9 (0.72–11.7)	0.13	0.46 (0.03–7.8)	0.59	0.91 (0.37–2.23)	0.84	0.87 (0.28–2.71)	0.81
Missing	1.28 (0.58–2.84)	0.55	0.85 (0.26–2.71)	0.78	1.16 (0.60–2.23)	0.67	0.94 (0.48–1.86)	0.87	1.17 (0.65–2.1)	0.61	2.36 (0.60–9.24)	0.22	2.09 (0.16–26.6)	0.57	1.49 (0.65–3.44)	0.35	0.92 (0.31–2.72)	0.88
<i>NPM1</i>																		
Negative (reference)	1		1		1		1		1		1		1		1		1	
Positive	0.63 (0.25–1.58)	0.33	1.63 (0.45–5.93)	0.46	0.81 (0.38–1.7)	0.57	0.68 (0.29–1.56)	0.36	0.90 (0.47–1.7)	0.74	0.62 (0.14–2.68)	0.52	6.04 (0.35–106)	0.22	1.32 (0.54–3.23)	0.55	1.14 (0.36–3.59)	0.83
Missing	1.07 (0.47–2.45)	0.86	1.95 (0.55–6.99)	0.30	1.25 (0.63–2.48)	0.53	1.27 (0.63–2.58)	0.51	1.11 (0.6–2.06)	0.74	0.65 (0.16–2.61)	0.54	1.86 (0.08–45.2)	0.70	1.05 (0.42–2.62)	0.91	1.1 (0.34–3.6)	0.88
Center (futility)	0.20		0.50	0.22	0.22	0.17	0.19	0.034	0.15	0.07	0.034	0.034	0.15	0.07	0.034	0.07	0.05	0.05

FluTBI 2 Gy fludarabine total-body-irradiation (200 cGy), *FB2* fludarabine/busulfan, *NRM* nonrelapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* refined graft-versus-host disease-free, relapse-free survival, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic graft-versus-host disease, *ext. cGVHD* extensive chronic graft-versus-host disease, *NA* not available, *Tx* transplantation, *CMV* cytomegalovirus, *KPS* Karnofsky performance score, *FLT3-ITD* FMS-like tyrosine kinase 3 internal tandem duplication, *NPM1* nucleophosmin 1

Fig. 1 **a** Outcome in patients transplanted from MSD. Comparisons of cumulative incidence (CI) of relapse (RI), nonrelapse mortality (NRM) and chronic GVHD (cGVHD), comparisons of probability of GVHD-free-relapse-free survival (GRFS), leukemia-free survival (LFS) and overall survival (OS) in patients transplanted from MSD after conditioning with FB2 vs. FluTBI2Gy. **b** Outcome in patients transplanted

from MUD. Comparisons of cumulative incidence (CI) of relapse (RI), nonrelapse mortality (NRM) and chronic GVHD (cGVHD), comparisons of probability of GVHD-free-relapse-free survival (GRFS), leukemia-free survival (LFS) and overall survival (OS) in patients transplanted from MUD after conditioning with FB2 vs. FluTBI2Gy

multivariate analysis, a trend for a lower incidence of extensive cGVHD in patients treated with FB2 with in vivo TCD compared to those with FluTBI2Gy was observed. Moreover, in patients treated with FB2 without in vivo TCD a higher NRM rate and a trend for more total cGVHD was observed in comparison to FluTBI2Gy. This is in accordance with the known protective effect of using in vivo TCD in terms of cGVHD [30–34]. The FluTBI2Gy regimen is generally used without in vivo TCD in order to obtain stable engraftment. A pioneering study by Storb et al. in dogs, using low-dose TBI alone for conditioning showed that the type of post-transplant immunosuppression is crucial [17].

Sex-mismatch, i.e. transplants from a female donor to a male recipient, has been reported to have worse outcomes [35–37]. In our study this is also evident (Tables 2, 3, S1). However, the rates of sex mismatch were similar in both conditioning regimen groups (20.58% vs. 17.94%, $p = 0.27$, in FB2 and FluTBI2Gy, respectively). In addition, rates of sex-mismatch were balanced between FB2 and FluTBI2Gy groups in the MSD as well as the MUD subgroups (data not shown). Multivariate analyses were adjusted for this variable and the effect of conditioning is independent of sex matching.

Chen et al. reported a study using either the FB2 or FB4 regimens in 217 patients of which 149 had AML [38]. In the

Table 3 Multivariate analysis: patients transplanted from MUD

	RELAPSE		NRM		LFS		OS		GRFS		aGVHD II-IV		aGVHD III-IV		cGVHD		Ext. cGVHD	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
FluTBI vs. FB2	0.89 (0.62–1.28)	0.53	0.86 (0.58–1.26)	0.43	0.88 (0.68–1.14)	0.34	1.00 (0.75–1.34)	0.98	1.35 (1.02–1.79)	0.03	0.82 (0.54–1.23)	0.34	0.60 (0.27–1.37)	0.23	2.44 (1.60–3.72)	<0.0001	4.59 (2.35–8.96)	<0.0001
Age (per 10y)	1.18 (0.73–1.92)	0.51	1.98 (1.18–3.31)	0.01	1.49 (1.05–2.12)	0.03	1.43 (0.99–2.07)	0.05	1.18 (0.86–1.63)	0.31	0.85 (0.53–1.35)	0.49	1.41 (0.61–3.24)	0.42	0.76 (0.49–1.16)	0.20	1.37 (0.76–2.45)	0.29
Year of Tx	0.97 (0.90–1.03)	0.32	0.93 (0.86–1.00)	0.05	0.95 (0.9–1.00)	0.04	0.96 (0.91–1.02)	0.18	0.98 (0.93–1.03)	0.34	0.99 (0.92–1.06)	0.66	0.94 (0.83–1.07)	0.37	1.01 (0.95–1.09)	0.70	0.99 (0.89–1.1)	0.87
Cytogenetics																		
Good/ intermediate (reference)	1		1		1		1		1		1		1		1		1	
Poor	2.14 (1.3–3.5)	0.003	1.1 (0.62–1.95)	0.75	1.59 (1.1–2.31)	0.01	1.33 (0.9–1.96)	0.15	1.24 (0.88–1.75)	0.23	1.26 (0.78–2.03)	0.35	1.06 (0.41–2.71)	0.91	0.96 (0.60–1.54)	0.87	1.15 (0.58–2.29)	0.69
NA/failed	1.58 (0.96–2.59)	0.07	1.26 (0.75–2.11)	0.38	1.42 (0.99–2.02)	0.06	1.3 (0.90–1.88)	0.17	1.23 (0.89–1.72)	0.21	1.23 (0.77–1.98)	0.39	1.79 (0.71–4.47)	0.22	0.91 (0.57–1.44)	0.68	0.82 (0.44–1.54)	0.54
Pat. CMV pos	0.71 (0.48–1.03)	0.07	1.49 (0.97–2.3)	0.07	1.00 (0.76–1.32)	0.99	1.15 (0.86–1.55)	0.35	0.89 (0.69–1.15)	0.38	1.11 (0.76–1.62)	0.60	0.96 (0.49–1.87)	0.91	1.24 (0.87–1.78)	0.24	0.93 (0.56–1.52)	0.76
Don. CMV pos	1.23 (0.83–1.8)	0.30	0.98 (0.66–1.46)	0.92	1.09 (0.83–1.43)	0.55	1.02 (0.77–1.36)	0.87	1.13 (0.88–1.46)	0.34	1.32 (0.92–1.88)	0.13	1.21 (0.64–2.29)	0.55	1.05 (0.74–1.5)	0.79	1.31 (0.80–2.13)	0.28
F->M	0.63 (0.33–1.2)	0.16	1.92 (1.18–3.13)	0.01	1.17 (0.80–1.71)	0.42	1.2 (0.81–1.79)	0.37	1.18 (0.82–1.69)	0.38	1.1 (0.66–1.85)	0.72	0.81 (0.30–2.14)	0.67	1.33 (0.83–2.12)	0.24	1.39 (0.72–2.68)	0.33
Time diag to Tx (mo)	0.98 (0.93–1.03)	0.35	1.00 (0.97–1.02)	0.74	0.99 (0.97–1.01)	0.35	0.99 (0.97–1.01)	0.42	0.99 (0.97–1.01)	0.33	0.99 (0.96–1.02)	0.52	1.00 (0.95–1.04)	0.84	0.99 (0.97–1.02)	0.64	1.00 (0.96–1.03)	0.84
KPS≥90	1.11 (0.75–1.64)	0.60	0.86 (0.58–1.29)	0.48	0.98 (0.74–1.29)	0.88	1.08 (0.80–1.45)	0.63	1.00 (0.77–1.29)	1.00	1.18 (0.81–1.71)	0.40	0.99 (0.51–1.89)	0.97	1.00 (0.69–1.44)	1.00	0.87 (0.51–1.48)	0.61
FLT3-ITD																		
Negative (reference)	1		1		1		1		1		1		1		1		1	
Positive	1.99 (0.93–4.3)	0.08	0.40 (0.16–0.96)	0.04	0.94 (0.52–1.69)	0.82	0.72 (0.37–1.4)	0.34	0.70 (0.39–1.25)	0.23	0.83 (0.38–1.81)	0.64	0.14 (0.03–0.76)	0.02	0.33 (0.15–0.72)	0.01	0.55 (0.18–1.67)	0.29
Missing	1.2 (0.50–2.9)	0.69	0.69 (0.31–1.55)	0.37	0.89 (0.49–1.63)	0.71	1.0 (0.53–1.88)	0.99	0.85 (0.48–1.52)	0.59	1.13 (0.51–2.49)	0.76	0.12 (0.03–0.49)	0.003	0.45 (0.22–0.92)	0.03	0.89 (0.33–2.39)	0.82
NPM1																		
Negative (reference)	1		1		1		1		1		1		1		1		1	
Positive	0.58 (0.24–1.38)	0.22	2.75 (1.20–6.29)	0.02	1.25 (0.68–2.32)	0.47	1.24 (0.63–2.44)	0.53	1.74 (0.97–3.12)	0.06	0.92 (0.43–1.96)	0.83	2.18 (0.59–8.07)	0.24	2.52 (1.16–5.49)	0.02	3.54 (1.18–10.6)	0.02
Missing	0.81 (0.36–1.87)	0.63	1.38 (0.60–3.15)	0.45	1.07 (0.59–1.93)	0.83	1.01 (0.54–1.88)	0.99	1.16 (0.66–2.04)	0.61	0.62 (0.29–1.35)	0.23	3.26 (0.84–12.7)	0.09	1.45 (0.71–2.98)	0.31	1.11 (0.42–2.9)	0.84
Center (fertility)	0.41		0.92		0.30		0.28		0.10		0.17		0.06		0.06		0.002	

FluTBI 2Gy fludarabine total-body-irradiation (200 cGy), *FB2* fludarabine/busulfan, *NRM* nonrelapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* refined graft-versus-host disease-free, relapse-free survival, *aGVHD* acute graft-versus-host disease, *cGVHD* chronic graft-versus-host disease, *ext. cGVHD* extensive chronic graft-versus-host disease, *NA* not available, *Tx* transplantation, *CMV* cytomegalovirus, *KPS* Karnofsky performance score, *FLT3-ITD* FMS-like tyrosine kinase 3 internal tandem duplication, *NPM1* nucleophosmin 1

FB2 group, ATG was not used and 14% of patients received transplants from mismatched donors. In these patients the cumulative incidence rate of aGVHD II-IV at 200 days post transplantation was 17% and the rate of cGVHD at 2 years was 41.5%. In our study, in FB2 patients, aGVHD II-IV at day 100 and cGVHD was observed in 22.7% and 33.4%, respectively. This difference in cGVHD rates may be explained by differences in donor selection and the use of ATG in 79% of patients in the FB2 group in our study.

In a prospective multicenter phase II study using the FB2 regimen in older AML patients in CR, of which 52% had received transplantation from unrelated donors and had received ATG, aGVHD II-IV, cGVHD and extensive cGVHD was observed in 9.6%, 28% and 11%, respectively, which is comparable to our study [16].

Acute GVHD II-IV has been reported in 40–52% of AML patients receiving allogeneic transplants following FluTBI2Gy conditioning [19, 20]. Chronic GVHD was observed in 43% and extensive cGVHD in 36% of patients. In our study we observed aGVHD II-IV, cGVHD and extensive cGVHD in 22.3%, 50.0% and 29.8% of patients respectively, in the FluTBI2Gy group. The differences may be explained by the fact that the studies published by Hegenbart et al. [19] and Gyurkocza et al. [20] included mismatched donors in 34% and 12% of cases, respectively, whereas we only included MSDs and MUDs.

Adding ATG to FluTBI2Gy conditioning is currently not standard in many centers because of the crucial role of donor-derived T cells for stable engraftment. Nevertheless, few studies have demonstrated its feasibility and the results suggest that the rates of cGVHD can be reduced [39–42].

Due to its retrospective nature our study has several limitations. We do not know the reasons for choosing the FB2 or FluTBI2Gy regimen for a specific patient as this was the physician's preference and center policy; thus patient bias and selection cannot be excluded. Also, the type and dose of ATG were often missing. Furthermore, data on measurable residual disease at the time of transplant were available only in a minority of patients. In these, however, no differences in terms of molecular remission rate between the two conditioning groups were observed. Also, differences in year of transplant, KPS and missing molecular markers may have an impact on outcome. Therefore, these variables were incorporated into the multivariate analyses. Despite the above-mentioned limitations inherent to most retrospective studies, given the large homogenous study population we believe that the results obtained may be of importance to the alloSCT field.

In conclusion, our registry-based study shows that in AML CR1 patients aged ≥ 60 years transplanted using PBSCs from a MUD FB2 with in vivo TCD showed lower incidence of chronic GVHD, extensive cGVHD and improved GRFS when compared to FluTBI2Gy without

TCD. FluTBI2Gy was associated with less NRM compared to FB2 in patients receiving a graft from MSDs without in vivo TCD and overall resulted in similar outcome including RI, LFS, OS, aGVHD and death related to GVHD or infection. The choice of FluTBI2Gy vs. FB2 is therefore guided by center experience and preference. These results merit confirmation in a well-designed prospective trial.

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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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Affiliations

Thomas Heinicke¹ · Myriam Labopin² · Emmanuelle Polge² · Dietger Niederwieser³ · Uwe Platzbecker³ · Henrik Sengelov⁴ · Goda Choi⁵ · Jan Cornelissen⁶ · Didier Blaise⁷ · Jürgen Kuball⁸ · Gwendolyn van Gorkom⁹ · Nicolaas Schaap¹⁰ · Victoria Potter¹¹ · Franciane Paul¹² · Bipin N. Savani¹³ · Arnon Nagler^{14,15} · Mohamad Mohty²

¹ Department of Hematology and Oncology, Otto-von-Guericke University, Magdeburg, Germany

² Department of Hematology and Cell Therapy and ALWP EBMT Office, Hospital Saint Antoine Paris, Paris, France

³ Medical Clinic and Polyclinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Leipzig, Germany

⁴ Bone Marrow Transplant Unit L 4043, National University Hospital, Rigshospitalet, Copenhagen, Denmark

⁵ Department of Hematology, University Medical Center Groningen (UMCG), Groningen, The Netherlands

⁶ Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

⁷ Institut Paoli Calmettes, Department of Hematology, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France

⁸ Department of Haematology, University Medical Centre, Utrecht, The Netherlands

⁹ University Hospital Maastricht Dept. Internal Med.Hematology/Oncology, Maastricht, Maastricht, The Netherlands

¹⁰ Department of Hematology, Radboud University Medical Centre, Nijmegen, The Netherlands

¹¹ Department of Haematological Medicine, GKT School of Medicine, King's College Hospital, London, UK

¹² Département d'Hématologie Clinique, CHU Lapeyronie, Montpellier, France

¹³ Department of Medicine, Division of Hematology-Oncology, Vanderbilt University Medical Center, Brentwood, TN, USA

¹⁴ Hematology Division and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer and Tel Aviv University, Tel-Aviv, Israel

¹⁵ ALWP EBMT Office, Hospital Saint Antoine Paris, Paris, France