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RESEARCH ARTICLE

Fludarabine versus cyclophospamide in combination with myeloablative total body irradiation as conditioning for patients with acute myeloid leukemia treated with allogeneic hematopoietic cell transplantation. A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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Abstract

Total body irradiation (TBI) at a dose of 12 Gy combined with cyclophosphamide (CyTBI12Gy) is one of the standard myeloablative regimens for patients with acute myeloid leukemia (AML) treated with allogeneic hematopoietic cell transplantation (allo-HCT). In clinical practice, cyclophosphamide may be substituted with fludarabine (FluTBI12Gy) to reduce toxicity. We retrospectively compared outcomes of CyTBI12Gy with FluTBI12Gy for patients with AML treated in complete remission

(CR) with allo-HCT from either a matched sibling or unrelated donor. Of 1684 adults who met inclusion criteria, 109 patients in each group were included in a matched-pair analysis. The cumulative incidence of relapse at 2 years was 25% in the FluTBI12Gy compared to 28% in the CyTBI12Gy group ($p = .44$) while non-relapse mortality (NRM) was 17% versus 19%, ($p = .89$) respectively. The rates of leukemia-free survival and overall survival were 65% versus 54% ($p = .28$) and 70% versus 60.5% ($p = .17$). Cumulative incidence of grade 2–4 acute graft-versus-host disease (GVHD) was significantly lower for FluTBI12Gy than CyTBI12Gy (16% vs. 34%, $p = .005$), while the incidences of grade 3–4 acute GVHD and chronic GVHD did not differ significantly. The probability of GVHD and relapse-free survival was 49% in the FluTBI12Gy and 41% in the CyTBI12Gy group ($p = .17$). We conclude that for patients with AML treated with allo-HCT in CR, cyclophosphamide may be substituted with fludarabine in a regimen based on TBI at a dose of 12 Gy without negative impact on the efficacy. FluTBI12Gy is associated with reduced risk of grade 2–4 acute GVHD and encouraging survival rates.

1 | INTRODUCTION

Acute myeloid leukemia (AML) is the most frequent indication for allogeneic hematopoietic cell transplantation (allo-HCT).[1] The anti-leukemic effect of the procedure relies on pre-transplant conditioning and post-transplant graft-versus-leukemia reaction conferred by donor-derived lymphocytes. For younger patients myeloablative conditioning is preferred as it is associated with reduced risk of relapse compared to reduced intensity or non-myeloablative regimens.[2,3] It may either be based on chemotherapy alone or total body irradiation (TBI). Prospective, randomized trials showed comparable results for both options.[4] Retrospective comparisons have suggested higher efficacy of TBI at the cost of increased toxicity.[5,6] Potential advantages of TBI include high-dose homogeneity to the whole body regardless of blood supply, no sparing of "sanctuary" sites such as the central nervous system, and less possibility of cross-resistance with other antineoplastic agents.

The classical irradiation-based myeloablative regimen consists of fractionated TBI at a dose of 12 Gy combined with cyclophosphamide (Cy) at a total dose of 120 mg/kg (CyTBI12Gy).[7] Although CyTBI12Gy is highly effective, it is also associated with significant risk of early and late toxicities.[8] Early organ complications include severe mucositis, diarrhea, cardiac and pulmonary toxicity, hemorrhagic cystitis and sinusoidal obstruction syndrome.[9] Late events, including deterioration of endocrine and renal function, pneumonitis, and second malignancies may lead to increased mortality and impaired quality of life.[10] In order to improve tolerance, Cy may be substituted with fludarabine (Flu). Results of a prospective, randomized trial demonstrated that the combination of TBI at a reduced dose (8 Gy) with Flu was associated with survival comparable to CyTBI12Gy.[11] In clinical practice, Flu may also be combined with TBI at a dose of 12Gy (FluTBI12Gy) in order to increase regimen efficacy. However, safety and efficacy of FluTBI12Gy has not been evaluated so far.

The goal of this study was to retrospectively compare outcomes of CyTBI12Gy with FluTBI12Gy for patients with AML in first or second complete remission (CR1 or CR2) treated with allo-HCT from either a matched sibling (MSD) or unrelated donor (URD).

2 | METHODS

2.1 | Study design and data collection

This was a retrospective, multicenter analysis. Data were provided by the registry of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a non-profit, scientific society representing more than 600 transplant centers, mainly located in Europe, which 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. Since 1990, all patients have provided informed consent authorizing the use of their personal information for research purposes. The validation and quality control program includes verification of the computer printout of the entered data, cross-checking with the national registries, and on-site visits to selected teams. The study was approved by the ALWP of the EBMT institutional review board and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2 | Criteria for selection

The inclusion criteria were as follows: (1) patients with AML who underwent their first allo-HCT in CR1 or CR2 between January 2009 and June 2020; (2) age ≥ 18 years; (3) transplantation from either an HLA-MSD or URD; (4) the use of peripheral blood or bone marrow as a source of stem cells; (5) the use of one of the following conditioning regimes: CyTBI12Gy or FluTBI12Gy. The use of anti-thymocyte globulin as part of conditioning was allowed while transplantations with ex vivo T-cell depletion or use of cord blood as a source of stem cells were excluded from the analysis.

TABLE 1 Patient, donor, and transplant-related characteristics

	FluTBI12	CyTBI12	*p*
N	109	109	
Median patient age, years (range)	38 (18–69)	40 (18–60)	.87
Cytogenetic risk group, *n* (%)			
Standard	9 (8%)	9 (8%)	1.00
Intermediate	38 (35%)	38 (35%)	
High	14 (13%)	14 (13%)	
Unknown	48 (44%)	48 (44%)	
Disease status			
CR1	85 (78%)	85 (78%)	1.00
CR2	24 (22%)	24 (22%)	
Median year of transplantation (range)	2016 (2009–2020)	2012 (2009–2020)	<.0001
Karnofsky performance status score			
≥90%	83 (76%)	78 (72%)	.44
<90%	26 (24%)	31 (28%)	
Donor type			
HLA-identical sibling	26 (37%)	26 (32.5%)	.81
10/10 HLA matched unrelated	36 (51%)	43 (54%)	
9/10 HLA mismatched unrelated	8 (11%)	11 (14%)	
Unrelated, HLA compatibility unknown	39	29	
Patient sex			
Male	67 (61.5%)	66 (61%)	.89
Female	42 (38.5%)	43 (39%)	
Donor sex			
Male	69 (63%)	71 (65%)	.78
Female	40 (37%)	38 (35%)	
Donor/patient sex			
Female/male	20 (18%)	20 (18%)	1.00
Other combinations	89 (82%)	89 (82%)	
Patient CMV serological status			
Positive	61 (57%)	73 (68%)	.11
Negative	46 (43%)	35 (32%)	
Missing	2	1	
Donor CMV serological status			
Positive	49 (45%)	49 (45%)	1.00
Negative	59 (55%)	59 (55%)	
Missing	1	1	
Source of stem cells			
Peripheral blood	105 (96%)	105 (96%)	1.00
Bone marrow	4 (4%)	4 (4%)	
In vivo T-cell depletion			
Yes	64 (59%)	57 (52%)	.34
No	45 (41%)	52 (48%)	
Post-transplant cyclophosphamide as part of immunosuppression			
Yes	7 (6%)	3 (3%)	.22
No	102 (94%)	106 (97%)	

Abbreviations: CMV, cytomegalovirus; CR, complete remission; Cy, cyclophosphamide; Flu, fludarabine; HLA, human leukocyte antigen; TBI, total body irradiation.

TABLE 2 Matched-pair analysis: Results of allo-HCT according to the type of conditioning.

	FluTBI12	CyTBI12	HR (95%CI)	*p*
N	109	109		
Relapse incidence	20% (12–28)	27% (19–36)	1.58 (0.77–3.23)	.21
Non-relapse mortality	15% (9–23)	19% (12–27)	1.07 (0.46–2.49)	.88
Leukemia-free survival	65% (55–74)	54% (44–63)	1.34 (0.79–2.26)	.28
Overall survival	70% (59–79)	60.5% (50–69)	1.52 (0.83–2.78)	.17
GVHD-free, relapse-free survival	49% (38.5–59)	41% (32–51)	1.38 (0.87–2.2)	.17
Acute GVHD grade 2–4	16% (10–23.5)	34% (25–43)	2.35 (1.3–4.25)	.005
Acute GVHD grade 3–4	7% (3–12)	10% (5–17)	1.87 (0.61–5.71)	.27
Chronic GVHD	39% (29–49)	43% (33–53)	1.4 (0.81–2.43)	.23
Extensive chronic GVHD	16% (9–25)	18% (11–26)	1.7 (0.65–4.43)	.28

Note: Results are reported as probabilities at 2 years (95% confidence interval, CI) and hazard ratios (95%CI).

Abbreviations: CI, confidence interval; Cy, cyclophosphamide; Flu, fludarabine; GRFS, GVHD-free, relapse-free survival; GVHD, graft-versus-host disease; HR, hazard ratio; TBI, total body irradiation.

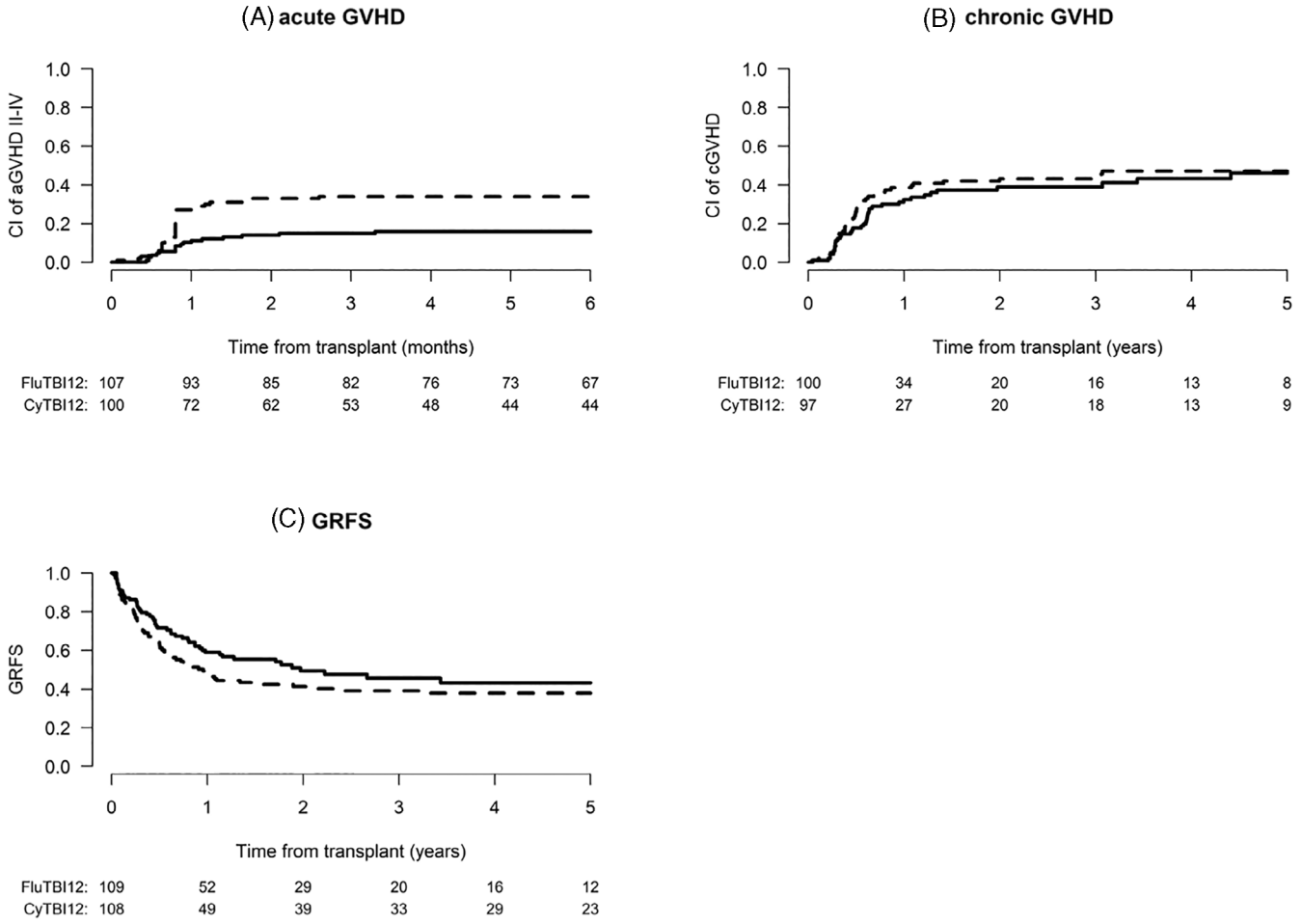

FIGURE 1 The incidence of graft-versus-host disease according to the type of conditioning regimen. Solid lines: FluTBI12, dashed lines: CyTBI12. GVHD, graft-versus-host disease; GRFS, graft-versus-host- and relapse-free survival.

2.3 | Statistical analysis

The groups were compared in a matched-pair analysis. From a total population of patients meeting the inclusion criteria, final cohorts were selected using exact matching for cytogenetic risk groups, disease status at allo-HCT (CR1/CR2), donor type (MSD/URD) as well as stem cell source (peripheral blood/bone marrow), and nearest neighbor for recipient age, donor and

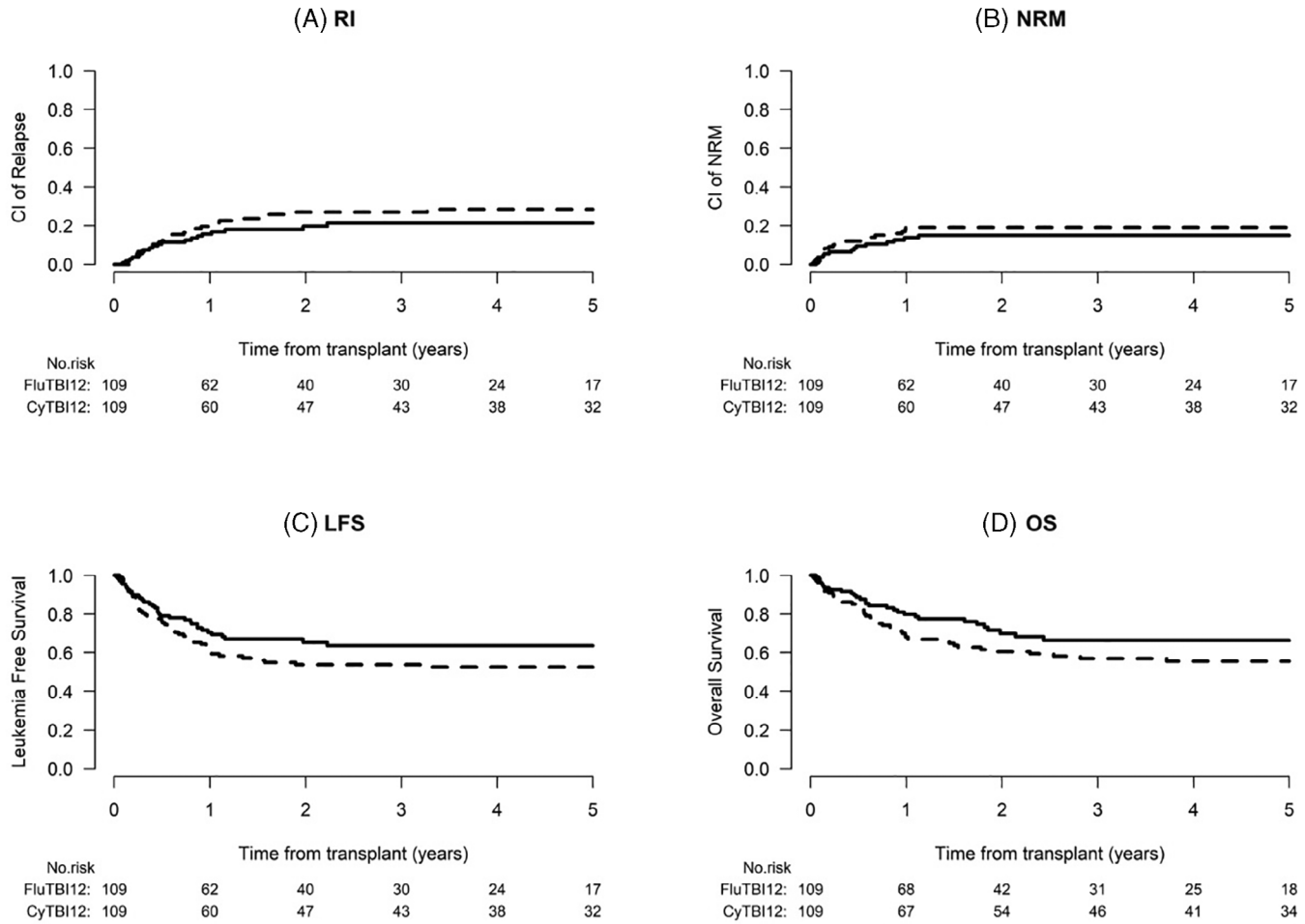

FIGURE 2 Results of allo-HCT for patients with acute myeloid leukemia according to the type of conditioning regimen. Solid lines: FluTBI12, dashed lines: CyTBI12. NRM, non-relapse mortality; RI, relapse incidence; LFS, leukemia-free survival; OS, overall survival.

recipient sex, Karnofsky performance score and the use of in vivo T-cell depletion.

Leukemia-free survival (LFS) was the primary endpoint. Secondary endpoints were: (1) overall survival (OS), (2) relapse incidence (RI), (3) non-relapse mortality (NRM), (4) incidence of grade 2–4 and grade 3–4 acute graft-versus-host disease (GVHD), (5) incidence of chronic GVHD and extensive chronic GVHD, and (6) survival free from grade 3–4 acute GVHD, chronic GVHD, and relapse (GRFS).[12] All outcomes were censored at 2 years.

Patients' characteristics were compared using the Mann–Whitney *U* test for continuous variables, and the chi-squared or Fisher's exact test for categorical variables. Probabilities of LFS, OS, and GRFS were calculated using the Kaplan–Meier estimator. Cumulative incidence curves were used to estimate the probabilities of RI, NRM, acute and chronic GVHD in a competing-risks setting.[13] Univariate analyses were performed using the log-rank test for LFS, OS, and GRFS, and Gray's test was used to compare cumulative incidence estimates.[14]

All tests were two-sided with the type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 24.0 (IBM Corp., Armonk, NY) and R 3.5.3 (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/).

3 | RESULTS

3.1 | Patients, donors, and allo-HCT procedure

Overall, 1684 patients met the inclusion criteria, out of whom 1463 were treated with CyTBI12Gy and 121 received a FluTBI12Gy conditioning regimen. The decision to choose FluTBI12Gy was based on center strategy in 52 (43%) patients while it was individual physician's decision in 45 (37%) patients. In remaining 24 (20%) cases the reason remained unknown. The matched-pair analysis included 109 patients in each group.

Details on patient, donor, and transplant-related characteristics did not differ significantly between the study groups except for year of transplantation (Table 1). Patients in the FluTBI12Gy group were transplanted more recently than those in the CyTBI12Gy group

(median year: 2016 vs. 2012, $p < .0001$). In both groups, 78% of patients were in CR1 at allo-HCT while the remainder were in CR2. Most patients received an allo-HCT from a URD, using peripheral blood as a source of stem cells. In both cohorts, more than half of the patients were treated with in vivo T-cell depletion, while cyclosporin A combined with short-course methotrexate was the most common immunosuppressive protocol.

In the FluTBI12Gy group, among 65 patients with available data, TBI was administered most frequently in 3 ($n = 35$, 54%), 6 ($n = 20$, 31%), or 4 ($n = 9$, 14%) fractions. In the CyTBI12Gy cohort, among 51 individuals with available data, the most frequent number of TBI fractions was 6 ($n = 28$, 55%), 4 ($n = 12$, 24%), and 2 ($n = 7$, 14%). The median total dose of fludarabine was 150 mg/m^2 (interquartile range, IQR: 120–150) while the median total dose of cyclophosphamide was 120 mg/kg (IQR: 120–120).

3.2 | Engraftment and GVHD

The engraftment rate was 98.2% and 100% in the FluTBI12Gy and CyTBI12Gy groups, respectively, ($p = .5$), results not shown. Median time to neutrophil recovery (>0.5 $\times$ 10^9/L) was 17 days (9–38) and 18 (11–44) respectively ($p = .02$).

The incidence of grade 2–4 acute GVHD was significantly higher in the CyTBI12Gy than the FluTBI12Gy group (34% vs. 16%; hazard ratio = 2.35, 95% confidence interval, 1.35–4.25; $p = .005$). The incidences of grade 3–4 acute GVHD as well as overall and extensive chronic GVHD were comparable between the study groups (Table 2, Figure 1).

3.3 | Relapse and NRM

The median follow-up was 27 months for the FluTBI12Gy group and 63 months for the CyTBI12Gy group.

The RI at 2 years was 20% for patients treated with FluTBI12Gy compared to 27% in the CyTBI12Gy group ($p = .21$), while NRM was 15% and 19% respectively ($p = .88$) (Table 2, Figure 1).

The most frequent causes of death in both groups were: original disease (46.2% for TBI/Flu and 51.3% for TBI/Cy, $p = .66$), infections (23.1% in both groups, $p = 1.00$), GVHD (3.8% and 15.4%, respectively, $p = .14$). Multiorgan failure and cardiac toxicity were reported as causes of death in two patients, both in the FluTBI12Gy group, results not shown.

3.4 | Survival

The probability of LFS was 65% for FluTBI12Gy group compared to 54% in the CyTBI12Gy group ($p = .28$), while OS rates were 70% and 60.5% respectively ($p = .17$) (Table 2, Figure 2). The probability GRFS was 49% in the FluTBI12Gy group and 41% in the CyTBI12Gy group ($p = .17$).

4 | DISCUSSION

In this registry-based study, we compared for the first time, outcomes of allo-HCT using FluTBI12Gy with those of the classical myeloablative conditioning with CyTBI12Gy in patients with AML in CR. All survival outcomes including RI were comparable between the two groups while the incidence of grade II-IV acute GVHD was significantly reduced in FluTBI12Gy patients.

Cy is an alkylating agent with strong immunosuppressive properties, which was incorporated in conditioning regimens as early as in the 1970s, initially in combination with TBI, and later-on with busulfan (Bu).[15,16] It contributes to elimination of host lymphocytes thus facilitating engraftment. Cy also has direct anti-leukemic activity, however, its contribution to overall efficacy of the allo-HCT procedure has not been well-defined.[17] High doses of Cy are associated with some specific toxicities, including hemorrhagic cystitis and cardiotoxicity.[18] They may also increase overall tissue damage when combined with TBI or Bu, which, in turn, may facilitate activation of alloreactive donor-derived T-cells and initiation of acute GVHD.[19]

Flu, a purine analogue, is a potent immunosuppressive drug, but its direct anti-leukemic activity in AML has never been documented. The drug was found to potentiate metabolism of cytarabine by increasing intracellular concentration of its active metabolite, arabinosyl cytosine triphosphate.[20,21] For patients with acute leukemias, Flu has been incorporated into several salvage regimens like FLAG-IDA, always in combination with cytarabine, while never as a single agent.[22] The drug is generally well-tolerated. Its side effects are restricted mainly to neurotoxicity, including leukoencephalopathy, which is, however, a very rare event.[23] Therefore, it may be assumed that the use of Flu in conditioning instead of Cy may ensure engraftment, while reduce the risk of organ damage. On the other hand, its effect on the risk of relapse is theoretically a matter of concern.

Substitution of Cy with Flu in AML was a subject of five randomized controlled trials.[11,24–27] Four studies focused on combination with myeloablative doses of Bu, showing conflicting results. One study from Beijing was prematurely terminated due to increased incidence of severe pneumonia in the BuFlu group.[24] In another study, the use of BuFlu was associated with reduced regimen-related toxicity without significant impact on NRM, RI, and survival.[25] The Korean study demonstrated an increased risk of relapse as well as decreased LFS and OS for patients assigned to the BuFlu arm compared to BuCy.[26] Finally, in an Italian study, restricted to patients aged between 40 and 65 years, the use of BuFlu was associated with a significantly reduced risk of NRM without significant impact on LFS and OS.[27] A meta-analysis, including four randomized trials and 11 studies which were either single-arm intervention trials compared with historical controls or retrospective studies, confirmed a reduced risk of NRM at 100 days after BuFlu compared to BuCy.[28]

The combination of TBI with Flu was compared with CyTBI12Gy in a prospective, randomized study in Germany, restricted to patients with AML aged 18–60 years.[11] The total dose of TBI in the Flu arm was reduced to 8 Gy. The use of FluTBI was associated with decreased incidence of severe mucositis and reduced NRM, which

was particularly prominent for patients aged between 41 and 60 years. No difference regarding RI and probability of LFS was evident.[11] The authors concluded that substitution of Cy with Flu, when combined with TBI, is characterized by better tolerance while maintaining anti-leukemic potential. In our study, we focused on the combination of Flu with a fully myeloablative dose of TBI, that is, 12 Gy. The population of our FluTBI12Gy group was similar to the FluTBI8Gy in the German trial, however, our study included patients in both CR1 and CR2, while the prospective trial[11] was restricted to patients in CR1. The upper age limit was 69 and 60 years respectively. Despite this, the incidences of both relapse and NRM appeared similar (25% at 2 years vs. 28% at 3 years and 17% vs. 13% respectively). As in the German study, we could not find any significant difference between FluTBI12Gy and CyTBI12Gy with respect to LFS or OS rates.

The ALWP of the EBMT proposed definitions of the intensity of conditioning regimens taking into account prediction of all (early and late) NRM as well as relapse.[29] Weight scores were assigned to all components of most frequently used regimens. Their sum enabled classification of the regimens into three groups: low, intermediate, and high transplant conditioning intensity (TCI). According to the proposed algorithm, CyTBI12Gy has a TCI score of 4, which places it in the category of high intensity regimens, associated with high risk of NRM, while the TCI score for FluTBI12Gy is 3, an intermediate intensity protocol, described also as a "reduced toxicity regimen with myeloablative potential". In this registry-based study we were unable to analyze particular transplant-related complications and therefore precise evaluation of the toxicity of the regimens was impossible. However, we found significant differences regarding the risk of grade II-IV acute GVHD, which was more than two times lower for FluTBI12Gy compared to CyTBI12Gy. In view of similar patient and transplant characteristics in both study cohorts, this finding suggests decreased tissue damage related to the conditioning with FluTBI12Gy supporting its categorization as a "reduced toxicity" regimen. On the other hand, it was shown that Flu, when administered to patients with chronic lymphocytic leukemia as part of their primary therapy before allo-HCT, may also modulate the host immune system, thereby reducing the severity of GVHD encountered in patients undergoing this treatment.[30]

Our study has some additional limitations pertinent to its retrospective nature. As shown in a previously published European survey, high heterogeneity of the TBI procedure may be expected between centers with regard to dose fractionation, dose rates, beam energy, treatment unit and technique as well as dosimetry and organ shielding.[7] Such differences could not be controlled for in our analysis and they might have affected both tolerance and efficacy of the treatment. Another study limitation was lack of detailed molecular characteristics of the disease. The status of *NPM1*, *FLT3*, and other gene mutations with documented prognostic value was reported for only a minority of patients and could not be included in the analysis. Finally, results of the study might potentially have been biased by a center effect as the choice of regimen was determined by center policy.

We conclude that for patients with AML treated with allo-HCT in CR1 or CR2, Cy may be substituted with Flu in a regimen based on TBI at a dose of 12 Gy without negative impact on efficacy. FluTBI12Gy is associated with a reduced risk of grade 2–4 acute GVHD and encouraging LFS and OS rates. In view of our findings, it is justifiable to use FluTBI12Gy instead of CyTBI12Gy although prospective, randomized trials are needed to draw definitive conclusions.

AUTHOR CONTRIBUTIONS

Sebastian Giebel designed the study, interpreted the results, and wrote the manuscript; Myriam Labopin designed the study, performed statistical analysis, interpreted results, and reviewed the manuscript; Thomas Schroeder, Ryszard Swoboda, Johan Maertens, Jean Henri Bourhis, Giovanni Grillo, Urpu Salmenniemi, Inken Hilgendorf, Nicolaus Kröger, Xavier Poiré, Jan J. Cornelissen, Mutlu Arat contributed data, interpreted results, and reviewed the manuscript; Bipin Savani, Alexandros Spyridonidis, Arnon Nagler, Mohamad Mohty designed the study, interpreted results, and reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Dataset is part of the EBMT registry. It may be accessed upon request.

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REFERENCES

1. Passweg JR, Baldomero H, Chabannon C, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. *Bone Marrow Transplant*. 2021;56(7):1651-1664.
2. Passweg JR, Labopin M, Cornelissen J, et al. Acute Leukemia Working Party of the European Blood and Marrow Transplant Group (EBMT). Conditioning intensity in middle-aged patients with AML in first CR: no advantage for myeloablative regimens irrespective of the risk group-an observational analysis by the Acute Leukemia Working Party of the EBMT. *Bone Marrow Transplant*. 2015;50(8):1063-1068.
3. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *Clin Oncol*. 2020;38(12):1273-1283.
4. Socié G, Clift RA, Blaise D, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood*. 2001;98(13):3569-3574.
5. Nagler A, Rocha V, Labopin M, et al. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen—a report from the acute leukemia working party of the European group for blood and marrow transplantation. *J Clin Oncol*. 2013;31(28):3549-3556.

6. Giebel S, Labopin M, Sobczyk-Kruszelnicka M, et al. Total body irradiation + fludarabine compared to busulfan + fludarabine as "reduced-toxicity conditioning" for patients with acute myeloid leukemia treated with allogeneic hematopoietic cell transplantation in first complete remission: a study by the Acute Leukemia Working Party of the EBMT. *Bone Marrow Transplant*. 2021;56(2):481-491.
7. Giebel S, Miszczyk L, Slosarek K, et al. Extreme heterogeneity of myeloablative total body irradiation techniques in clinical practice: a survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Cancer*. 2014;120(17):2760-2765.
8. Potdar RR, Gupta S, Giebel S, et al. Current status and perspectives of irradiation-based conditioning regimens for patients with acute leukemia undergoing hematopoietic stem cell transplantation. *Clin Hematol Int*. 2019;1(1):19-27.
9. Buchali A, Feyer P, Groll J, Massenkeil G, Arnold R, Budach V. Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation. *Radiother Oncol*. 2000;54(2):157-162.
10. Leiper AD. Late effects of total body irradiation. *Arch Dis Child*. 1995;72(5):382-385.
11. Bornhäuser M, Kienast J, Trenschel R, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic hematopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. *Lancet Oncol*. 2012;13(10):1035-1044.
12. Kanate AS, Nagler A, Savani B. Summary of scientific and statistical methods, study endpoints and definitions for observational and registry-based studies in hematopoietic cell transplantation. *Clin Hematol Int*. 2020;2(1):2-4.
13. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706.
14. Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496-509.
15. Buckner CD, Clift RA, Fefer A, Neiman PE, Storb R, Thomas ED. Treatment of blastic transformation of chronic granulocytic leukemia by high dose cyclophosphamide, total body irradiation and infusion of cryopreserved autologous marrow. *Exp Hematol*. 1974;2(3):138-146.
16. Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. *N Engl J Med*. 1983;309(22):1347-1353.
17. Brown RA, Herzig RH, Wolff SN, et al. High-dose etoposide and cyclophosphamide without bone marrow transplantation for resistant hematologic malignancy. *Blood*. 1990;76(3):473-479.
18. Fraiser LH, Kanekal S, Kehrer JP. Cyclophosphamide toxicity. *Char Avoid Prob Drugs*. 1991;42(5):781-795.
19. Zeiser R, Blazar BR. Acute graft-versus-host disease—biologic process, prevention, and therapy. *N Engl J Med*. 2017;377(22):2167-2179.
20. Gandhi V, Estey E, Keating MJ, Plunkett W. Fludarabine potentiates metabolism of cytarabine in patients with acute myelogenous leukemia during therapy. *J Clin Oncol*. 1993;11(1):116-124.
21. Avramis VI, Wiersma S, Krailo MD, et al. Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a phase I/II study in pediatric patients with relapsed leukemias. The Children's Cancer Group. *Clin Cancer Res*. 1998;4(1):45-52.
22. Dinndorf PA, Avramis VI, Wiersma S, et al. Phase I/II study of idarubicin given with continuous infusion fludarabine followed by continuous infusion cytarabine in children with acute leukemia: a report from the Children's Cancer Group. *J Clin Oncol*. 1997;15(8):2780-2785.
23. Beitinjaneh A, McKinney AM, Cao Q, Weisdorf DJ. Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2011;17(3):300-308.
24. Liu DH, Xu LP, Zhang XH, et al. Substitution of cyclophosphamide in the modified Bucy regimen with fludarabine is associated with increased incidence of severe pneumonia: a prospective, randomized study. *Int J Hematol*. 2013;98(6):708-715.
25. Liu H, Zhai X, Song Z, et al. Busulfan plus fludarabine as a myeloablative conditioning regimen compared with busulfan plus cyclophosphamide for acute myeloid leukemia in first complete remission undergoing allogeneic hematopoietic stem cell transplantation: a prospective and multicenter study. *J Hematol Oncol*. 2013;6:15.
26. Lee JH, Joo YD, Kim H, et al. Randomized trial of myeloablative conditioning regimens: busulfan plus cyclophosphamide versus busulfan plus fludarabine. *J Clin Oncol*. 2013;31(6):701-709.
27. Rambaldi A, Grassi A, Masciulli A, et al. Busulfan plus cyclophosphamide versus busulfan plus fludarabine as a preparative regimen for allogeneic haemopoietic stem-cell transplantation in patients with acute myeloid leukaemia: an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2015;16(15):1525-1536.
28. Ben-Barouch S, Cohen O, Vidal L, Avivi I, Ram R. Busulfan fludarabine vs busulfan cyclophosphamide as a preparative regimen before allogeneic hematopoietic cell transplantation: systematic review and meta-analysis. *Bone Marrow Transplant*. 2016;51(2):232-240.
29. Spyridonidis A, Labopin M, Savani BN, et al. Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients. *Bone Marrow Transplant*. 2020;55(6):1114-1125.
30. Mehta J, Powles R, Singhal S, et al. T cell-depleted allogeneic bone marrow transplantation from a partially HLA-mismatched unrelated donor for progressive chronic lymphocytic leukemia and fludarabine-induced bone marrow failure. *Bone Marrow Transplant*. 1996;17(5):881-883.

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