

## ARTICLE



# Total body irradiation plus fludarabine versus busulfan plus fludarabine as a myeloablative conditioning for adults with acute myeloid leukemia treated with allogeneic hematopoietic cell transplantation. A study on behalf of the Acute Leukemia Working Party of the EBMT

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Cyclophosphamide is frequently substituted with fludarabine (Flu) in conditioning regimens before allogeneic hematopoietic cell transplantation (allo-HCT). We aimed to compare retrospectively, total body irradiation (12 Gy) plus Flu (FluTBI12) versus busulfan (Bu) plus Flu (FB4) as a myeloablative conditioning before allo-HCT in patients with acute myeloid leukemia (AML). Out of 3203 patients who met the inclusion criteria, 109 patients treated with FluTBI12 and 213 treated with FB4 were included in a final matched-pair analysis. In both groups, median patient age was 41 years, first or second complete remission (CR1/CR2) proportion was 78%/22%, allo-HCT from an unrelated donor was performed in 78% of patients. The probabilities of leukemia-free survival and overall survival at 2 years in FluTBI12 and FB4 groups were 65% vs. 60% ( $p = 0.64$ ) and 70% vs. 72% ( $p = 0.87$ ), respectively. The cumulative incidence of relapse was 19% vs. 29% ( $p = 0.11$ ), while non-relapse mortality was 16% vs. 11%, respectively ( $p = 0.13$ ). There were no statistical differences in both acute and chronic graft-versus-host disease (GVHD) incidence. The probability of GVHD-free, relapse-free survival (GRFS) was 49% for both groups. FluTBI12 and FB4 are comparable myeloablative regimens before allo-HCT in AML patients transplanted in CR1 and CR2.

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## INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a proven curative method for patients with acute myeloid leukemia (AML) at high risk of relapse. Standard myeloablative conditioning (MAC) includes the use of either busulfan (Bu) or total body irradiation (TBI) in combination with cyclophosphamide (Cy). The choice of conditioning regimen constitutes a challenge due to the lack of evidence of the superiority of one over another combination [1, 2]. Nevertheless, in the last decade, Cy has been substituted with fludarabine (Flu) both in chemotherapy and TBI-based regimens in order to minimize

regimen-related toxicity. In the meta-analysis comprising 15 trials on Bu-based conditioning, a similar efficacy with lower toxicity of Flu versus Cy was shown [3]. The data on the combination of TBI with Flu before allo-HCT for AML patients are very limited. In one study by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT), TBI at a dose of 8 Gy in combination with Flu was associated with improved survival in patients under the age of 50 years and increased non-relapse mortality (NRM) in older patients when compared to Bu/Flu [4]. However, the regimens used in that study are considered as reduced-toxicity conditioning and

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studies comparing Flu with TBI or Bu at myeloablative doses are lacking. The combination of Flu with TBI at a dose of 12 Gy (FluTBI12) before haploidentical transplantations resulted in low rates of NRM (13% at 4 years), acceptable cumulative incidence of relapse (27%) and clinically significant graft versus host disease (GVHD) in 17% (for acute GVHD grade III–IV) and in 23% (for moderate to severe chronic GVHD) of patients with various hematological malignancies, mainly with acute leukemias [5]. In turn, the MAC consisting of Flu and Bu (FB4) was shown to be superior when compared to Cy with Bu in relation to transplant-related mortality in older AML patients [6]. Given the encouraging results of FluTBI12 and FB4 as MAC before allo-HCT we aimed to compare these two regimens in patients with AML in their first or second remission (CR1 or CR2) before allo-HCT from a human leukocyte antigen-matched sibling or unrelated donor (HLA-MSD or URD).

## SUBJECTS AND METHODS

### Study design and data collection

This was a retrospective, multicenter analysis. Data were provided by the registry of the ALWP of the 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 print-out 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.

### Criteria for selection

The inclusion criteria were as follows: 1) patients aged  $\geq 18$  years with AML who underwent their first allo-HCT in CR1 or CR2 between 2009 and 2020, 2) transplantation from either an HLA-MSD or URD, 3) the use of peripheral blood or bone marrow as a source of stem cells; 3) the use of one of the following conditioning regimens: TBI at a dose of 12 Gy plus Flu (FluTBI12) or intravenous busulfan at a dose of 12.8 mg/kg (4 days) plus Flu (FB4). The use of cord blood as a source of stem cells as well as transplantations with ex vivo T-cell depletion were exclusion criteria.

### Statistical analysis

Leukemia-free survival (LFS) was the primary study endpoint. Secondary endpoints were: 1) overall survival (OS), 2) relapse incidence (RI); 3) NRM; 4) incidence of grade II–IV acute graft-versus-host disease (GVHD); 5) incidence of chronic GVHD; 6) survival free from grade III–IV acute GVHD, chronic GVHD, and relapse (GRFS) [7].

Patients' characteristics were compared using the Mann-Whitney or Kruskal-Wallis test for continuous variables, and the chi-squared or Fisher's exact test for categorical variables.

For each patient receiving FluTBI12, two separate matched controls receiving FB4 were identified using exact and propensity-score matched criteria. Exact matching was used for donor type (HLA-MSD/URD), stem cell source (peripheral blood/bone marrow), cytogenetic risk group, as well as disease status at allo-HCT (CR1/CR2), and nearest neighbor for recipient age, donor and recipient sex, Karnofsky performance score, and the use of in vivo T-cell depletion.

The probabilities of OS, LFS, and GRFS were calculated using the Kaplan-Meier estimate. The probabilities of relapse incidence (RI), NRM, acute and chronic GVHD were estimated using cumulative incidence curves [8]. Comparisons were performed using Cox model [9] and cluster-robust standard errors were used to account for dependence between observations within matched pairs. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). All tests were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA) and R 4.0.2 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

## RESULTS

Out of 3203 patients meeting the inclusion criteria, 121 were treated with FluTBI12 and 3082 received FB4. The final matched-pair analysis included 109 and 213 patients, respectively. The patients were well matched with standardized mean difference estimates of less than 5% for all matched parameters. The basic characteristics of patients, donors and allo-HCT procedure are well balanced between study groups, except for patients' serological status for cytomegalovirus (CMV) being positive in 57.9% of patients in FluTBI12 group and in 77.9% of patients in FB4 group ( $p < 0.001$ ). About 78% of patients in both groups were transplanted in CR1 and from a URD. The distribution of AML risk groups was the same in FluTBI12 and FB4 groups. Detailed patient and donor characteristics are shown in Table 1.

All patients in the FB4 group engrafted while graft failure was diagnosed in 1.8% of patients in the FluTBI12 group ( $p = 0.12$ ). The incidence of acute GVHD grade II–IV as well as grade III–IV did not differ significantly between study groups. Similarly, there were no differences between FluTBI12 and FB4 groups in relation to chronic GVHD, including the extensive type (Table 2). The incidence of both acute and chronic GVHD as well as GRFS are shown in Fig. 1.

Two-year RI was 19.2% of patients in FluTBI12 and 29.4% of patients in FB4 (HR = 1.55 (95% CI: 0.9–2.66);  $p = 0.11$ ). The NRM was 15.6% in the FluTBI12 group and 10.9% in the FB4 group, (HR = 0.62 (95% CI: 0.34–1.15);  $p = 0.13$ ). The probability of LFS was 65.2% in FluTBI12 and 59.8% in FB4 (HR = 1.1 (95% CI: 0.73–1.67);  $p = 0.64$ ), while OS was 69.7% and 72.1%, respectively (HR = 0.96 (95% CI: 0.61–1.52);  $p = 0.87$ ) (Table 2, Fig. 2).

The most frequent causes of death included original disease (48.3% in FluTBI12 and 67.2% in FB4,  $p = 0.09$ ), infections (20.7% and 16.4%,  $p = 0.62$ ) and GVHD (6.9% and 14.8%,  $p = 0.29$ ). Only one patient in the FluTBI12 group and no patient in the FB4 group died as a consequence of cardiac toxicity (3.4% and 0%, respectively,  $p = 0.14$ ).

## DISCUSSION

In this study, we retrospectively compared TBI-based versus Bu-based MAC in combination with Flu in AML patients transplanted in CR1 or CR2. The results of this study provide no evidence of the superiority of one over another conditioning regimen before allo-HCT with respect to RI, OS, LFS, NRM, and GVHD incidence.

The comparison of TBI-based versus chemotherapy-based conditioning in AML patients yields ambiguous results. In the previous study comparing two RICs before allo-HCT in AML patients we showed improved LFS and OS as well as a tendency towards a reduced risk of relapse in FluTBI patients under the age of 50 years when compared to patients treated with Flu plus Bu. However, the FluTBI regimen was associated with an increased incidence of NRM in older patients [4]. As a consequence of those results, in this study we hypothesized that TBI at a myeloablative dose of 12 Gy would be at least as effective as Bu-based MAC.

TBI-based conditioning provides a homogenous dose distribution to the whole body, independently from the blood supply to the leukemic cells and it is not influenced by variability in drug absorption, metabolism, biodistribution or clearance kinetics as in the case of chemotherapy-based regimens. However, the practice of irradiation modes, including dose fractionation and dose rate as well as beam energy, dosimetry and organ shielding differ significantly around the world, making this conditioning very heterogeneous [10, 11]. Initially, TBI was administered as a single fraction [12]. However, its toxicity, especially fatal radiation pneumonitis led this approach to being abandoned and fractionated doses of TBI have become the standard of care. Nevertheless, a consistent pattern of dose fractionation of TBI in AML patients has not been established so far. TBI at a dose of

**Table 1.** Patient-, donor- and transplant-related characteristics.

|                                          | <b>FluTBI12 (n = 109)</b> | <b>FB4 (n = 213)</b> | <b>p value</b> |
|------------------------------------------|---------------------------|----------------------|----------------|
| Median patient age, years (range)        | 41 (18.2–68.8)            | 41.4 (18.7–67.4)     | 0.99           |
| Patient sex, n (%)                       |                           |                      |                |
| • Male                                   | 67 (61.5%)                | 133 (62.4%)          | 0.86           |
| • Female                                 | 42 (38.5%)                | 80 (37.6%)           |                |
| Cytogenetic risk group, n (%)            |                           |                      |                |
| • standard                               | 9 (8.3%)                  | 17 (8%)              | 1              |
| • intermediate                           | 45 (41.3%)                | 90 (42.3%)           |                |
| • high                                   | 13 (11.9%)                | 25 (11.7%)           |                |
| • unknown                                | 42 (38.5%)                | 81 (38%)             |                |
| Disease status at transplantation, n (%) |                           |                      |                |
| • CR1                                    | 85 (78%)                  | 168 (78.9%)          | 0.85           |
| • CR2                                    | 24 (22%)                  | 45 (21.1%)           |                |
| Median year of transplantation (range)   | 2017 (2009–2020)          | 2016 (2009–2020)     | 0.063          |
| Donor type, n (%)                        |                           |                      |                |
| • HLA-identical sibling                  | 24 (32.4%)                | 48 (27.7%)           | 0.38           |
| • 10/10 HLA matched unrelated            | 40 (54.1%)                | 89 (51.4%)           |                |
| • 9/10 HLA mismatched unrelated          | 10 (13.5%)                | 36 (20.8%)           |                |
| • Unrelated, HLA compatibility unknown   | 35                        | 40                   |                |
| Donor sex, n (%)                         |                           |                      |                |
| • Male                                   | 68 (62.4%)                | 132 (62%)            | 0.94           |
| • Female                                 | 41 (37.6%)                | 81 (38%)             |                |
| Donor/patient sex                        |                           |                      |                |
| • Female/male                            | 20 (18.3%)                | 47 (22.1%)           | 0.44           |
| • Other combinations                     | 89 (81.7%)                | 166 (77.9%)          |                |
| Karnofsky performance status score       |                           |                      |                |
| • <90%                                   | 28 (25.7%)                | 47 (22.1%)           | 0.47           |
| • ≥90%                                   | 81 (74.3%)                | 166 (77.9%)          |                |
| Source of stem cells                     |                           |                      |                |
| • Bone marrow                            | 3 (2.8%)                  | 6 (2.8%)             | 1              |
| • Peripheral blood                       | 106 (97.2%)               | 207 (97.2%)          |                |
| Patient CMV serological status           |                           |                      |                |
| • Positive                               | 62 (57.9%)                | 162 (77.9%)          | 0.0004         |
| • Negative                               | 45 (42.1%)                | 46 (22.1%)           |                |
| • Missing                                | 2                         | 5                    |                |
| Donor CMV serological status             |                           |                      |                |
| • Positive                               | 50 (46.3%)                | 115 (54%)            | 0.19           |
| • Negative                               | 58 (53.7%)                | 98 (46%)             |                |
| • Missing                                | 1                         | 0                    |                |
| In vivo T-cell depletion                 |                           |                      |                |
| • Yes                                    | 69 (63.3%)                | 133 (62.4%)          | 0.88           |
| • No                                     | 40 (36.7%)                | 80 (37.6%)           |                |
| The use of PTCy                          |                           |                      |                |
| • Yes                                    | 8 (7.3%)                  | 28 (13.1%)           | 0.12           |
| • No                                     | 101 (92.7%)               | 185 (86.9%)          |                |

TBI total body irradiation, FB4 fludarabine plus busulfan, HLA human leukocyte antigen, CR, complete remission, CMV cytomegalovirus, PTCy post transplant cyclophosphamide.

12 Gy given once or twice a day over 3 or 4 days resulted in similar outcomes in patients with acute leukemias [13]. In the more recent analysis from the Japanese registry, Ueda et al. showed better OS and lower RI of 4-fractionated when compared to 6-fractionated 12 Gy TBI before allo-HCT in AML patients

transplanted in non-CR, but not for those in CR. Simultaneously, the authors did not report any differences between studied groups in relation to the incidence of acute GVHD, extensive chronic GVHD, interstitial pneumonia, or sinusoidal obstruction syndrome of the liver after allo-HCT [14].

TBI as MAC has been mainly combined with Cy at a dose of 120 mg/kg. In a prospective French study, Blaise et al. showed the superiority of CyTBI over Cy with oral Bu in relation to disease-free survival (DFS), OS, RI, and NRM in AML patients transplanted in CR1 [15]. In the retrospective study by the ALWP of the EBMT, CyTBI was associated with a lower risk of relapse without significant difference in DFS and OS when compared to intravenous Bu with Cy in AML patients transplanted in CR1 or CR2 [1].

In recent years, Cy has been substituted with Flu in order to minimize conditioning-related toxicity. The combination of Flu with TBI was initially created as a reduced intensity conditioning (RIC) with TBI at a dose of 8 Gy [16]. A German study group

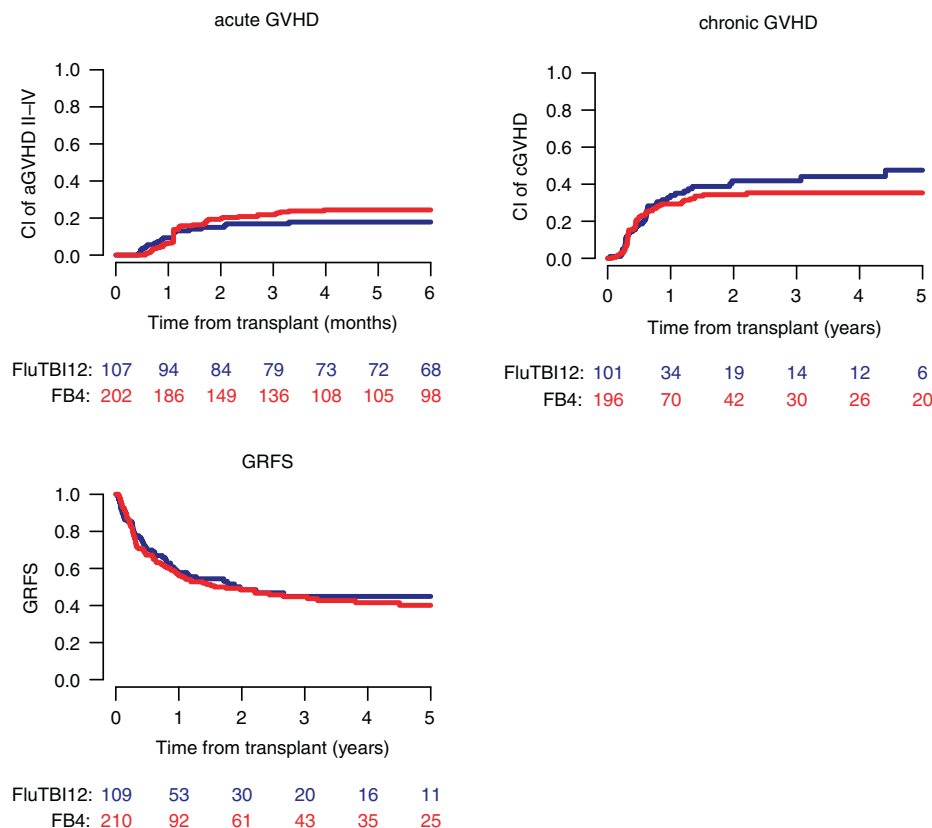
showed comparable results of CyTBI at a dose of 12 Gy and FluTBI at a dose of 8 Gy in relation to RI, NRM, DFS and OS in AML patients transplanted in CR1, however, the FluTBI regimen was associated with reduced incidence of severe oral mucositis as well as reduced NRM in the patients above the age of 40 years [17].

The data on the use of Flu in combination with TBI at a myeloablative dose of 12 Gy in AML patients are very limited. Solomon et al. presented the outcomes of FluTBI12 used as MAC before haploidentical (haplo-HCT) in patients with hematological malignancies, including 42 patients with AML. In the subset of 45 patients with AML and myelodysplastic syndrome (MDS) the authors showed an estimated 4-year OS, DFS and cumulative RI of 65%, 61%, and 25%, respectively. These results did not differ

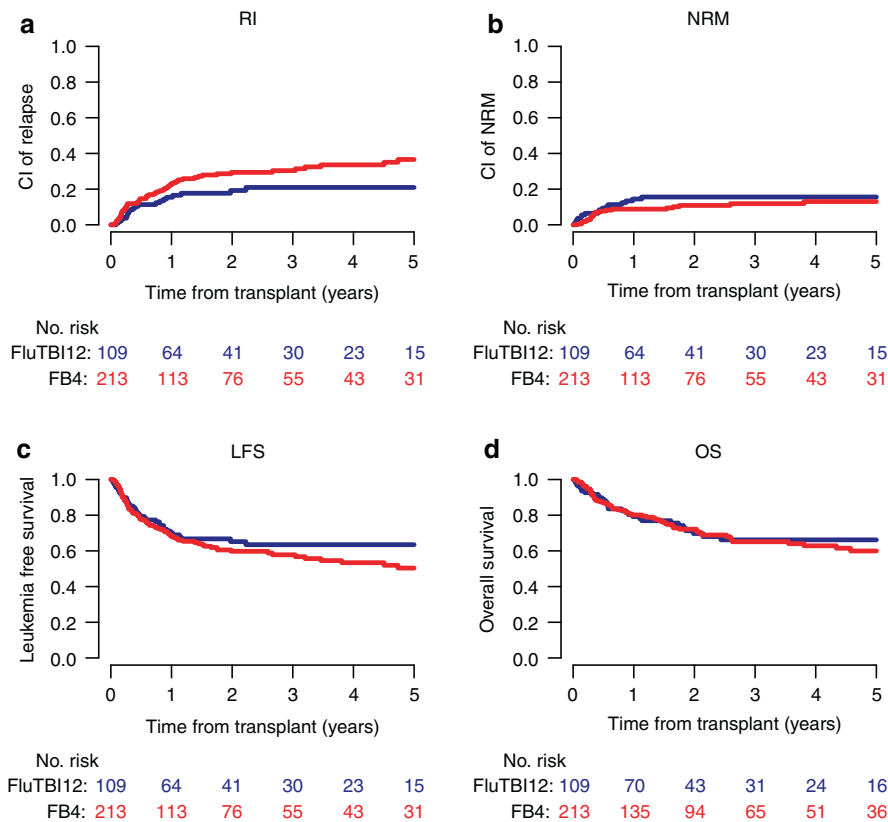
**Table 2.** Results of allo-HCT according to the type of conditioning.

|                        | FluTBI12 (n = 109) | FB4 (n = 213)     | HR (95%CI)       | p value |
|------------------------|--------------------|-------------------|------------------|---------|
| Relapse incidence      | 19.2% [12–27.7]    | 29.4% [22.8–36.2] | 1.55 (0.9–2.66)  | 0.11    |
| Non-relapse mortality  | 15.6% [9.3–23.3]   | 10.9% [6.8–15.9]  | 0.62 (0.34–1.15) | 0.13    |
| Leukemia-free survival | 65.2% [54.8–73.7]  | 59.8% [52.1–66.6] | 1.1 (0.73–1.67)  | 0.64    |
| Overall survival       | 69.7% [58.9–78.2]  | 72.1% [64.8–78.2] | 0.96 (0.61–1.52) | 0.87    |
| GRFS                   | 48.5% [38–58.3]    | 48.5% [40.8–55.7] | 0.95 (0.67–1.36) | 0.79    |
| Acute GVHD grade 2–4   | 17.8% [11.2–25.7]  | 24.4% [18.7–30.5] | 1.49 (0.86–2.6)  | 0.16    |
| Acute GVHD grade 3–4   | 7.5% [3.5–13.6]    | 6% [3.3–9.9]      | 0.83 (0.34–2.07) | 0.7     |
| Chronic GVHD           | 41.8% [31.3–52]    | 34.3% [27.1–41.6] | 0.77 (0.52–1.15) | 0.2     |
| Extensive chronic GVHD | 16.4% [9.3–25.2]   | 15.9% [10.7–21.9] | 0.96 (0.52–1.78) | 0.9     |

TBI total body irradiation, FB4 fludarabine plus busulfan, HR hazard ratio, CI confidence interval, GVHD graft-versus-host disease, GRFS GVHD-free, relapse-free survival, CR complete remission, CMV cytomegalovirus.



**Fig. 1** Graft versus host disease (GVHD) in FluTBI12 and FB4 group. The incidence of acute GVHD; the incidence of chronic GVHD; GVHD and relapse-free survival (GRFS).



**Fig. 2** Results of allo-HCT in FluTBI12 and FB4 group. NRM non-relapse mortality, RI relapse incidence, LFS leukemia-free survival, OS overall survival.

significantly when compared to the subset of ALL patients and appear very encouraging [5].

The non-TBI-containing conditioning before allo-HCT in AML patients is based on high-dose chemotherapy, mostly including alkylating agents. Bu plus Cy has become a standard of chemotherapy-based MAC, however, both drugs can result in the decrease in the levels of glutathione in hepatocytes leading to an exacerbated risk of serious hepatic injuries [18]. Therefore, Cy has recently been substituted with Flu that interacts synergistically with Bu in relation to antileukemic activity, being simultaneously detoxified in a different way minimizing hepatic injury. In a prospective, randomized study, Liu et al. showed significantly lower regimen-related toxicity and death while comparable antileukemic activity in AML patients treated with FluBu compared to CyBu [19]. In another randomized study, FluBu was shown to lower transplant-related mortality without impairing the antileukemic activity of the regimen [6]. On the basis of these results, Rambaldi et al. suggested FluBu conditioning to be a new standard of care for AML patients undergoing allogeneic transplantation [6].

In this study, we showed for the first time the similar efficacy and safety of TBI-based and Bu-based MAC in combination with Flu before allo-HCT in AML patients transplanted in CR1 or CR2. This finding is in line with another study by the ALWP of the EBMT, in which TBI-based MAC was compared to chemotherapy-based regimens in AML patients before haplo-HCT showing no evidence of advantage of one over another type of conditioning [20].

The current study has some limitations mainly resulting from its retrospective nature. The limited number of subjects enrolled to this study lowers the strength of evidence. Although all patients in the FluTBI12 group were given the myeloablative dose of 12 Gy, there is no uniform standard of TBI procedure among centers reporting patients to this study, which makes the FluTBI12 group

not fully homogenous. Another limitation is the lack of detailed molecular characteristics of AML and MRD status before transplantation, which are strong predictors of transplant outcomes. The lack of data on therapy-related toxicity made the comparison of the studied regimens incomplete. Therefore, randomized studies with strictly selected patients with data on the particular molecular status of AML, as well as with a consistent scheme of TBI are needed.

In conclusion, we showed that TBI-based and Bu-based myeloablative regimens in combination with Flu before allo-HCT are comparable in relation to efficacy and safety in AML patients transplanted in CR1 and CR2. Therefore, the choice between these two MAC regimens should be based on patients' medical history, availability of TBI, and the experience of the center in using a particular MAC regimen.

#### DATA AVAILABILITY

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

#### REFERENCES

1. Nagler A, Rocha V, Labopin M, Unal A, Ben Othman T, Campos A, 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;31:3549–56.
2. Nagler A, Savani BN, Labopin M, Polge E, Passweg J, Finke J, et al. Outcomes after use of two standard ablative regimens in patients with refractory acute myeloid leukaemia: a retrospective, multicentre, registry analysis. *Lancet Haematol*. 2015;2:e384–e392.
3. 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 Transpl.* 2016;51:232–40.
4. Giebel S, Labopin M, Sobczyk-Kruszelnicka M, Stelljes M, Byrne JL, Fegueux N, 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 Transpl.* 2021;56:481–91.
  5. Solomon SR, Solh M, Zhang X, Morris LE, Holland HK, Bashey A. Fludarabine and total-body irradiation conditioning before ablative haploidentical transplantation: long-term safety and efficacy. *Biol Blood Marrow Transpl.* 2019;25:2211–6.
  6. Rambaldi A, Grassi A, Masciulli A, Boschini C, Micò MC, Busca 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;16:1525–36.
  7. 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;2:2–4.
  8. 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;18:695–706.
  9. Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496–509.
  10. Giebel S, Miszczyk L, Slosarek K, Moukhtari L, Ciceri F, Esteve J, 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;120:2760–5.
  11. Fog LS, Wirth A, MacManus M, Downes S, Grace M, Moggré A, et al. Total body irradiation in Australia and New Zealand: results of a practice survey. *Phys Eng Sci Med.* 2020;43:825–35.
  12. Atkinson JB, Mahoney FJ, Schwartz IR, Hesck JA. Therapy of acute leukemia by whole-body irradiation and bone marrow transplantation from an identical normal twin. *Blood.* 1959;14:228–34.
  13. Belkacemi Y, Labopin M, Giebel S, Loganadane G, Miszczyk L, Michallet M, et al. Single-dose daily fractionation is not inferior to twice-a-day fractionated total-body irradiation before allogeneic stem cell transplantation for acute leukemia: a useful practice simplification resulting from the SARASIN study. *Int J Radiat Oncol Biol Phys.* 2018;102:515–26.
  14. Ueda N, Konuma T, Aoki J, Takahashi S, Ozawa Y, Mori T, et al. Prognostic impact of the fractionation of total body irradiation for patients with acute myeloid leukemia undergoing myeloablative allogeneic hematopoietic cell transplantation. *Transpl Cell Ther.* 2021;27:185.e1–185.e6.
  15. Blaise D, Maraninchi D, Archimbaud E, Reiffers J, Devergie A, Jouet JP, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytosar versus Cytosar-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood.* 1992;79:2578–82.
  16. Stelljes M, Bornhauser M, Kroger M, Beyer J, Sauerland MC, Heinecke A, et al. Conditioning with 8-Gy total body irradiation and fludarabine for allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia. *Blood.* 2005;106:3314–21.
  17. Bornhäuser M, Kienast J, Trensche R, Burchert A, Hegenbart U, Stadler M, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic haemopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. *Lancet Oncol.* 2012;13:1035–44.
  18. Ciurea SO, Andersson BS. Busulfan in hematopoietic stem cell transplantation. *Biol Blood Marrow Transpl.* 2009;15:523–36.
  19. Liu H, Zhai X, Song Z, Sun J, Xiao Y, Nie D, 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.
  20. Dholaria B, Labopin M, Angelucci E, Ciceri F, Diez-Martin JL, Bruno B, et al. Impact of total body irradiation- vs chemotherapy-based myeloablative conditioning on outcomes of haploidentical hematopoietic cell transplantation for acute myelogenous leukemia. *Am J Hematol.* 2020;95:1200–8.

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## AUTHOR CONTRIBUTIONS

RS and SG interpreted results and wrote the manuscript. ML performed the statistical analysis. RS, SG, TS, NK, MA, BS, AS, RMH, VP, AB, IYA, AR, HO, JS, AN, and MM provided patient data and reviewed the final version of the manuscript. SG, BS, AS, AN, and MM designed the study and interpreted the results.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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