Enhancing myeloablative fludarabine-busulfan conditioning with total marrow irradiation in high-risk myeloid disease

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Maahs *et al*. present the results of the first prospective phase II trial combining high-dose total marrow irradiation (TMI, 9 Gy) with myeloablative intravenous fludarabine and busulfan (FluBu4) in adults with high-risk myeloid neoplasms undergoing allogeneic hematopoietic cell transplantation (allo-HCT).[1] The study provides initial evidence that this intensified approach can significantly decrease the risk of relapse in patients with aggressive disease without an increase in toxicity, which represents possibly the most important goal in the conditioning-regimen research area. Allo-HCT remains a cornerstone in the treatment of high-risk myeloid neoplasms, such as acute myeloid leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms, especially in patients with adverse cytogenetics or refractory/relapsed disease. Although relapse rates decrease with myeloablative conditioning (MAC) regimens, transplant-related mortality continues to limit the success of allo-HCT in these cases.[2] Total body irradiation (TBI)-based MAC regimens are an example of this concept. Despite being well known for their anti-relapse activity, their toxicity limits their use worldwide.[3] Some research groups have addressed this issue by working on less toxic ways to deliver irradiation, such as TMI, in which critical organs receive only 20-70% of the prescribed dose compared to 100% with TBI, in order to improve efficacy and reduce toxicity.[4]

The study by Maahs *et al*. demonstrated that the combination of FluBu4 with TMI 9 Gy in 30 patients with high-risk myeloid neoplasms (acute myeloid leukemia, myelodysplastic syndromes, and chronic myeloid leukemia in blast phase) undergoing allo-HCT achieved a disease-free survival of 65% and an overall survival of 72% at 12 months, with a relapse and transplant-related mortality rate of 20% over a median follow-up of more than 4 years. Notably, this regimen was well tolerated. Grade 3-4 extramedullary toxicities included mucositis in 57% of patients, nausea/vomiting in 10%, and diarrhea in 7%, which compare favorably with the toxicities of MAC plus TBI regimens.[1] Acute grade 3-4 graft-*versus*-host disease (GvHD) was observed in 13% of patients, and moderate/severe chronic GvHD in 37%. These results on its efficacy and toxicity profile could be competitive with those of other MAC regimens, especially considering the selected high-risk population.

MAC regimens remain essential for achieving cure in high-risk myeloid neoplasms; however, their intensification is limited by significant organ toxicity. Given this, it is relevant to compare the FluBu4 plus TMI regimen with other contemporary regimens, as shown in Table 1. In the case of TBI-based regimens, a prospective, randomized clinical trial showed no significant differences in 3-year overall survival (37% *vs*. 50%; hazard ratio=0.88; *P*=0.74) between FluBu4 and FluBu4 plus low-dose TBI (400 cGy) regimens.[5] However, the group of patients who received TBI showed a higher incidence of acute GvHD grades 2-4 (64% *vs*. 29%; *P*=0.02), likely due to more tissue damage from radiation. In the TBI-free MAC regimen setting, FluBu4 was shown to be superior to busulfan plus cyclophosphamide (CyBu4) in a randomized study.[6] In that study, FluBu4 maintained the same anti-leukemia activity while improving transplant-related mortality at 1 year (8% *vs*. 17%; *P*=0.026). Another fundamental randomized study in myeloid diseases (reduced-intensity setting) showed that treosulfan plus fludarabine (FluTreo10) was not inferior to reduced-intensity FluBu2 in acute myeloid leukemia/myelodysplastic syndrome patients aged 50 to 70 years. Patients treated with FluTreo10 had a better 24-month event-free survival (64% *vs*. 50%; *P*<0.01) and overall survival (71% *vs*. 56%; *P*<0.01), a lower transplant-related mortality (12% *vs*. 28%), without differences in the rate of relapse/progression.[7] Because of these randomized studies, FluBu4 is considered a standard

Table 1. Comparison of main conditioning regimens in allogeneic hematopoietic cell transplantation for myeloid malignancies.

Regimen and study	Relapse rate at 1-3 years	NRM/TRM at 1-3 years	EFS/DFS at 1-3 years	Key toxicities
FluBu4 standard (Rambaldi *et al.* 2015)	At 2 years: 31%	2-year NRM: 9%	2-year DFS: 59%	Grade ≥3 GI events: 21%; grade ≥3 infections 10%
FluTreo (Beleen *et al.* 2020)	At 2 years: 25%	2-year TRM: 12%	2-year EFS: 64%	Grade 3 GI toxicity: 11%
TBF (Saraceni *et al.* 2023)	At 2 years: 16%	2-year NRM: 19%	2-year DFS: 65%	Grade 2-4 acute GvHD: 29%
FluBu4 + TMI 9 Gy (Maahs *et al.* 2025)	At 1 year: 20%	1-year TRM: 20%	1-year DFS: 65%	Grade 3-4 mucositis: 57%; nausea/vomiting: 10%; diarrhea: 7%

NRM: non-relapse mortality; TRM: transplant-related mortality; EFS: event-free survival; DFS: disease-free survival; FluBu4: intravenous fludarabine and busulfan (4 days); GI: gastrointestinal; GvHD: graft-*versus*-host disease; FluTreo: fludarabine-treosulfan; TBF: thiotepa-busulfan-fludarabine; TMI: total marrow irradiation; Gy: Gray.

MAC regimen and FluTreo10 a standard reduced-intensity conditioning for myeloid diseases. In the reduced-toxicity setting, the aim of thiotepa, busulfan, and fludarabine (TBF), widely used in haploidentical or alternative-donor transplants with post-transplant cyclophosphamide GvHD prophylaxis, is to enhance the antitumor effect by incorporating thiotepa into the regimen. In a retrospective study by the European Society for Blood and Marrow Transplantation (EBMT), no significant differences were found between TBF and treosulfan-based conditioning regarding 24-month non-relapse mortality (19% *vs*. 14%; *P*=0.31), relapse (16% *vs*. 18%; *P*=0.75), and overall survival (73% *vs*. 76%, *P*=0.53).[8] Although data are still limited, the clinical results of FluBu4 plus TMI suggest that it has greater efficacy than other commonly used conditioning regimens, especially in the high-risk population. Considering the adverse profile of the cohort, the incidence of relapse was low (20% at 12 months), as shown in Figure 1. Despite the data coming from a small series of patients without haploidentical donors, these results align with experiences accumulated in other centers regarding promising survival rates and disease control.[4] Furthermore, no patient in the FluBu4 plus TMI group had long-term grade 4 solid-organ toxicities. These results indicate that TMI, unlike TBI, does not add significant additional toxicity beyond what already exists with FluBu4.[9]

In conclusion, the combination of FluBu4 with high-dose TMI demonstrates a promising therapeutic profile, with survival rates, disease control, and low toxicity comparable to those of current regimens, positioning it as a safe alternative and justifying its investigation in multicenter trials, possibly using post-transplant cyclophosphamide GvHD prophylaxis.

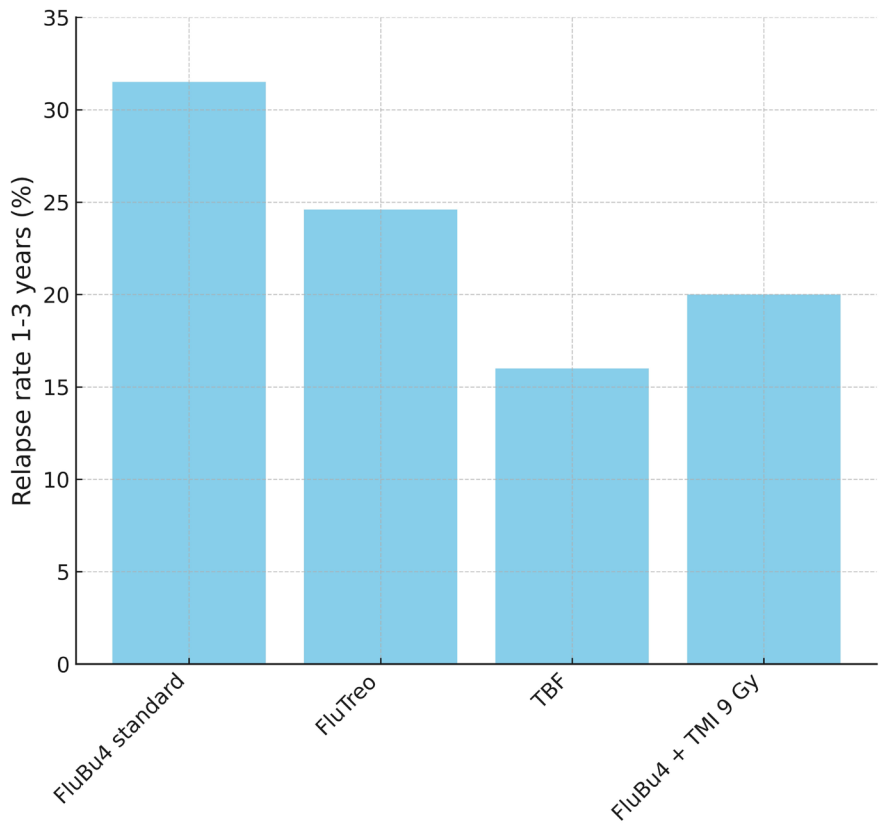

Figure 1. Comparison of relapse rates by conditioning regimen in allogeneic hematopoietic cell transplantation for myeloid malignancies. FluBu4: intravenous fludarabine and busulfan (4 days); FluTreo: fludarabine-treosulfan; TBF: thiotepa-busulfan-fludarabine; TMI: total marrow irradiation; Gy: Gray.

Disclosures

AS has received honoraria for lectures from Takeda, BMS/Celgene, MSD, Janssen, Amgen, Novartis, Gilead Kite, Sanofi, Roche and Alexion; has provided consultancy services for Takeda, BMS/Celgene, Novartis, Janssen, Gilead and Sanofi; and has received research support from Takeda and BMS/Celgene. AS is also President of GETH-TC and EBMT. AM has received honoraria for lectures from Takeda, BMS, Gilead and Sanofi; and has been a member of advisory boards for Merck and Jazz Pharma. FM has no conflicts of interest to disclose.

Contributions

FM, AM and AS wrote and reviewed the manuscript.

References

1. Maahs L, Avila AM, Koshy M, et al. Intensified conditioning with high-dose total marrow irradiation and myeloablative chemotherapy reduces relapse risk without increasing toxicity in allogeneic hematopoietic stem cell transplant for high-risk myeloid malignancies: a phase II study. Haematologica. 2026;111(1):177-183.
2. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
3. Salhotra A, Stein AS. Role of radiation based conditioning regimens in patients with high-risk AML undergoing allogenic transplantation in remission or active disease and mechanisms of post-transplant relapse. Front Oncol. 2022;12:802648.
4. Wong JYC, Liu A, Han C, et al. Total marrow irradiation (TMI): addressing an unmet need in hematopoietic cell transplantation - a single institution experience review. Front Oncol. 2022;12:1003908.
5. Suh HC, Rowley SD, Kaur S, et al. Prospective, randomized, comparative study of myeloablative fludarabine/busulfan and fludarabine/busulfan/total body irradiation conditioning in myeloid diseases. Cancers (Basel). 2025;17(7):1140.
6. 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.
7. Beelen DW, Trenschel R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. Lancet Haematol. 2020;7(1):e28-39.
8. Saraceni F, Labopin M, Raiola AM, et al. Thiotepa-busulfan-fludarabine compared to treosulfan-based conditioning for haploidentical transplant with posttransplant cyclophosphamide in patients with acute myeloid leukemia in remission: a study from the Acute Leukemia Working Party of the EBMT. Hemasphere. 2023;7(10):e952.
9. Maahs L, Patel P, Koshy M, et al. High dose total marrow irradiation (TMI) does not increase long-term toxicity of myeloablative fludarabine/busulfan (FluBu4) conditioning regimen in allogeneic hematopoietic stem cell transplantation (HSCT). Eur J Haematol. 2024;113(1):110-116.