Intensified conditioning with high-dose total marrow irradiation and myeloablative chemotherapy reduces risk of relapse without increasing toxicity in allogeneic hematopoietic stem cell transplant for high-risk myeloid malignancies: a phase II study

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Received: February 4, 2025.
Accepted: June 6, 2025.
Early view: June 19, 2025.

https://doi.org/10.3324/haematol.2025.287457

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Abstract

The intensity of the conditioning regimen in hematopoietic stem cell transplantation (HSCT) correlates with the risk of relapse, however its potential benefit may be outweighed by the associated risk of toxicity. The addition of total marrow irradiation (TMI) to myeloablative conditioning provides an opportunity to increase intensity with minimal additional toxicity. In this phase II clinical trial, 30 patients with high-risk myeloid malignancies underwent allogeneic HSCT using myeloablative TMI at 9 Gy in combination with standard myeloablative fludarabine/intravenous busulfan (FluBu4) chemotherapy. The study included patients with matched related donors (N=10) receiving TMI/FluBu4 and patients with matched unrelated (N=14) or one-antigen mismatched unrelated (N=6) donors receiving TMI/FluBu4 and rabbit anti-thymocyte globulin. All patients achieved sustained engraftment. Grade 3-4 extramedullary toxicities were mucositis in 59% (N=17), nausea/vomiting in 10% (N=3) and diarrhea in 7% (N=2) of the patients. Acute graft-*versus*-host disease (GvHD) grade 3 or 4 was seen in four patients (13.3%). Moderate/severe chronic GvHD was observed in 11 patients (36.7%). With a median follow-up of 1,483 days (range, 63-2,260 days) for patients alive, the overall survival and disease-free survival at 1 year were 72.4% and 65.5%, respectively. GvHD-free relapse-free survival at 1 year was 41.4%. Of 30 patients in the study, six relapsed/progressed (20%) and five of them died of the disease (16.7%), whereas six patients (20%) died of transplant-related causes. We conclude that a myeloablative regimen with TMI at 9 Gy and FluBu4 was well tolerated and achieved encouraging results in patients with myeloid malignancies at high risk of relapse (clinicaltrials.gov identifier: NCT03121014).

Introduction

The survival of patients with high-risk myeloid malignancies is poor with chemotherapy alone.[1-5] While a myeloablative allogeneic hematopoietic stem cell transplant (HSCT) remains the best therapeutic option, the survival of these patients is still limited by high rates of relapse.[6,7] Attempts to increase myeloablative conditioning regimens prior to HSCT have resulted in increased toxicity and transplant-related mortality (TRM).[8-10]

For decades, allogeneic HSCT was consistently performed using myeloablative conditioning based on total body irradiation (TBI) at 10-14 Gy, or busulfan at 16 mg/kg (oral administration) or 12.8 mg/kg (intravenous), in combination with cyclophosphamide or more recently fludarabine.[10-13] However, the use of high-dose TBI has progressively declined, particularly in HSCT for myeloid malignancies, due to high rates of transplant-related toxicity, leading to long-term adverse effects, such as interstitial pneumonitis, cognitive deficits, cataracts and renal insufficiency.[14-16] Currently, the combination of myeloablative fludarabine and intravenous busulfan with targeted dosing for 4 days

(FluBu4) is a standard myeloablative conditioning in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).[10,12,13,17,18] Nevertheless, while it increases survival in high-risk patients, it fails to prevent relapse in 8% to 20% of cases.[10,12,13,17,18] To potentially address this issue, our institution studied the role of total marrow irradiation (TMI), a technique utilizing intensity-modulated radiation therapy with volumetric modulated arc therapy to irradiate the bone marrow while minimizing the doses delivered to healthy tissues.[19-24] We initially completed a phase I clinical trial showing that targeting marrow cancer cells with myeloablative FluBu4 chemotherapy and progressively higher doses of TMI up to 12 Gy did not increase TRM.[25]

Subsequently, we developed a prospective phase II study of allogeneic HSCT conditioned with FluBu4 and a myeloablative dose of TMI (9 Gy), with the primary objective of obtaining at least 50% disease-free survival (DFS) at 12 months in patients with high-risk myeloid disorders. The clinical results obtained in 30 patients with a median follow-up of 832 days are presented here.

Methods

Study design

Adult patients between 18-65 years of age with AML, MDS or chronic myeloid leukemia (CML) at high risk of relapse were enrolled in a phase II clinical trial between 2017 and 2024. High risk of relapse for AML was defined as relapsed or refractory disease, and poor-risk AML in first complete remission (CR1), as defined by the European LeukemiaNet recommendations.[26,27] MDS risk was defined by poor-risk cytogenetics (including 3q abnormalities, 7/7q- or complex cytogenetics), high Revised International Prognostic Scoring System score (R-IPSS intermediate-2 or higher), treatment-related disease, MDS diagnosed before 21 years of age, progression or refractoriness to hypomethylating agents, and life-threatening cytopenias.[28] CML patients were eligible if they had a prior history of accelerated or blast phase disease. Other criteria for the enrollment of patients were according to standard eligibility criteria for myeloablative HSCT (available in the *Online Supplementary Data*).

The primary endpoint of the study was DFS of at least 50% at 1 year. The expected DFS for high-risk patients conditioned with FluBu4 alone is around 30%.[17,29] We anticipated an increase to 50% with the addition of TMI. Using a Simon two-stage optimal design with an α of 0.05 and power of 0.8, recruitment continued until a total of 18 patients survived to 1 year without relapse. Secondary endpoints included overall survival (OS), rate of graft-*versus*-host disease (GvHD), GvHD-free relapse-free survival (GRFS; defined as survival free of relapse, graft failure, grade 2-4 acute GvHD, chronic GvHD requiring systemic treatment, or death), TRM, time to neutrophil and platelet engraftment, and severity of mucosal and gastrointestinal toxicity.

The study was approved by the University of Illinois institutional review board. Informed consent was obtained from all patients. Procedures followed were in accordance with national and institutional ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013.

Conditioning regimen

Patients received intravenous busulfan from days -5 to -2 at varying doses to target the total area under the concentration curve of 4,800 μM/min, fludarabine 40 mg/m^2 daily (total 160 mg/m^2) on days -5 to -2, and palifermin 60 μg/kg daily intravenously on days -8 to -6. Patients receiving allografts from unrelated donors or related donors with one-antigen mismatch also received rabbit anti-thymocyte globulin (Thymoglobulin, Genentech, Cambridge, MA, USA).

Total marrow irradiation

TMI was administered as fractions of 1.5 Gy twice a day on days -3 to -1 (total of 9 Gy), approximately 8 hours apart. This TMI dose was established based on a phase I trial previously conducted at our institution.[25] The details of the irradiation technique have been described by our group.[21] Briefly, treatment plans were performed using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). Three subplans were devised (head, chest and pelvis) due to the width and length limitations on linear accelerator-based treatments. Skeletal bone (including cranium, mandible, sternum, ribs, complete vertebral body, pelvis, femoral head and upper half of the femur) was defined and contoured as the planning target volume using computed tomography images. A 3 mm margin was added to the planning target volume to account for possible setup errors.

Results

Demographics

The baseline characteristics of th participants are listed in Table 1. A total of 32 patients were enrolled. Two of the 32 patients were not transplanted, in one case because of rapid disease progression and in the other because of severe worsening of performance status before starting the conditioning regimen. The characteristics of the patients who did receive a transplant are shown in Table 1. The median age at the time of transplantation was 52 years (range, 20-68), the female-to-male ratio was 17:13, race was not Caucasian in 43% of patients, and the majority of patients had a diagnosis of AML (N=21). All patients were classified as being at high risk of relapse. In detail, the three patients with favorable-risk AML at diagnosis received at least three lines of treatment and were trans-

planted at the time of their second complete remission (CR2). The patient with low-risk MDS had a 5q deletion and was refractory to treatment with lenalidomide.

Transplant characteristics

The characteristics of the HSCT are summarized in Table 2. The majority of donors were male (N=21). The median comorbidity score for the population of patients was 3 (range, 0-7). Out of the 30 analyzable patients who received TMI, ten received allografts from matched related donors, 14 from matched unrelated donors, and six from one-antigen mismatched unrelated donors. Most patients received other lines of treatment prior to transplantation, except for three MDS patients who were transplanted with untreated disease. AML patients received a median of two lines of treatment prior to HSCT (range, 1-7). The median CD34 cell dose was $8.5x10^6$/kg. Most patients were positive for cytomegalovirus (N=25), while 17 out of 30 donors were negative for cytomegalovirus.

Engraftment

All patients displayed timely primary hematopoietic engraftment, except for two patients who died during the transplant admission before engraftment could occur. One patient died from refractory AML before engrafting platelets on transplant day 25. The second patient died of septic shock prior to both neutrophil and platelet engraftment on transplant day 19. There were no cases of graft failure. The median number of days for engraftment was 14 (range, 9-22) for neutrophils and 15 (range, 9-43) for platelets. The median number of transfusions was three for both packed red blood cells and platelets (Table 3). The cumulative incidence of both neutrophil and platelet engraftment is shown in Figure 1.

Transplant outcomes and toxicity

With a median follow up of 1,483 days (range, 63-2,260 days) at data cutoff, the OS for all 32 enrolled patients was 59%. The 1-year OS for patients who were transplanted was 72% and the 1-year DFS was 65% (Table 3). One of the patients alive at data cutoff had a relapse of CML 6 months after HSCT but achieved a major molecular remission on tyrosine-kinase inhibitor therapy after transplant. Five AML patients were transplanted with active disease: three were alive and in remission at 1 year and at data cutoff, while two died of relapsed disease. The rate of grade 3-4 acute GvHD was 13%, with only one patient having grade

Table 1. Baseline characteristics of 30 patients with high-risk myeloid malignancies undergoing hematopoietic stem cell transplantation with FluBu4/TMI conditioning.

Characteristics	Values
Age at transplant, years, median (range)	52 (20-68)
Gender, N (%)	
Male	13 (43)
Female	17 (57)
Race, N (%)	
White	17 (57)
Black	5 (17)
Hispanic	8 (27)
Diagnosis, N (%)	
Acute myeloid leukemia	21 (70)
Favorable risk	2 (7)
Intermediate risk	5 (17)
Adverse risk	13 (43)
CR1	12 (40)
CR2	3 (10)
Refractory	5 (17)
Myelodysplastic syndrome	6 (20)
Low risk	1 (3)
Intermediate risk	3 (10)
High/very high risk	1 (3)
Chronic myeloid leukemia	3 (10)
Accelerated phase	1 (3)
Blast crisis	2 (7)

FluBu4/TMI: myeloablative fludarabine/busulfan + total marrow irradiation; CR1: first complete remission; CR2: second complete remission.

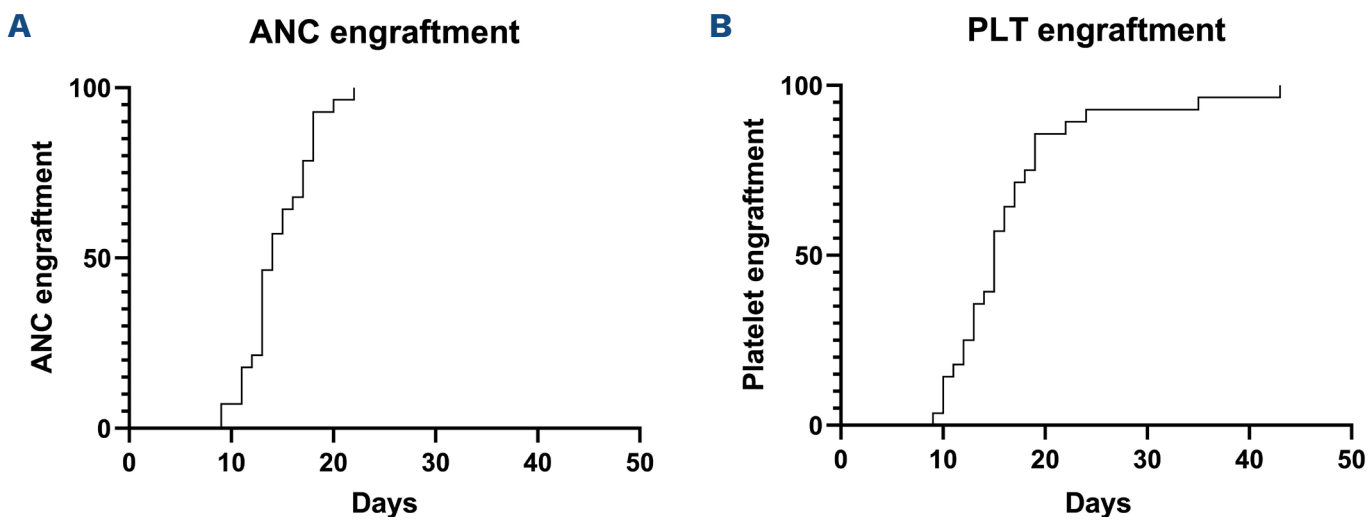

Figure 1. Cumulative incidence of neutrophil and platelet engraftment among 30 patients with high-risk myeloid malignancies undergoing hematopoietic stem cell transplantation with myeloablative fludarabine/busulfan + total marrow irradiation conditioning. (A) Neutrophil engraftment. (B) Platelet engraftment. ANC: neutrophil; PLT: platelet.

Table 2. Transplant characteristics of 30 patients with high-risk myeloid malignancies undergoing hematopoietic stem cell transplantation with FluBu4/TMI conditioning.

Characteristics	Values
Patient:donor gender, N (%)	
Female:female	7 (23)
Female:male	10 (33)
Male:male	11 (37)
Male:female	2 (7)
Comorbidity score, median (range)	3 (0-7)
HLA matching, N (%)	
MRD	10 (33)
MUD	14 (47)
MMUD	6 (20)
N of prior treatments, median (range)	2 (0-7)
Acute myeloid leukemia	2 (1-7)
Myelodysplastic syndrome	1 (0-1)
Chronic myeloid leukemia	3 (2-4)
CD34+ cell dose, x10^6/kg, median (range)	8.5 (2.4-19.9)
CMV status, patient/donor, N (%)	
Positive/positive	10 (33)
Positive/negative	15 (50)
Negative/positive	3 (10)
Negative/negative	2 (7)

FluBu4/TMI: myeloablative fludarabine/busulfan + total marrow irradiation; HLA: human leukocyte antigens; MRD: matched related donor; MUD: matched unrelated donor; MMUD: one-antigen mismatched unrelated donor; N: number; CD34: cluster of differentiation 34; CMV: cytomegalovirus.

Table 3. Transplant outcomes of 30 patients with high-risk myeloid malignancies undergoing hematopoietic stem cell transplantation with FluBu4/TMI conditioning.

Outcomes	Values
Hospital stay, days, median (range)	31 (23-96)
Engraftment, days, median (range)	
Neutrophils, N=29	14 (9-22)
Platelets, N=28	15 (9-43)
Transfusions, median (range)	
PRBC	3 (0-20)
Platelets	3 (0-18)
Mucositis, N (%)	
Any	29 (97)
Grade 3-4	17 (57)
Acute GvHD, N (%)	
Grade 2-4	7 (23)
Grade 3-4	4 (13)
Chronic GvHD, N (%)	
Mild	3 (10)
Moderate	6 (20)
Severe	5 (17)
Cytomegalovirus, N (%)	
Reactivation	11 (37)
Infection	4 (13)
Follow up, days, median (range)	1,483 (63-2,260)
Survival, N (%)	
OS at data cutoff	19 (63)
OS at year, N=29	21 (72)
DFS at data cutoff	18 (60)
DFS at year, N=29	19 (65)
GRFS at data cutoff	10 (33)
GRFS at year, N=29	12 (41)
Mortality, N (%)	
Disease-related mortality	5 (17)
Transplant-related mortality	6 (20)

FluBu4/TMI: myeloablative fludarabine/busulfan + total marrow irradiation; PRBC: packed red blood cells; GvHD: graft-*versus*-host disease; OS: overall survival; DFS: disease-free survival; GRFS: GvHD-free relapse-free survival.

4 (3%). The rate of moderate-to-severe chronic GvHD was 37%. Of the 30 patients who received an allogeneic HSCT, 19 (63%) were alive and 18 (60%) were free of relapse. The cumulative OS and DFS for 30 transplanted patients are shown in Figure 2A, B.

Six patients (20%) relapsed or had refractory disease after transplantation and five (17%) died of relapse, while six patients died of other causes (3 from septic shock, 1 from disseminated toxoplasmosis, 1 from idiopathic pneumonia and 1 from unknown causes). The cumulative incidence of relapse is shown in Figure 2C, and non-relapse mortality in Figure 2D. Finally, the GRFS rates at 1-year and at data cutoff were 41% and 33%, respectively; the cumulative incidence is shown in Figure 2E.

A total of 29 patients (97%) experienced mucositis, with a maximum grade of 4 in two patients (7%). Grade 3 mucositis affected 15 patients (50%). Nausea or vomiting was experienced by 28 patients (93%), with three grade 3 cases (10%) and no grade 4 cases. All patients experienced diarrhea, but only two patients (7%) had grade 3 and none had grade 4. Other toxicities (listed in detail in *Online Supplementary Table S1*) included dermatological (20%, none grade 3 or higher), transaminitis (10%, all grade 3), hyperbilirubinemia (7%, all grade 3), acute kidney injury (10%, including one case of grade 4), cardiac arrhythmias (10%, including one case of grade 3 atrial fibrillation), venous thromboembolism (7%, none grade 3 or higher), episcleritis (3%), eye pain (3%), respiratory failure (grade 4 in one patient, 3%, from volume overload), menorrhagia (3%), encephalopathy (3%) and pneumonitis (grade 1 in one patient, 3%). Twenty (67%) patients experienced neutropenic fever and 20 (67%) had documented infections (*Online Supplementary Table S2*). The most common infectious complication was *Clostridium difficile*, seen in six patients (20%). A total of four patients (13%) died from infectious complications.

Discussion

To our knowledge, this is the first study to report on the

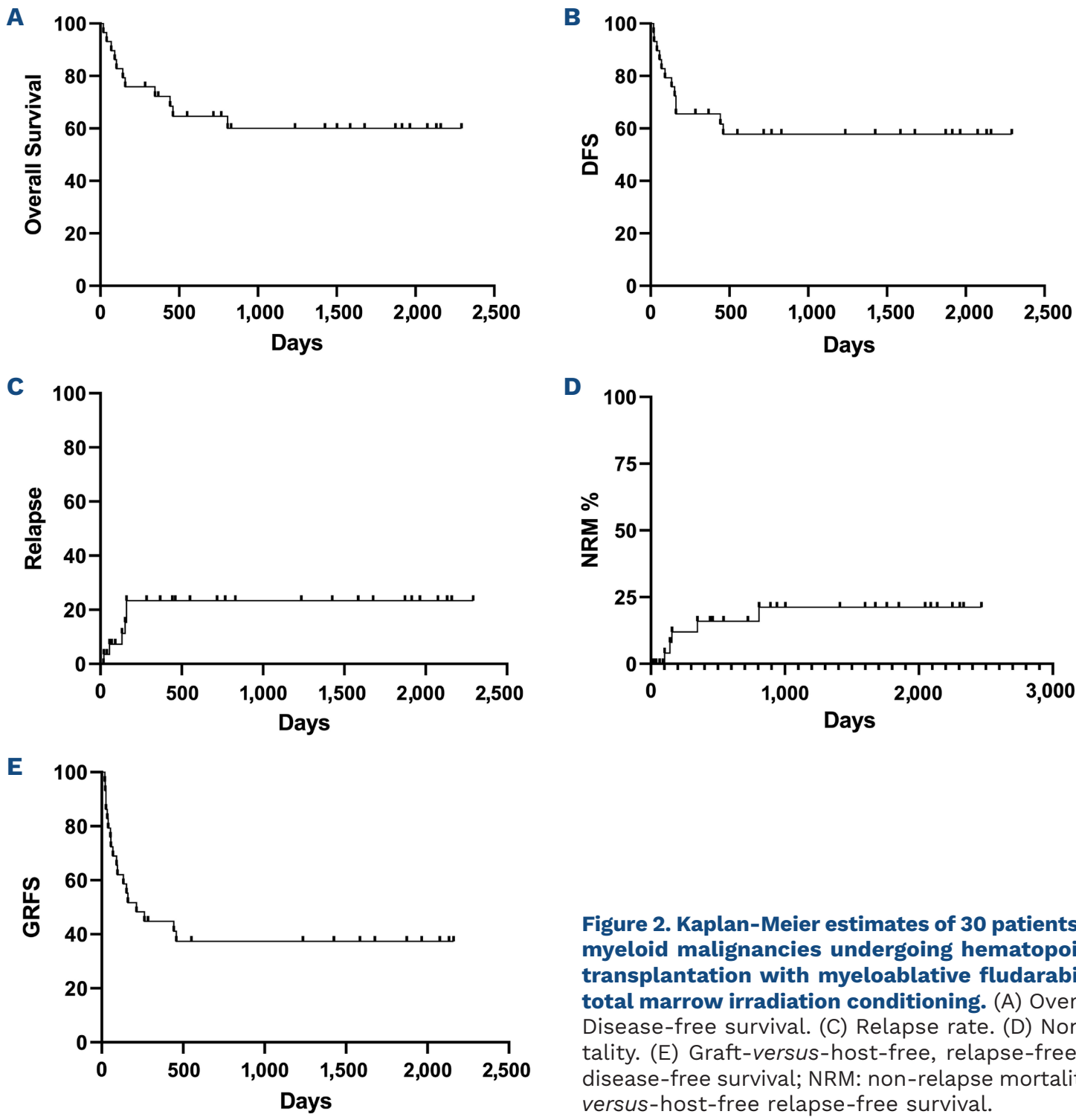

Figure 2. Kaplan-Meier estimates of 30 patients with high-risk myeloid malignancies undergoing hematopoietic stem cell transplantation with myeloablative fludarabine/busulfan + total marrow irradiation conditioning. (A) Overall survival. (B) Disease-free survival. (C) Relapse rate. (D) Non-relapse mortality. (E) Graft-*versus*-host-free, relapse-free survival. DFS: disease-free survival; NRM: non-relapse mortality; GRFS: graft-*versus*-host-free relapse-free survival.

efficacy of combining high doses of TMI with a standard myeloablative preparative regimen prior to allogeneic HSCT. Here, we demonstrated that adding TMI at a dose of 9 Gy to myeloablative FluBu4 is an effective conditioning regimen for allogeneic HSCT for high-risk myeloid malignancies. In addition, we demonstrated that this combination has acceptable toxicity and TRM.

Previous studies have shown that the addition of radiation to myeloablative conditioning can increase the efficacy of the regimen. Russell *et al*. added TBI at 4 Gy to myeloablative doses of fludarabine and busulfan in 89 patients with AML.[30] In high-risk patients, the regimen containing TBI (median follow up 31 months) resulted in an improved DFS (46% *vs*. 15% in high-risk patients) and relapse rate (RR) (33% *vs*. 79%).[30] In our study, with the addition of TMI, the DFS and RR were 60% and 20%, respectively. In a different study, by Clift *et al*., TBI was combined with cyclophosphamide and compared at doses of 12 Gy and 15.75 Gy in patients undergoing HSCT for AML.[9] The group that received the higher dose of TBI had lower relapse rates (8% *vs.* 23%); however, the OS was similar (59% *vs.* 59%) due to an increase in TRM (32% *vs.* 12%).[9] When compared to our study, the RR, OS and TRM are similar, even though our study included only high-risk patients. Similar results were observed in a recent analysis by Sabloff *et al*., who compared intermediate (13-13.75 Gy) and high doses (14 Gy) of TBI with the standard dose of 12 Gy.[31] Furthermore, several studies have reported on the efficacy of FluBu4 without TMI.[10,17,32,33] These studies have included patients of all risk groups and had similar outcomes to those of our study, which focused exclusively on high-risk patients.[10,17,32,33] Our data compare favorably with those in a previous report from our group, which described outcomes of HSCT in high-risk patients with FluBu4 as the preparative regimen.[17] In that study, with a median follow-up of 737 days, the OS, DFS, TRM and

RR were 35%, 31%, 19% and 46%, respectively.[17] Similarly, most patients in that cohort had AML. In contrast, our study included a greater proportion of female patients (57% *vs*. 44%), older patients (median age 52 *vs*. 44) and more transplants from matched unrelated donor (68% *vs*. 53%).[17] These data suggest that the addition of TMI to myeloablative FluBu4 in our study enhanced the efficacy of the conditioning regimen without significantly increasing transplant-related mortality, consistent with findings from previously published TMI studies.[21,25,34,35]

As previously reported with both TBI and TMI, the most frequent grade 3 or higher adverse event was mucositis (57% of the patients).[11,15,25,36] Previously reported rates of grade 3 or higher mucositis with fludarabine/busulfan alone range from 24-45%.[10,32] However, it should be noted that regimens containing TBI have reported grade 3 or higher mucositis rates as high as 94-100%.[37,38] Other toxicities were evaluated and found to be similar to those previously reported with fludarabine/busulfan alone.[32] Additionally, our group has recently demonstrated that the incidence of long-term adverse events with FluBu4/TMI is comparable to that with FluBu4 alone, further indicating that the added toxicity from TMI is acceptable.[39]

In alternative to combining myeloablative irradiation with myeloablative chemotherapy, recent studies have utilized a very high dose of total marrow and lymphoid irradiation, at 20 Gy, to replace standard TBI 12 Gy in acute leukemia patients.[40] This approach did not increase organ toxicity since the irradiation outside the marrow and lymphoid organs was comparable to that observed with TBI and produced a 31% progression-free survival at 2 years in patients with leukemic marrow involvement at the time of transplant.[40]

Irradiation of the bone marrow has also been explored using the monoclonal radioimmunoconjugate I-131 apamistamab (Iomab-B), which targets CD45 and selectively delivers high-dose radiation to the bone marrow. Early results from the Sierra trial were recently reported, showing rapid engraftment and a favorable toxicity profile when Iomab-B was added to fludarabine and TBI at 2 Gy.[41] Furthermore, the study reported high rates of early remission in patients undergoing HSCT with active disease.[41]

Our results demonstrate that the addition of TMI at a high dose (9 Gy) to myeloablative FluBu4 is an effective and well-tolerated preparative regimen for allogeneic HSCT for patients with high-risk myeloid malignancies. Future randomized phase III studies are needed to establish the benefit of incorporating targeted bone marrow irradiation techniques, such as TMI or radio-conjugated antibodies (Iomab-B), into myeloablative chemotherapy compared to chemotherapy alone.

Disclosures

No conflicts of interest to disclose.

Contributions

PP, MK, BA and DR designed the study. LM, AMA and DR collected the data and wrote the manuscript. KA and ZC performed the statistical analyses. KS, CU, CG, MS, PR, JQ, EZ and NM reviewed the manuscript.

Data-sharing statement

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

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