Association between the choice of the conditioning regimen and outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis

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Abstract

Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment for myelofibrosis. However, the optimal conditioning regimen either with reduced-intensity conditioning (RIC) or myeloablative conditioning (MAC) is not well known. Using the Center for International Blood and Marrow Transplant Research database, we identified adults aged ≥18 years with myelofibrosis undergoing allo-HCT between 2008-2019 and analyzed the outcomes separately in the RIC and MAC cohorts based on the conditioning regimens used. Among 872 eligible patients, 493 underwent allo-HCT using RIC (fludarabine/busulfan n=166, fludarabine/melphalan n=327) and 379 using MAC (fludarabine/busulfan n=247, busulfan/cyclophosphamide n=132). In multivariable analysis with RIC, fludarabine/melphalan was associated with inferior overall survival (hazard ratio [HR]=1.80; 95% confidenec interval [CI]: 1.15-2.81; *P*=0.009), higher early non-relapse mortality (HR=1.81; 95% CI: 1.12-2.91; *P*=0.01) and higher acute graft-*versus*-host disease (GvHD) (grade 2-4 HR=1.45; 95% CI: 1.03-2.03; *P*=0.03; grade 3-4 HR=2.21; 95%CI: 1.28-3.83; *P*=0.004) compared to fludarabine/busulfan. In the MAC setting, busulfan/cyclophosphamide was associated with a higher acute GvHD (grade 2-4 HR=2.33; 95% CI: 1.67-3.25; *P*<0.001; grade 3-4 HR=2.31; 95% CI: 1.52-3.52; *P*<0.001) and inferior GvHD-free relapse-free survival (GRFS) (HR=1.94; 95% CI: 1.49-2.53; *P*<0.001) as compared to fludarabine/busulfan. Hence, our study suggests that fludarabine/busulfan is associated with better outcomes in RIC (better overall survival, lower early non-relapse mortality, lower acute GvHD) and MAC (lower acute GvHD and better GRFS) in myelofibrosis.

Introduction

Myelofibrosis is a chronic myeloproliferative neoplasm arising either *de novo* (primary) or secondary to antecedent essential thrombocytosis or polycythemia vera. Despite the recent advances in disease biology and treatment options such as Janus activating kinase (JAK) inhibitors, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only potentially curative option.[1-3] The availability of reduced intensity conditioning (RIC) and the choice of donors have expanded the scope of allo-HCT for these patients who are often older adults.[4] While several factors influence outcomes of allo-HCT, conditioning intensity and conditioning regimen are aspects that could be tailored to improve the outcomes. Currently, both myeloablative conditioning (MAC) and RIC platforms are available for allo-HCT in myelofibrosis.[5-12] A large study from the European Group for Blood and Marrow Transplant (EBMT) compared the outcomes of allo-HCT with RIC *versus* MAC in myelofibrosis and demonstrated comparable results with both approaches, but better graft-*versus*-host disease (GvHD)-free -and relapse-free survival (GRFS) with MAC.[9] However, the optimal conditioning regimen either with RIC or MAC is not well known. While some studies have previously compared different RIC regimens with varying results,[10-12] similar comparative studies with MAC are lacking and no studies have demonstrated a survival difference based on the conditioning regimen. Hence, we sought to determine the outcomes of allo-HCT for myelofibrosis based on the choice of the conditioning regimen, separately with RIC and MAC.

Methods

Study objective

Our objectives were to compare the overall survival, disease-free survival, non-relapse mortality, relapse, incidence of acute GvHD, chronic GvHD and GRFS based on the choice of the conditioning regimen used with RIC or MAC.

Data source

CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. It comprises a voluntary network of more than 450 transplantation centers worldwide that contribute data on consecutive allo-HCT to a centralized statistical center.[13] Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Patients provided written informed consent for research. The Institutional Review Boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Study population

Adults aged ≥18 years with a diagnosis of myelofibrosis (chronic phase) who underwent allo-HCT between the period 2008-2019 and data reported to the CIBMTR were identified. The cohort was then selected to focus on the most common conditioning regimens used in RIC (fludarabine/busulfan *vs*. fludarabine/melphalan] and MAC (fludarabine/busulfan *vs*. busulfan/cyclophosphamide] setting (*Online Supplementary Figure S1*). Conditioning regimens were classified in the CIBMTR dataset based on prior published data.[14,15] The donor groups included matched related donors, eight of eight (HLA-A, -B, -C and -DRB1) matched unrelated donors and seven of eight matched unrelated donors. Key exclusion criteria were allo-HCT from haploidentical donor, syngeneic donor, cord blood, and *ex vivo* T-cell depleted or CD34 selected grafts. In addition, 51 patients in fludarabine/busulfan MAC group who received

post-transplant cyclophosphamide (post-Cy) were excluded as there were no such corresponding patients in busulfan/cyclophosphamide MAC group.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics with median and range for continuous variables and proportions for categorical variables. Outcomes were compared separately in RIC and MAC cohorts based on the conditioning regimens. Definitions of the outcomes are provided in the *Online Supplementary Appendix*. Cumulative incidence estimates were calculated for competing risks outcomes including acute GvHD, chronic GvHD, non-relapse mortality, and relapse. Kaplan-Meier method was used to estimate the probabilities for survival. In order to evaluate for other relevant factors that could influence the outcomes, multivariable Cox regression analysis was used (see below for the variables included). The proportional hazards assumption was examined and covariates that violate the proportional hazards assumption were added as time-dependent covariates. In the absence of binary endpoints, hazard ratio (HR) and confidence limits were reported. A pairwise comparison within the non-reference groups was also performed in multivariable models to demonstrate their effect and shown as contrasts. Variables included in multivariable analysis were age, race/ethnicity, disease subtype (primary *vs.* post essential thrombocythemia [ET] or polycythemia vera [PV]), dynamic international performance scoring system (DIPSS) score, hematopoietic cell transplantation comorbidity index (HCT-CI), Karnofsky performance scale (KPS), systemic symptoms, splenic radiation, splenomegaly, interval from diagnosis to allo-HCT, ruxolitinib use pretransplant, donor-recipient HLA-match, sex match, cytomegalovirus (CMV) match, stem cell source, GvHD prophylaxis (tacrolimus based *vs.* cyclosporine based *vs.* post-Cy *vs.* others), use of antithymocyte globulin (ATG)/alemtuzumab, and year of transplant. A stepwise selection method was used to identify the final model with a significance level of 0.05 and only variables reaching that statistical significance were shown. In addition, adjusted univariate estimates were provided for outcomes that were significantly associated with conditioning regimen. Fine and Gray model was used for analysis of non-relapse mortality, GvHD and relapse.[16] Center effect was tested using the score test proposed by Commenges and Andersen and marginal Cox models were used for further adjustments.[17] Center effect was noted to be significant only for chronic GvHD and was adjusted accordingly. Missing category was included in the models as one group to avoid loss of data and power.[18] All analyses were performed at a two-sided significance level of 0.05 using SAS 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

Of 872 eligible patients, 493 underwent allo-HCT using RIC (fludarabine/busulfan n=166, fludarabine/melphalan n=327) and 379 using MAC (fludarabine/busulfan n=247, busulfan/cyclophosphamide n=132). Key baseline characteristics of the patients are summarized (Table 1; *Online Supplementary Tables S1* and *S2*; unadjusted univariate estimates in *Online Supplementary Tables S3* and *S4*). In the RIC cohort, compared to fludarabine/busulfan patients, fludarabine/melphalan patients had longer median interval from diagnosis to allo-HCT (37 *vs.* 22 months, *P*=0.02), lower proportion with antithymocyte globulin/alemtuzumab use (25% *vs.* 52%, *P*<0.01), and higher proportion with pretransplant ruxolitinib use (61% *vs.* 49%, *P*=0.03). In the MAC cohort, compared to fludarabine/busulfan patients, busulfan/cyclophosphamide patients had younger age (median age 55 *vs.* 60 years, *P*<0.01), higher proportion with low-intermediate risk disease (61% *vs.* 54%, *P*=0.03), higher proportion with bone marrow graft (12% *vs.* 4%, *P*<0.01), lower proportion with antithymocyte globulin/alemtuzumab use (5% *vs.* 45%, *P*<0.01), and lower proportion with pretransplant ruxolitinib use (43% *vs.* 59%, *P*<0.01). Median follow-up of the cohort was 26 (range, 3-150) months.

Overall survival

In multivariable analysis (Table 2), overall survival in the RIC setting was significantly worse with fludarabine/melphalan (HR=1.80; 95% CI: 1.15-2.81; *P*=0.009, 2-year adjusted overall survival 54.4% *vs.* 60.9%) as compared to fludarabine/busulfan (Figure 1). In the MAC setting, overall survival was not significantly different between based on the conditioning regimen (busulfan/cyclophosphamide HR=1.14; 95% CI: 0.75-1.71; *P*=0.54) (Figure 2). Other factors significantly associated with overall survival were donor-recipient HLA match (higher risk with unrelated donors in the MAC setting) and the use of antithymocyte globulin/alemtuzumab (higher risk in the RIC setting) (*Online Supplementary Tables S5* and *S6*).

Disease-free survival

In multivariable analysis (Table 2), disease-free survival was not significantly different based on the conditioning regimen used in RIC (fludarabine/melphalan HR=1.03; 95% CI: 0.77-1.38; *P*=0.85) or MAC (busulfan/cyclophosphamide HR=1.03; 95% CI: 0.77-1.38; *P*=0.83) settings (*Online Supplementary Figures S2* and *S3*). Other factors significantly associated with disease-free survival were Karnofsky performance status (higher risk with lower score in MAC) and pretransplant ruxolitinib use (higher risk in MAC) (*Online Supplementary Tables S5* and *S6*).

Table 1. Key baseline characteristics.

Characteristic	Reduced intensity conditioning			Myeloablative conditioning		
	Flu/Bu (N=166)	Flu/Mel (N=327)	*P*	Flu/Bu (N=247)	Bu/Cy (N=132)	*P*
Age in years, median (range)	63 (44-75)	63 (38-78)	0.88	60 (27-74)	55 (24-67)	<0.01*
Disease type, N (%) Primary Post ET Post PV	 132 (80) 14 (8) 20 (12)	 242 (74) 45 (14) 40 (12)	0.22	 191 (77) 20 (8) 36 (15)	 100 (76) 13 (10) 19 (14)	0.85
Median time from diagnosis to HCT in months (range)	22 (3-393)	37 (3-594)	0.02*	25 (2-490)	38 (3-377)	0.41
DIPSS Score, N (%) Low/intermediate-1 Intermediate-2/high Missing	 71 (43) 69 (42) 26 (16)	 107 (33) 168 (51) 52 (16)	0.07	 134 (54) 93 (38) 20 (8)	 80 (61) 34 (26) 18 (14)	0.03*
Donor type, N (%) HLA-identical sibling 8/8-matched unrelated 7/8 matched unrelated	 48 (29) 107 (64) 11 (7)	 94 (29) 205 (63) 28 (9)	0.75	 79 (32) 142 (57) 26 (11)	 53 (40) 62 (47) 17 (13)	0.15
ATG/alemtuzumab use, N (%) No Yes	 79 (48) 87 (52)	 246 (75) 81 (25)	<0.01*	 135 (55) 112 (45)	 125 (95) 7 (5)	<0.01*
Graft type, N (%) Bone marrow Peripheral blood	 6 (4) 160 (96)	 13 (4) 314 (96)	0.84	 11 (4) 236 (96)	 16 (12) 116 (88)	<0.01*
Pretransplant ruxolitinib, N (%) No Yes Missing	 84 (51) 82 (49) 0	 125 (38) 201 (61) 1	0.03*	 101 (41) 146 (59) 0	 75 (57) 57 (43) 0	<0.01*

*P<0.05 significant. Flu: fludarabine; Bu: busulfan; Mel: melphalan; Cy: cyclophosphamide; ET: essential thrombocytosis; PV: polycythemia vera; HCT: hematopoietic cell transplantation; DIPSS: dynamic international prognostic scoring system; ATG: antithymocyte globulin.

Non-relapse mortality

In the RIC setting, there was a significantly higher risk of early non-relapse mortality with fludarabine/melphalan as compared to fludarabine/busulfan (17.4% *vs.* 4.3%, HR=1.81; 95% CI: 1.12-2.91; *P*=0.01). Beyond 6 months the risk of non-relapse mortality was low with fludarabine/melphalan (HR=0.46; 95% CI: 0.23-0.91; *P*=0.02) (Table 2; *Online Supplementary Figure S4*) (cut-off of 6 months was chosen due to non-proportional hazard). No significant differences in non-relapse mortality were seen with the MAC-based on the conditioning regimens (busulfan/cyclophosphamide HR=1.36; 95% CI: 0.83-2.21; *P*=0.22) (*Online Supplementary Figure S5*). The other factor significantly associated with non-relapse mortality was donor-recipient HLA-match (higher risk with unrelated donors in MAC) (*Online Supplementary Tables S5* and *S6*).

Relapse

The risk of relapse was not significantly different based on the conditioning regimen used in RIC or MAC (RIC - fludarabine/melphalan HR=0.85; 95% CI: 0.64-1.12; *P*=0.25; MAC - busulfan/cyclophosphamide HR=0.92; 95% CI: 0.64-1.32; *P*=0.65) (*Online Supplementary Figures S6* and *S7*; *Online Supplementary Tables S5* and *S6*). Other factors significantly associated with relapse were Karnofsky performance status (higher risk with poor score in MAC), pretransplant ruxolitinib use (higher risk in MAC) and year of transplant (higher risk with recent period in RIC).

Graft-*versus*-host disease

In the RIC setting, fludarabine/melphalan was associated with a significantly higher risk of acute GvHD grade 2-4 (fludarabine/melphalan 40%, fludarabine/busulfan 35.3%, HR=1.45; 95% CI: 1.03-2.03; *P*=0.03) and grade 3-4 (fludarabine/melphalan 21.8%, fludarabine/busulfan 12.1%, HR=2.21; 95% CI: 1.28-3.83; *P*=0.004) (*Online Supplementary Figures S8* and *S9*). In the MAC setting, busulfan/cyclophosphamide was associated with a significantly higher risk of acute GvHD grade 2-4 (busulfan/cyclophosphamide 58.9%, fludarabine/busulfan 34.4%; HR=2.33; 95% CI: 1.67-3.25; *P*<0.001) and grade 3-4 (busulfan/cyclophosphamide 32.6%, fludarabine/busulfan 11.9%; HR=2.31; 95% CI: 1.52-3.52; *P*<0.001) (*Online Supplementary Figures S10* and *S11*). Chronic GvHD was significantly associated with donor-re-

Table 2. Multivariable analysis of outcomes based on conditioning regimen.

Reduced intensity conditioning				Myeloablative conditioning			
Outcome	**HR**	**95% CI**	***P***	**Outcome**	**HR**	**95% CI**	***P***
Overall survival**				Overall survival			0.54
≤6 months			0.009*	Flu/Bu	1.00	Ref.	
Flu/Bu	1.00	Ref.		Bu/Cy	1.14	0.75-1.71	
Flu/Mel	1.80	1.15-2.81					
>6 months							
Flu/Bu	1.00	Ref.	0.35				
Flu/Mel	0.82	0.53-1.26					
Disease-free survival**				Disease-free survival			0.83
≤6 months				Flu/Bu	1.00	Ref.	
Flu/Bu	1.00	Ref.	0.85	Bu/Cy	1.03	0.77-1.38	
Flu/Mel	1.03	0.77-1.38					
>6 months							
Flu/Bu	1.00	Ref.	0.76				
Flu/Mel	0.95	0.68-1.34					
NRM**				NRM			0.22
≤6 months				Flu/Bu	1.00	Ref.	
Flu/Bu	1.00	Ref.	0.01*	Bu/Cy	1.36	0.83-2.21	
Flu/Mel	1.81	1.12-2.91					
>6 months							
Flu/Bu	1.00	Ref.	0.02*				
Flu/Mel	0.46	0.23-0.91					
Relapse			0.25	Relapse			0.65
Flu/Bu	1.00	Ref.		Flu/Bu	1.00	Ref.	
Flu/Mel	0.85	0.64-1.12		Bu/Cy	0.92	0.64-1.32	
Acute GvHD grade 2-4**				Acute GvHD grade 2-4**			
≤2 months				≤2 months			
Flu/Bu	1.00	Ref.	0.03*	Flu/Bu	1.00	Ref.	<0.001*
Flu/Mel	1.45	1.03-2.03		Bu/Cy	2.33	1.67-3.25	
>2 months				>2 months			
Flu/Bu	1.00	Ref.	0.18	Flu/Bu	1.00	Ref.	0.69
Flu/Mel	0.71	0.43-1.17		Bu/Cy	0.88	0.46-1.68	
Acute GvHD grade 3-4**				Acute GvHD grade 3-4			
≤2 months			0.004*	Flu/Bu	1.00	Ref.	<0.001*
Flu/Bu	1.00	Ref.		Bu/Cy	2.31	1.52-3.52	
Flu/Mel	2.21	1.28-3.83					
>2 months							
Flu/Bu	1.00	Ref.	0.48				
Flu/Mel	0.89	0.64-1.24					
Chronic GvHD			0.55	Chronic GvHD			0.36
Flu/Bu	1.00	Ref.		Flu/Bu	1.00	Ref.	
Flu/Mel	0.91	0.67-1.25		Bu/Cy	1.21	0.80-1.84	
GRFS			0.32	GRFS			<0.001*
Flu/Bu	1.00	Ref.		Flu/Bu	1.00	Ref.	
Flu/Mel	1.11	0.90-1.35		Bu/Cy	1.94	1.49-2.53	

*P<0.05 significant; **outcomes separated by time points due to non-proportional hazard. Flu: fludarabine; Bu: busulfan; Mel: melphalan; Cy: cyclophosphamide; NRM: non-relapse mortality; GvHD: graft-*versus*-host disease; GRFS: GvHD-free relapse-free survival.

cipient HLA-match (higher risk with 7/8 matched unrelated donors in RIC) and pretransplant ruxolitinib use (lower risk in MAC), but not by the conditioning regimen (*Online Supplementary Tables S5* and *S6*).

Graft-*versus*-host disease-free relapse-free survival

In the RIC setting, GRFS was not significantly different between fludarabine/busulfan and fludarabine/melphalan (HR=1.11; 95% CI: 0.90-1.35; P=0.32) (*Online Supplementary Figure S12*). However, in the MAC setting, busulfan/cyclophosphamide was associated with significantly inferior GRFS (HR=1.94; 95% CI: 1.49-2.53; P<0.01) (2-year adjusted probability 5.1% *vs.* 19.4%) as compared to fludarabine/busulfan (Table 2; Figure 3). Other factors significantly associ-

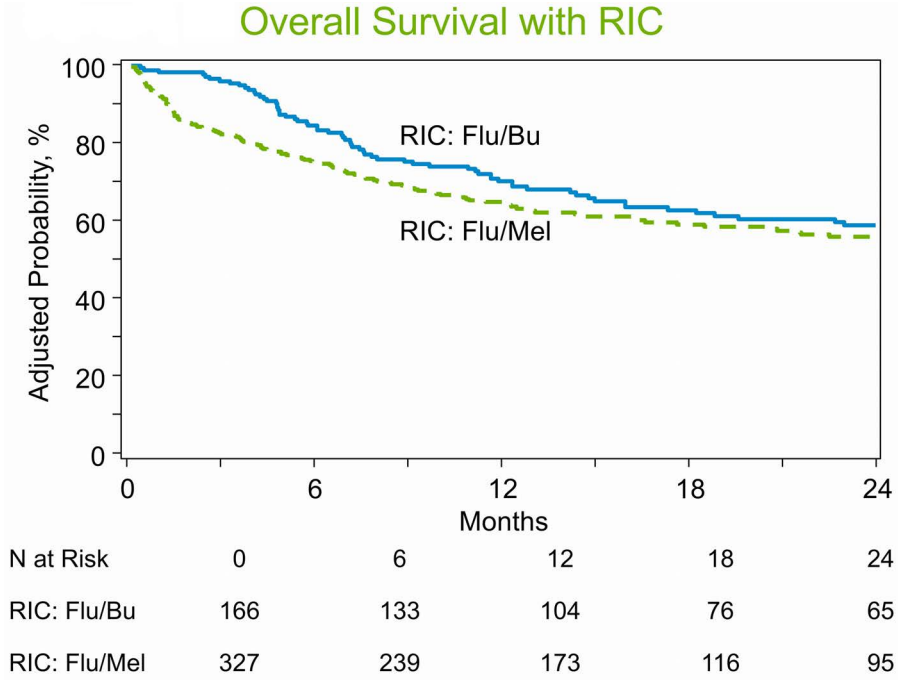


Figure 1. Overall survival with reduced-intensity conditioning. RIC: reduced-intensity conditioning; Flu: fludarabine; Bu: busulfan; Mel: melphalan.

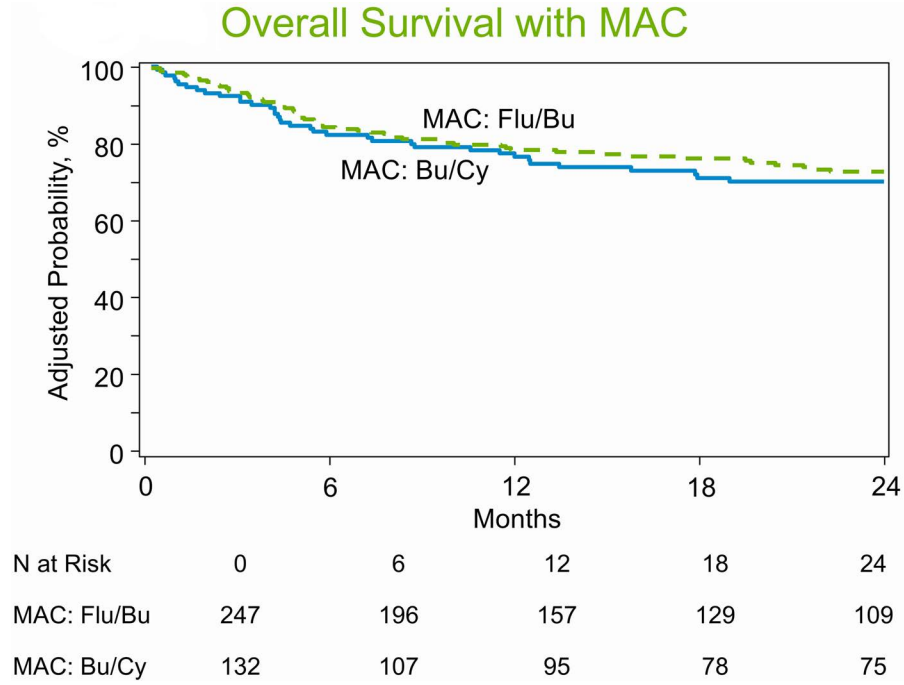


Figure 2. Overall survival with myeloablative conditioning. MAC: myeloablative conditioning; Flu: fludarabine; Bu: busulfan; Mel: melphalan.

ated with GRFS included recipient age (in MAC) and donor-recipient HLA-match (higher risk with unrelated donors in MAC) (*Online Supplementary Tables S5* and *S6*).

Engraftment

The rates of neutrophil engraftment (30 days) were significantly better with fludarabine/busulfan in RIC (fludarabine/busulfan 95.1% *vs.* fludarabine/melphalan 92.4%; P=0.006) and MAC (fludarabine/busulfan 95.2% *vs.* busulfan/cyclophosphamide 87.2%; P=0.02). The rate of platelet engraftment (100 days) was better with fludarabine/busulfan in the RIC setting (RIC - fludarabine/busulfan 84.4% *vs.* fludarabine/melphalan 73.9%; P<0.001; MAC - fludarabine/busulfan 86.1% *vs.* busulfan/cyclophosphamide 83.7%; P=0.27).

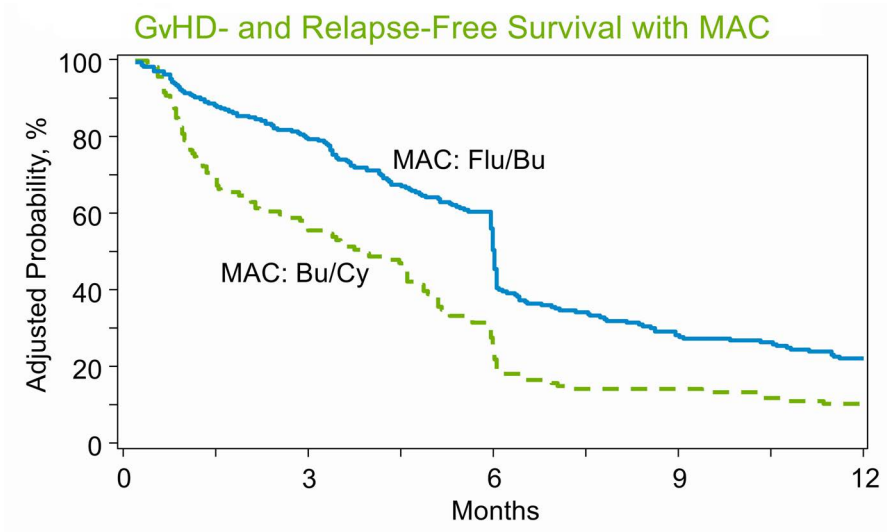
Additional analyses

In the RIC cohort, we investigated whether the outcomes differed based on the dose of melphalan (100 *vs.* 140 mg/m^2) used in fludarabine/melphalan group. As shown in the *Online Supplementary Table S7*, the outcomes did not significantly vary based on the dose of melphalan (shown as contrasts between melphalan 100 *vs.* 140 mg/m^2).

Discussion

Our study highlights the significant differences in outcomes of allo-HCT for myelofibrosis based on the choice of the conditioning regimen. Fludarabine/busulfan conditioning was associated with superior overall survival, lower early non-relapse mortality and lower acute GvHD (all with RIC), and lower acute GvHD and superior GRFS with MAC. A key aspect of conditioning strategy is its ability be tailored in order to improve the outcomes. Events such as non-relapse mortality and GvHD that affect the morbidity and mortality after allo-HCT could be influenced by the conditioning strategy and efforts to minimize these complications are vital to improve the long-term success. Although RIC and MAC platforms are clinically decided based on factors such as age, comorbidities, performance status, and other aspects that are often not modifiable, our results illustrate the influence of common conditioning regimens used in these settings and provides valuable information for choosing the appropriate regimen in clinical practice.

Prior retrospective studies have evaluated the impact of conditioning intensity and regimen in myelofibrosis, albeit with variable results and certain key differences compared to our study.[5-12] A study by Robin *et al.* included 160 patients with myelofibrosis from two European centers (Paris [fludarabine/busulfan] or Hamburg [fludarabine/melphalan]), but with antithymocyte globulin given for all patients who received fludarabine/busulfan conditioning.[11] Another CIBMTR study by Gupta *et al.* included only patients with primary myelofibrosis and RIC (fludarabine/TBI *vs.* fludarabine/melphalan *vs.* fludarabine/busulfan) between 1997-2010 with a relatively younger patient population (median age 55 years).[10] Hence, the differences in the study population, the nature of the cohort (registry- *vs.* individual center-based), treatment received and variations in time period included could have contributed to the differences in results noted between the current study and prior studies. To date, prospective studies of conditioning regimen in myelofibrosis are single-arm or comparative studies with smaller sample size.[19,20,21] For example, a phase II study by Patriarca *et al.* prospectively compared fludarabine/busulfan and fludarabine/thiotepa for allo-HCT in 60 patients with myelofibrosis and showed similar outcomes



N at Risk	0	3	6	9	12
MAC: Flu/Bu	241	110	41	31	26
MAC: Bu/Cy	127	35	15	11	10

Figure 3. Graft-*versus*-host-disease-free relapse-free survival with myeloablative conditioning. MAC: myeloablative conditioning; CY: cyclophosphamide; GvHD: graft-*versus*-host disease; Flu: fludarabine; Bu: busulfan; Mel: melphalan.

with both these regimens.[21] Hence, our study addresses the knowledge gap in this area using a larger dataset with a comparison of commonly reported conditioning regimens. Unfortunately, due to the limited number of patients receiving other less common conditioning regimens such as fludarabine/thiotepa, these regimens could not be compared in our study. Additionally, given the results of a large EBMT study showing no difference in overall survival between MAC and RIC,[9] we did not compare the outcomes of MAC *versus* RIC in our analysis which also helped to minimize the heterogeneity in comparisons.

Apart from the conditioning regimen, factors such as donor-recipient HLA-match, performance status and use of antithymocyte globulin/alemtuzumab influenced the outcomes similar to prior studies. The imbalances in baseline characteristics were adjusted in multivariable models and there were no significant interactions noted between the baseline characteristics and main effect (conditioning regimen). Antithymocyte globulin/alemtuzumab was associated with worse overall survival in RIC and was more commonly used with fludarabine/busulfan regimens. Despite this, an early survival advantage was noted with fludarabine/busulfan in RIC. The association between the outcomes and factors such as the route of busulfan administration (oral *vs.* intravenous, targeted *vs.* non-targeted; *data not shown*) and the dose of melphalan (in RIC) were also investigated and none was found. In MAC, ruxolitinib prior to allo-HCT was associated with higher risk of relapse, inferior disease-free survival, higher risk of acute GvHD and lower risk of chronic GvHD. Although prior studies indicate the feasibility and safety of ruxolitinib therapy prior to allo-HCT,[22,23] we could not evaluate the possible mechanisms behind these differences due to limited information on the duration, dose, response, and other aspects of ruxolitinib therapy. Other factors such as the role of splenectomy, spleen size or splenic radiation therapy and their association with outcomes could not be evaluated due to the small number of patients with those interventions.

Despite the large sample size, our study is limited by the retrospective design and lack in-depth information on factors such as genomic mutations and therapies for myelofibrosis given pre- and post-allo-HCT that could affect the outcomes.[24,25] The lack of detailed information on genomic mutations precluded further analyses and calculation of molecular risk scores (such as MIPSS70, MYSEC-PM etc.). For example, a study by Gagelman *et al.* investigated the prognostic significance of somatic mutations in myelofibrosis patients undergoing allo-HCT and identified that *ASXL1* and non-CALR/MPL driver mutations were associated with poor outcomes. This study also established a prognostic model with variables such as patient age, performance status, white blood count, platelet count, HLA-mismatched donor and molecular mutations. However, due to the lack of information on these aspects, we could not apply this scoring system in our study.[24] We also could not assess the reasons behind the choice of individual conditioning regimens used for these patients, understanding that centers could have their preferences while choosing conditioning regimens. However, we evaluated for center-effects in multivariable analyses and adjustments were made accordingly. As our study mainly focused on patients with chronic phase myelofibrosis, the role of conditioning strategy in advanced-phase disease (accelerated/blast phase) was not evaluated. Due to the nature of the GvHD reporting in the dataset, chronic GvHD was analyzed as a whole outcome without further stratification (mild, moderate, severe).

Our study demonstrates that fludarabine/busulfan-based conditioning is associated with superior overall survival, lower early non-relapse mortality, and lower acute GvHD with RIC and lower acute GvHD and superior GRFS with MAC. The results provide valuable information for tailoring the conditioning strategies to minimize non-relapse mortality and GvHD and improve survival. Prospective comparative studies are warranted to confirm these results and identify the ideal conditioning regimen in myelofibrosis.

Disclosures

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Contributions

GM, WS, SK and NE conceived and designed the study, collected and assembled the data, and wrote the manuscript. All authors performed data analysis and interpretation of data; and GM, WS and SK provided final approval of the manuscript. GM and WS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The views expressed in this article do not reflect the official policy or position of the NIH, the Department of the Navy, the Department of Defense, the HRSA, or any other agency of the US Government.

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Data-sharing statement

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