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Choosing a Reduced-Intensity Conditioning Regimen for Allogeneic Stem Cell Transplantation, Fludarabine/Busulfan versus Fludarabine Melphalan: A Systematic Review and Meta-Analysis

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Fludarabine with busulfan (FB) or melphalan (FM) are 2 more commonly used reduced-intensity conditioning (RIC) regimens for allogeneic stem cell transplantation (HCT).We present a systematic review and meta-analysis of studies comparing these 2 RIC regimens. We searched electronic databases from inception through November 1, 2017 for literature searches to identify relevant studies. A DerSimonian random effects model was used to measure efficacy outcomes; hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. Seven studies, including a total of 1955 patients, met criteria for inclusion, of which 6 were included in the overall pooled analysis because of repetition of some patients in 2 studies. Three studies were included in the subgroup analysis of acute myelogenous leukemia (AML)/myelodysplastic syndrome (MDS) and 2 in the subgroup analysis of lymphoid malignancies. Overall survival (OS) and progression-free survival were not statistically significantly different between the 2 RIC regimens in analysis of all studies. However, OS was better with FM in subgroup analysis of AML/MDS studies (HR, .83; 95% CI, .73 to .95). Nonrelapse mortality was lower with FB (HR, .64; 95% CI, .46 to .89), whereas relapse was lower with FM (HR, 1.52; 95% CI, 1.13 to 2.06) in the analysis of all studies. This meta-analysis shows that FB and FM are associated with a similar OS in patients undergoing HCT. Relapse rates are lower with FM but at the cost of higher nonrelapse mortality.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HCT) has evolved as a potential curative therapy for various hematologic malignancies [1,2]. Regimen-related toxicity and transplant-related mortality preclude the use of conventional myeloablative conditioning (MAC) regimens in patients who are older or have a poorer functional status. Reduced-intensity conditioning (RIC) regimens have extended the use of HCT in older and less fit patients who are not able to tolerate MAC regimens with HCT. These RIC regimens rely on the graft-versus-tumor effect mediated by immune cells transferred in the graft [3]. Reduced intensity was subsequently defined by consensus guidelines as an intermediate category that does not fit into either myeloablative or nonmyeloablative regimens and where cell recovery may occur spontaneously, although the duration of pancytopenia may be prolonged, enough to cause significant mortality and morbidity [4,5].

Of the various RIC regimens described in the literature, combination of fludarabine with reduced-intensity-dose busulfan (>9 mg/kg) or melphalan (140 mg/m^2) are the more commonly used regimens [6,7]. No prospective randomized trials have compared these 2 regimens to objectively guide the selection between these RIC regimens, and currently the choice largely depends on physician preference. The smaller retrospective studies comparing these 2 conditioning regimens have shown varying patterns of morbidity and mortality. Hence, we conducted this systematic review and meta-analysis to determine clinical outcomes with the use of RIC with fludarabine/busulfan (FB) versus fludarabine/melphalan (FM), using all available data in this regard.

METHODS

Data Sources and Searches

We conducted a comprehensive search to identify studies comparing the use of FM versus FB before HCT in reduced-intensity dosing in patients with

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hematologic malignancies. A literature search was conducted from database inception through November 1, 2017 with electronic databases Medline, Embase, and the Cochrane Central Register of Controlled Trials. To identify relevant abstracts we used various combinations of the terms, including "reduced intensity conditioning," "allogeneic transplant," "fludarabine," "busulfan," "melphalan," "myeloid malignancies," "acute myelogenous leukemia," "myelodysplastic syndrome," "lymphoma," and "acute lymphoblastic leukemia" in addition to phrases such as "comparison of conditioning regimens," "comparison of reduced intensity conditioning regimens," and "fludarabine melphalan versus fludarabine busulfan." Two reviewers (T.J. and M.B.S.) identified articles eligible for further review by performing a screen of abstracts and titles. If a study was deemed relevant, the article was obtained and reviewed. Any disagreements were resolved by a third reviewer (J.P.) if consensus was not possible. Supplementary Figure 1 elaborates on the search and selection process.

Study Selection

Our criteria included randomized controlled trial or observational studies that compared post-HCT outcomes in patients with hematologic malignancies who received either FM or FB in reduced-intensity doses of busulfan < 9 mg/kg and melphalan of 140 mg/m^2 for conditioning before HCT. These criteria applied for both systematic review and the meta-analysis. Studies published in English language in adult patients aged > 18 years were included. Abstracts from hematologic meetings were not included because the data are not peer reviewed at that stage and the details of the studies are not often available to conduct an in-depth analysis.

Endnote version X8 (Clarivate Analytics, Philadelphia, PA) was used to manage literature obtained from the initial search, and duplicates were identified and excluded. The remaining literature was screened by scanning titles and abstracts, applying the following exclusion criteria: nonhematologic malignancy indications for HCT or studies done in the pediatric age group for various conditions; abstracts, reviews, editorials, case reports, and meta-analyses; and comparisons between MAC and RIC dosing regimen and single-arm studies without a report on comparison of outcomes. Data reported for myeloablative doses of busulfan (>9 mg/kg) or for treosulfan were not included.

Data Collection and Outcome Measures

We extracted prespecified data elements from each study, including patient demographics and baseline characteristics, sample size, therapeutic agents and their respective dosing, overall survival (OS), progression-free survival (PFS), relapse, nonrelapse mortality (NRM), and acute and chronic graft-versus-host disease (GVHD). Two reviewers (T.J. and M.B.S.) independently extracted the various data outcomes. Corresponding authors for respective studies were contacted for any additional information, if necessary. Primary end outcomes of interest were OS and PFS reported at 3 years. Secondary outcomes included NRM at 3 years, relapse rate at 3 years, acute GVHD of grade II to IV and grade III to IV, and chronic GVHD.

Risk of Bias and Quality Assessment

Two authors independently evaluated included studies for methodologic features that protected their results from bias (T.J. and M.B.S.). The Newcastle-Ottawa Scale was used for assessing the quality of nonrandomized studies included in the meta-analysis by evaluating criteria for selection, comparability of the study groups, and ascertainment of outcomes.

Statistical Analysis and Data Synthesis

From each study we obtained the relative association measure and 95% confidence interval (CI). Because the included studies reported the data relevant to our analysis in the form of Kaplan-Meir curves, we extracted the desired effect measures and proportions at the desired time point from the curves. Using the proportions mentioned we constructed contingency tables for each study and pooled a relative risk and associated 95% CI for each dichotomous outcome. We chose the random effects method as the primary analysis because of its conservative summary estimate and incorporation between and within study variance using the using the DerSimonian method [8]. We used the hazard ratio (HR) provided by some of the included studies to conduct a pooled HR for survival outcomes. An estimate of the log HR can be obtained from statistics computed during a log-rank analysis; also, the log HR is estimated only approximately, and in some reviews it has been referred to as a log odds ratio [9]. We also extracted the available dichotomous data for acute and chronic GVHD as well as relapse to conduct a risk ratio analysis. Subgroup analyses were planned for different subsets of patients, that is, patients with myeloid malignancies (acute myelogenous leukemia [AML]/myelodysplastic syndrome [MDS]) and those with lymphoid malignancies.

To assess heterogeneity of treatment effect among trials, we used the I^2 statistic. The I^2 statistic represents the proportion of heterogeneity of treatment effect across a trial that is not attributable to chance or random error. Hence, a value of 50% reflects significant heterogeneity that is due to real differences in study populations, protocols, interventions, and outcomes [10]. The *P* value threshold for statistical significance was set at .05 for effect sizes. Analyses were conducted using OpenMeta[Analyst] [11]. The study was performed in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses work groups [12].

RESULTS

Patient and Study Characteristics

Seven studies [13-19] comprising a total 1955 patients with various hematologic malignancies met the criteria for inclusion in the meta-analysis after the screening process (Supplementary Figure 1). Study descriptions and patient characteristics are elaborated in Table 1. Further description of disease risk and disease status at HCT is elaborated in Supplementary Table 1. Two studies included AML/MDS patients [13,14], another 2 included lymphoid malignancies [16,19], 1 included myelofibrosis patients [17], and 2 studies included patients with multiple hematologic malignancies [15,18]. Some patients from the study by Yerushalmi et al. [19] (lymphoma patients only) were already included in a prior publication by Shimoni et al. [18] (all hematologic diagnosis); hence, the data from the study by Yerushalmi et al. [19] were not included in the analysis of all studies to avoid repetition but were included in the subgroup analysis for lymphoma studies, along with the study by Kekre et al. [16]. Additionally, the study by Kawamura et al. [15] elaborated the results of patients with AML and MDS separately along with reporting results for all hematologic malignancies, and these data on AML/MDS patients were only included in the subgroup analysis for AML/MDS studies in addition to the inclusion of data for pooled analysis of all studies. Of note, only data on the reduced-intensity dosing of busulfan (6.4 mg/kg i.v.) from this study were used, whereas the MAC dose group that received 12.8 mg/kg busulfan was excluded for the purpose of this meta-analysis. Hence, the subgroup analysis for AML and MDS patients included data from the 3 studies by Baron et al. [13], Damlaj et al. [14], and Kawamura et al [15].

Most studies included patients who received i.v. busulfan except 2 studies in which patients who received oral busulfan were also included [13,17]. From the study by Yerushalmi et al. [19], only the data from the FM and FB cohorts were included in the meta-analysis. Data on patients who received treosulfan along with fludarabine in this study were not included in this meta-analysis because they did not meet the study criteria.

Primary Outcomes: OS and PFS

All studies reported OS; 3 studies reported it at 3 years [15,16,19], 3 at 2 years [13,14,18], and 1 at 7 years [17]. Using the reported survival curve, we report OS at 3 years for all studies. PFS was reported in 5 studies [13-17].

Pooled analysis of all studies including 1861 patients (excluding the study by Yerushalmi et al. [19]) showed no statistically significant difference in OS between FB and FM (HR, .97; 95% CI, .83 to 1.20) (Figure 1A). In a subgroup analysis including only AML/MDS studies with an aggregate 1271 patients (Baron et al. [13], Damlaj et al. [14], and Kawamura et al. [15]), OS was statistically significantly better with FM compared with FB (HR, .83; 95% CI, .73 to .95) at 3 years (Figure 1B). In the combined analysis of 2 studies including patients (n = 230) with lymphoid malignancies only (Yerushalmi et al. [19] and Kekre et al. [16]), OS was not statistically different with either RIC regimen (HR, 1.31; 95% CI, .99 to 1.72). (Figure 1B).

There was no statistically significant difference in PFS between FB and FM in the pooled data from the 5 studies in which these data were available (HR, .93; 95% CI, .79 to 1.1)

Table 1
Study Details and Patient Characteristics

Author	No. of Patients	Patients in Each Arm	Median Age(yr)	Gender	Diagnosis	Conditioning Regimen	Study Period	GVH Prophylaxis	Donor Source	ATG Use
Kawamura BBMT 2017	886*	FM 423 FB 463	FM 59 (50-71) FB 61 (50 -74)	F = 336 M = 550	AML 497 ALL 138 MDS 251	Flu with mel 140 mg/m^2 Flu with Bu 6.4 mg/kg i. v.	2007 - 2014	Cyclosporine based or tacrolimus based	HLA matched or 1 allele mismatch sibling or unrelated donor	In vivo T cell depletion used in 8% patients
Damlaj BBMT 2016	134	FM 87 FB 47	FM 61 (33-72) FB 60 (18-67)	F = 50 M = 84	AML 97 MDS 37	Mel 140 mg/m^2 Bu 8 mg/kg i.v.	2008 - 2014	Cyclosporine mtx for sibling donor or tacrolimus mtx for unrelated donor	Related or unrelated donor	N.A.
Kekre BBMT 2016	136	FM 75 FB 61	FM 48.2 FB 42	F = 46 M = 90	HD NHL	Mel 140 mg/m^2 Bu 3.2-6.4 mg/kg i.v.	2007 - 2014	Sirolimus + tacrolimus or calcineurin inhibitor + mtx	HLA identical related donor, 8/8 and 7/8 allele HLA matched unrelated	none
Robin BBMT 2016	160	FM 55 FB 105	FM 55 FB 59	F = 64 M= 96	MF	Mel 140 mg/m^2 Bu 8mg/kg i.v.(or PO equivalent)	2005 - 2014	Cyclosporine + mtx or mycophenolate mofetil	Matched related, matched unrelated, mismatched unrelated	ATLG 30mg/kg for related donor, 60 mg/kg for unrelated
Baron Cancer 2015	394	FM 176 FB 218	FM 5 4 (21-71) FB 58 (23-76)	F= 187 M= 207	AML	Mel 130-150 mg/m2 Bu 7.1 - 8.9 mg/kg PO (n = 137) or 6 to 6.9 mg/kg i.v. (n = 81)	2000 - 2012	Cyclosporin + mtx or mycophenolate mofetil	HLA identical sibling donor	No ATG
Yerushalmi BMT 2015	94*	FM 56 FB 38	FM 50 FB 55	F= 30 M= 64	HD, NHL	Mel 100-140 mg/m2 Bu 6.4 mg/kg i.v.		Cyclosporin + mtx	Matched/mismatched sibling/unrelated donor	ATG 5mg/kg 3 doses for unrelated or mismatched donor
Shimoni Leukemia 2007	151	FM 79 FB 72	FM 51 (16-66) FB 56 (23-70)	F= 67 M= 80	AML, MDS, CML, MM, NHL, HD, CLL, ALL, PNH	Mel 100-140mg/m2 Bu 6.4 mg/kg i.v.		Cyclosporin + mtx	HLA compatible related or unrelated donor	ATG 5mg/kg day -3 to -1 for unrelated or mismatched donor

FM, Fludarabine melphalan; FB, fludarabine busulfan; Mtx, methotrexate; N.A. not available; AML, Acute Myeloid Leukemia, ALL, Acute Lymphoblastic Leukemia; MDS, Myelodysplastic syndrome; HD, Hodgkin's disease; NHL, Non-Hodgkin lymphoma; MF, Myelofibrosis; CML, Chronic Myeloid Leukemia; MM, Multiple Myeloma; CLL, Chronic Lymphocytic Leukemia; PNH, paroxysmal nocturnal hemoglobinuria

* Total number of patients in the study may be different. We state the number of patients evaluated for this meta-analysis

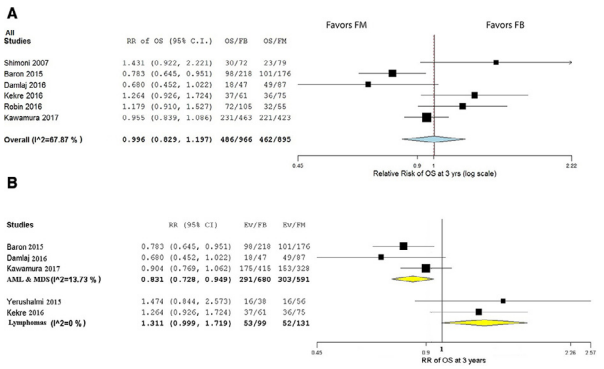

Figure 1. Forest plot of pooled estimates for OS: (A) All studies, (B) AML/MDS studies, and (C) lymphoma studies.

(Supplementary Figure 2A). Of the AML/MDS studies PFS was not separately reported by Kawamura et al. [15], and hence subgroup analysis was not performed for AML/MDS studies. PFS was also reported differently in the 2 lymphoid malignancies studies and hence was not performed for this hematologic diagnosis as well.

Nonrelapse Mortality

All studies provided data on NRM. As shown in Figure 2A, FB was associated with a lower NRM compared with FM, and this was statistically significant (HR, .64; 95% CI, .46 to .89) for overall analysis including a total 1861 patients. Subgroup analysis for studies including AML/MDS patients only (n = 1259) appeared to have lower NRM with FB, but this was not statistically significant (HR, .86; 95% CI, .67 to 1.1) as shown in Figure 2B [13-15]. In analysis of studies including patients with lymphoid malignancies only (n = 230), NRM was again statistically significantly lower with FB compared with FM (HR, .37; 95% CI, .23 to .60) (Figure 2B) [16,19]. Causes of NRM data as available from each study and overall are tabulated in Supplementary Table 2.

Relapse

Relapse data pooled from all 5 studies thta described relapse outcomes (n = 1710) showed a higher rate of relapse with FB compared with FM (HR, 1.52; 95% CI, 1.13 to 2.06) (Figure 3A). Among the 1259 patients undergoing HCT for AML/MDS, FB was associated with a higher rate of relapse compared with FM, but this was not statistically significant (HR, 1.94; 95% CI, .98 to 3.86) (Figure 3B). Relapse information from

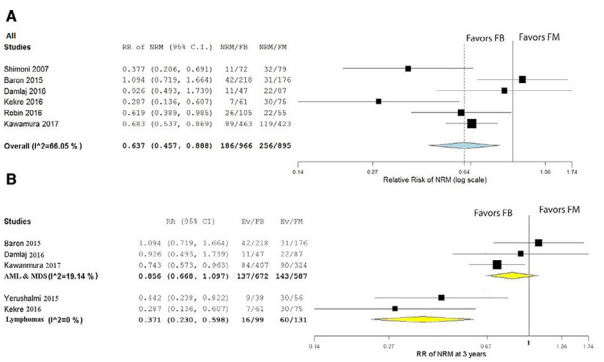

Figure 2. Forest plot for NRM: (A) All studies, (B) AML/MDS studies, and (C) lymphoma studies.

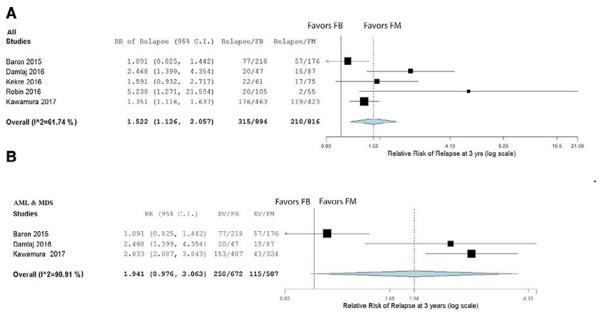

Figure 3. Forest plot for relapse: (A) All studies and (B) AML/MDS studies.

the lymphoma studies was not pooled because these results were described differently in the 2 studies.

Graft-versus-Host Disease

Acute GVHD was evaluated for all studies as grades II to IV and grades III to IV acute GVHD in a total of 1833 patients. A pooled analysis for all studies showed that grades II to IV acute GVHD was significantly less frequent in FB compared with FM, as shown in Supplementary Figure 3A (HR, .71; 95% CI, .56 to .91). Likewise, grades III to IV acute GHVD were statistically significantly less frequent with FB versus FM (HR, .50; 95% CI, .44 to .72) (Supplementary Figure 3B). Chronic GVHD, on the other hand, was not statistically different between the 2 RIC regimens (HR, .89; 95% CI, .69 to 1.14; data not shown). Because the use of antithymocyte globulin (ATG) was not consistent across studies and that could potentially affect GVHD outcomes, we separately analyzed the 3 studies in which ATG was used [17-19]. The results of acute GVHD grades II to IV and grades III to IV were both less frequent with FB (HR, .67 [95% CI, .45 to .98] and .43 [95% CI, .30 to .62], respectively) (Supplementary Figure 4).

Risk of Bias Assessment

The risk of bias is at least moderate given the study design of included studies, which are observational studies (Supplementary Table 3). Overall selection, comparability, and ascertainment were deemed adequate. One study included only patients who were aged > 50 years [15], and another study included patients who underwent sibling donor HCT only [13]. In 2 studies comparability may have been affected by more numerous high disease risk patients in the FM cohort in 1 study [16] and a higher number of sibling donor HCTs in the FM cohort in another study [18]. Risk of bias assessed based on the Newcastle-Ottawa Scale scoring system is elaborated in Supplementary Table 3.

DISCUSSION

HCT with a RIC regimen is a potential curative therapy for various hematologic malignancies [6]. The aim of this study was to conduct a meta-analysis and systematic review to compare clinical outcomes with the 2 most commonly used RIC regimens, FM and FB. The studies consisted of similar patients overall, conditioning regimen dosing, and GVH prophylaxis. There were variations in the ATG use based on institutional practice, pre-HCT treatment based on diagnosis, and disease status at HCT in some studies as detailed in Table 1 and Supplementary Table 1. Nevertheless, with an overall power of including around 2000 patients, our meta-analysis shows that, the outcomes overall are comparable in terms of OS and PFS when using FM and FB as the RIC regimen before HCT. This was despite the selection of older age [13,15,18] and lower

rates of sibling donors [15,17,18] in the FB cohort in various studies. This meta-analysis also allows for a deeper understanding of the patterns of morbidity and mortality post-HCT from a larger pooled data, which can enable selection of an individualized conditioning regimen for a particular diagnosis in a particular patient.

Relapse was lower with FM compared with FB in the overall analysis. However, because the risk of relapse is different for variable hematologic diagnosis, we did a subgroup analysis for individual diagnoses for patients undergoing HCT for AML/MDS. In patients with AML/MDS there was no statistically significant difference, although the overall HR still favored FM. This supports the popular belief that FM is a potentially more "intense" regimen compared with FB [20]. This information is particularly essential for patients with high disease risk undergoing HCT as FM may prove to be better in controlling disease. In AML patients treated with matched sibling donor HCT in the European Society for Blood and Marrow Transplantation study by Baron et al. [13], patients who underwent HCT in first complete remission had a similar OS and leukemia-free survival with FB and FM (2-year OS, 66% versus 59%, $P = .53$, and 2-year leukemia-free survival, 64% versus 55%, $P = .19$). However, when transplanted in second complete remission or beyond, known to be a higher risk condition, patients who received FM did significantly better in terms of OS as well leukemia-free survival compared with FB (2-year OS, 54% versus 32%, $P = .02$, and 2-year leukemia-free survival, 46% versus 30%, $P = .03$). Likewise, in the study by Kawamura et al. [15], patients with "high-risk" AML or MDS who received FM had lower relapses and better OS compared with those who received FB (3-year OS, 44.6% versus 34.8%, and 3-year disease-free survival, 39.2% versus 29.8%). Conversely, in the study in lymphoma patients reported by Kekre et al. [16], patients with low or intermediate disease risk index who received FB had a significantly better 3-year OS compared with those who received FM (62% versus 49%, $P = .02$).

Previous studies comparing RIC and MAC had shown higher relapses with RIC regimens confirming that a higher intensity regimen leads to better disease control in patients undergoing HCT [21,22]. However, most patients in these studies received FB as the RIC regimen. For example, the recent Blood and Marrow Transplant Clinical Trials Network 0901 trial that was closed early due to significantly higher relapses with RIC compared with MAC used FB in almost 80% patients [22]. Hence, the superiority of a MAC over a RIC regimen is not necessarily applicable to FM. In fact, a recent retrospective single-center study comparing FM with MAC regimen (busulfan/cyclophosphamide) showed similar relapse rates between the 2 regimens [23]. The data from our meta-analysis and these studies are thought-provoking if FM would be that "more intense RIC regimen" that can impart better disease control in patients who are not candidates for MAC.

The better disease control with FM comes at the cost of a higher NRM and higher GVHD rates compared with FB. NRM in lymphoid malignancies is of particular clinical significance because these patients are usually older with multiple comorbidities [24] and undergo multiple lines of therapy including high-dose therapy with autologous stem cell transplantation before receiving an HCT. This predisposes these patients to a higher risk of regimen-related toxicity; hence, a more intensive regimen such as FM could prove to be more deleterious. This is evidenced in the subgroup analysis of studies done in patients with lymphoid malignancies in our meta-analysis, where FB significantly improves NRM and has a more favorable OS, although not statistically significant for the latter. On a similar note, when MAC regimens were compared with RIC in patients with lymphomas or chronic lymphocytic leukemia in a retrospective study, higher NRM and lower OS was noted with MAC that was statistically significant in patients with HCT-specific comorbidity index of 1 or more [25]. All these results emphasize the importance of a more "tolerable" than a more "intense" regimen for patients with lymphoma undergoing HCT.

Disease status and overall patient performance status at the time of HCT are other significant factors to consider when selecting the RIC regimen. In the data from Shimoni et al. [18], which included a variety of hematologic malignancies, patients who were in remission at the time of HCT had a significantly superior OS with FB versus FM (72% versus 36%, $P = .03$). They also state that patients who underwent HCT with active disease had a lower risk of relapse, albeit a higher NRM. Additionally, in the study by Damlaj et al. [14], OS significantly improved in patients with Karnofsky performance status $\geq$ 90 when FM was used for conditioning regimen (75% with FM versus 48% with FB, $P = .03$). These findings indicate that FM may be a better regimen for patients undergoing HCT without a complete disease remission at HCT or beyond first complete remission. On the other hand, patients in the older age group or lower performance status may tolerate FB better especially when disease is in remission at the time of HCT.

As with any meta-analysis, there are various limitations in this study. The heterogeneous population from different institutes, tumor inclusion criteria ,and variations in busulfan dosing/administration (such as i.v. versus oral, daily versus every 6 hours, and with or without pharmacokinetic dose monitoring, as elaborated in Table 1) limit interpretation from these results. Second, in the GVHD analysis there are slight variations especially in the use of ATG in various studies and that should be kept in mind when interpreting those analyses. Third, all studies of relevance being retrospective observational studies in this meta-analysis may have resulted in some degree of selection bias in disease risk and disease status at HCT, as elucidated in Supplementary Table 3, and it is difficult to fully account for these differences. Nevertheless, a prospective study to compare these regimens is going to be challenging to conduct due to variability in practice at different centers. In that scenario a pooled analysis is 1 of the best available strategies to deduce outcome patterns and base usage schema.

In conclusion, HCT using RIC regimens show similar clinical outcomes with FM and FB conditioning in terms of OS. Both patient and disease factors can help choose a RIC regimen that would be most appropriate for an individual patient. FM is associated with better disease control but at the cost of higher NRM, whereas FB appears to be better tolerated with a lower NRM, especially when good disease control is achieved before HCT.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.11.016.

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