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Authors
Popat, Uday
Mehta, Rohtesh S
Bassett, Roland
et al.

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Optimizing the Conditioning Regimen for HCT in Myelofibrosis: Long-term Results of a Prospective Phase II Clinical Trial

Uday Popat[#,1], **Rohtesh S. Mehta**[1], **Roland Bassett**[3], **Piyanuch Kongtim**[1,2], **Julianne Chen**[1], **Amin M. Alousi**[#,1], **Paolo Anderlini**[#,1], **Stefan Ciurea**[1], **Chitra Hosing**[#,1], **Roy Jones**[#,1], **Partow Kebriaei**[#,1], **Issa Khouri**[#,1], **Richard Lindsay, PA**[1], **Yago Nieto**[#,1], **Amanda Olson**[1], **Betul Oran**[1], **Muzaffar H. Qazilbash**[#,1], **Gabriela Rondon**[1], **Elizabeth J. Shpall**[#,1], **Srdan Verstovsek**[#,1], **Borje S. Andersson**[#,1], **Richard E. Champlin**[#,1]

[1]Departments of Stem Cell Transplantation and Cellular Therapy University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. [2]Division of Hematology Department of Internal Medicine Faculty of Medicine Thammasat University,Thailand [3]Department of Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA.

Abstract

Background: Optimal conditioning regimen for older patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation (HCT) is not known. Likewise, role of dose intensity is not clear.

Methods: We conducted a non-randomized prospective phase II trial using low-dose, later escalated to high-dose (MAC) busulfan with fludarabine (Bu-Flu) in myelofibrosis patients up to 74 years. First 15 patients received intravenous busulfan 130 mg/m^2/day on days −3 and −2 ("low dose"); 31 received high dose – either 100 mg/m^2/day (days −5 to −2; n=4) or pharmacokinetic-guided area under the curve of 4,000 μmol.min (days −5 to −2; n=27). Primary endpoint was day 100 non-relapse mortality (NRM).

Findings: Median age was 58 years (interquartile range (IQR) 53–63). Dynamic international prognostic scoring system (DIPSS)-plus was intermediate (n=28) or high (n=18). Donors were

Corresponding author: Uday Popat, MD, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 423, Houston, TX 77030, Phone: 713-745-3055, Fax: 713-794-4902, upopat@mdanderson.org.

Authorship Contributions: U.P. conceptualized the study design, helped with interpretation of data, ensured compliance with regulatory requirements for the clinical trial; R.S.M. contributed to interpretation of data and wrote the manuscript; R.B. contributed to data analysis and figures and wrote the statistical section of the manuscript; J.C. and G.R., helped with data collection and provided clinical data; P.K., A.M.A., P.A., S.C., C.H., R.J., P.K., I.K., R.L., Y.N., A.O., B.O., M.H.Q., E.J.S.,S.V. enrolled patients in the study and monitored clinical responses. R.E.C. and B.S.A. enrolled patients in the study and monitored clinical responses and conceptualized the study design.

[#]Professor of Medicine

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related (n=19) or unrelated (n=27). Cumulative incidence of NRM was 9.7% (95% confidence interval (CI) 0-20.3) at day 100 and at 3 years in the high dose, while it was 0% in the low dose group at day 100, and increased to 20% (95% CI 0-41.9) at 3 years. With a median follow up of 5.1 years (IQR 3.8–6), 3-year relapse was 32.3% (95% CI 15.4-49.1) in high dose versus 53.3% (95% CI 26.6-80.1) in low dose; event-free survival was 58% (95% CI 43-78%) versus 27% (95% CI 12-62%), and overall survival was 74% (95% CI 60-91%) versus 60% (95% CI 40-91%) respectively. In multivariate analysis, high dose busulfan had a trend towards lower relapse (Hazard ratio (HR) 0.44, 95% CI, 0.18-1.07, p=0.07), with no impact on NRM.

Interpretation: Intensifying Bu-Flu regimen using pharmacokinetic-monitoring appears promising in reducing relapse without increasing non-relapse mortality.

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Trial registration: ClinicalTrials NCT00475020

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative approach for patients with myelofibrosis. Earlier HCT studies in myelofibrosis patients used myeloablative conditioning (MAC) and were restricted to younger patients, with a median age of about 40–50 years. Despite that, non-relapse mortality (NRM) was rather high, ranging from about 25–50% at 1 year. [1–4] However, as the median age at diagnosis of myelofibrosis is about 70 years,[5] most patients are unsuitable for MAC, but can undergo reduced intensity conditioning (RIC) HCT. There was limited data about the use of RIC regimens in myelofibrosis[6,7] when we initiated this prospective trial to evaluate the same. Since then, several studies, with a majority being retrospective, assessed the outcomes of RIC regimens in myelofibrosis,[6–16] and other novel combinations are being explored.[17]

Herein, we report long-term outcomes of our trial that investigated the safety and efficacy of intravenous (IV) busulfan and fludarabine (Bu-Flu) regimen in patients with myelofibrosis, and assessed the impact of busulfan dose intensity on outcomes. We began this trial with a low dose RIC regimen and sequentially escalated to a myeloablative, reduced toxicity regimen – the latter with busulfan pharmacokinetic dose monitoring.

PATIENTS AND METHODS

Study design and participants

This prospective open-label, non-randomized phase II trial was conducted at The MD Anderson Cancer Center (MDACC, Houston, TX, USA). The initial eligibility criteria included patients up to 70 years old with an intermediate or high risk myelofibrosis according to the Lille scoring system.[18] However, after safety was established (i.e., only 1 regimen-related death within 100 days) when 21 patients had been enrolled, the age limit was increased to 75 years. The protocol was amended to reflect this change on July 1, 2009 with the approval of the Institutional Review Board (IRB). Other eligibility criteria included the availability of at least 9/10 HLA-matched (at A, B, C, DR and DQ loci) related or

unrelated donor determined by high-resolution typing, adequate organ function - defined as serum creatinine < 1.6 mg/dl, ejection fraction ≥40%, direct bilirubin < 2 mg/dl, alanine aminotransferase ≤ 4 x upper normal limit, FEV1, FVC, or DLCO ≥40% of expected, and Zubrod performance status ≥2. Patients with transformation to acute myeloid leukemia (AML), HIV and uncontrolled active infections were excluded. The research was conducted in accordance with the Helsinki Declaration. All participants provided written informed consent before enrolment. This study was approved by the MDACC IRB (protocol 2005–0726). The study was registered with clinicaltrials.gov, NCT00475020.

Procedures - Conditioning Regimen and Supportive Care

All patients received Bu-Flu regimen, with fludarabine 40 mg/m^2/day IV daily from day −5 through −2, followed immediately upon completion by busulfan. First 14 patients received busulfan 130 mg/m^2/day IV daily on day −3 and −2 (“low dose” group). After observing higher than expected relapse rate at an interim analysis of 12 patients where 5 patients had relapsed, the protocol was amended on December 18, 2007 to increase the busulfan dose. We hypothesized that the administration of higher dose busulfan, especially with pharmacokinetic monitoring, would reduce relapse risk without increasing NRM. In case pharmacokinetic studies could not be performed due to logistical reasons, an alternative fixed-dose regimen of busulfan 100 mg/m^2/day IV from day −5 through −2 was allowed. All trial patients in this “high dose” busulfan group (n=27) received pharmacokinetic-guided IV busulfan based on a dose of IV busulfan 32 mg/m2 given on day −7, to target daily area under the plasma drug concentration-time curve (AUC) of 4,000 μmol.min ± 12% from day −5 through −2 (total 16,000 μmol.min) [Figure 1]. In addition to these 41 patients enrolled between June 2005 and May 2012, 5 patients were eligible for the trial but could not be enrolled due to insurance reasons. Those patients were treated off-protocol with the same regimen as the trial participants (1 with low dose and 4 with fixed high dose busulfan), and are included in this report to capture all similarly treated patients during the study period, given rarity of the disease. A total of 46 patients are included in this report – 15 in the “low dose” group and 31 in the “high dose” group.

Graft source was either bone marrow (BM) or granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood (PB). Graft-versus-host disease (GVHD) prophylaxis included tacrolimus from day −2, and methotrexate 5 mg/m^2 IV on days 1, 3, 6, and 11. All patients with an unrelated donor also received rabbit antithymocyte globulin (Thymoglobulin, Genzyme, Cambridge, MA) 2.5 mg/kg/day IV on days −3 through −1. The administration of G-CSF, prophylactic or therapeutic antimicrobials, antiepileptics, transfusions and other supportive care measures followed institutional standard practice.

Endpoints, definitions and statistical analyses

The primary objective was the safety, as determined by the incidence of NRM, with a goal to achieve <30% NRM rate at day 100. The method of Thall and Simon[19] was employed to perform interim safety monitoring. The total planned sample size was 30 patients. However, the protocol was amended after 12 patients were enrolled to increase the busulfan dose, with an intent to accrue 30 more patients.

The secondary objective was to assess efficacy, as determined by event free survival (EFS), overall survival (OS), incidences of acute GVHD (aGVHD), chronic GVHD (cGVHD) and relapse, and time to engraftment of neutrophils (absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days) and platelets (platelet count $\geq 20 \times 10^9$/L for 7 consecutive days without transfusion). Relapse was defined as progression to AML, recurrence of disease, secondary graft failure, recovery of autologous hematopoiesis or loss of donor chimerism. EFS was defined as the time from HCT until disease relapse, graft failure or death from any cause. OS was defined as the time from HCT until death from any cause. Acute and chronic GVHD were diagnosed and graded according to the standard criteria.[20,21]

The method of Gooley at al.[22] was used to estimate the cumulative incidence of relapse and death in a competing risks framework. Within this framework, proportional hazards regression models were fit to both relapse and NRM considering the competing risk of the other event using the method of Fine and Gray.[23] Kaplan-Meier analysis was performed to estimate OS and EFS. Cox proportional hazards regression analysis was done to assess the association between the endpoints (NRM, relapse, EFS and OS) and the covariates of interest, including age, donor type, busulfan dose, graft source, JAK2 positivity, CD34 dose and DIPSS-plus score. All patients were re-classified retrospectively according to the DIPSS-plus scoring system [24] at the time of analysis. We performed post-hoc analysis comparing the outcomes of patients who received low dose versus high dose busulfan. In addition to the analyses of all 46 patients, we conducted supplementary analyses of only those 41 patients who were enrolled on the trial.

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RESULTS

Baseline characteristics

A total of 46 patients up to 74 years of age, with a median age of 58 years (interquartile range (IQR), 53–63) were treated between June 2005 and May 2012. About half of the patients had an intermediate risk Lillie score (n=24, 52%); others had high risk (n=22, 48%). A majority had an intermediate-2 (n=27, 59%) or high risk (n=18, 39%) DIPSS-plus score. JAK2-V617F mutation status was known in all but 2 patients and was detectable in 26 patients (59%). Thirteen patients had no treatment prior to HCT; others received cytoreductive therapy with either hydroxyurea (n=11) or cytarabine (n=3), hypomethylating agent (n=11), JAK inhibitor (n=4), tyrosine kinase inhibitor (n=6) or another investigational drug (n=20) pre-HCT. The median time from diagnosis to transplantation was 23 months (IQR, 9–117). Half of the patients (n=23) had HLA-matched unrelated donor, 41% (n=19) had HLA-matched related and 4 (9%) had one-antigen mismatched unrelated donor. Graft

source was predominantly PB (n=41, 89%). About one-third (n=15) had HCT-CI index[25] of 3 or more. There were no differences between the groups [Table 1]. The median busulfan dose was 6.5 mg/kg IV (IQR, 6.3–7.0) in the low dose arm and 10.8 mg/kg IV (IQR, 8.6–12.4) in the high dose arm. The median follow-up of the surviving patients was 5.1 years (IQR, 3.8–6).

Non-relapse mortality—Three patients in the high dose and none in the low dose arm died without disease relapse/progression on or before day 100. The cumulative incidence of day 100 NRM was 6.7% (95% confidence interval (CI) 0-13.7); 9.7% (95% CI 0-20.3) in the high dose arm and 0% (95% CI 0-0) in the low dose arm. Beyond day 100, 5 patients died without disease relapse/progression – 3 in the low dose and 2 in the high dose arm. The cumulative incidence of NRM at 3 years was 9.7% (95% CI 0-20.3%) in the high dose versus 20% (95% CI 0-41.9%) in the low dose group. [Table 2, Figure 2]. There was no difference in the NRM between the low dose and the high dose arms over the length of the study, p=0.84. Findings remained unchanged when the analysis was restricted to the trial patients [Table S1]. There were no significant predictors of NRM in either univariate [Table S2] or multivariate analysis [Table 3].

Toxicities

Twenty-two patients experienced 44 grade ≥3 non-hematologic adverse events (AE) within day 100, graded as per the Common Terminology Criteria for Adverse Events (CTCAE) 4.0. The most common AE was infection (n=16) - mostly bacterial (n=13), one of which was fatal due to Stenotrophomonas maltophilia pneumonia. Sinusoidal obstruction syndrome occurred in 3 patients, including one terminal event. Diffuse alveolar hemorrhage occurred in 2 patients, one of which was fatal [Table S3]. Twenty-five patients died, mostly due to recurrence/persistence of myelofibrosis (n=14) [Table S4].

Engraftment and graft-versus-host disease—All patients engrafted with no primary graft failure. The median time to neutrophil engraftment was 13 days (IQR 12–15; range, 0–27) and that of platelet engraftment was 24 days (IQR, 14–30; range, 0–268).

The cumulative incidences of grade II-IV and III-IV aGVHD were 22.3% (95% CI 10.0-34.7%) and 6.8% (95% CI 0-14.4%), respectively. The 3-year cumulative incidence of cGVHD was 40.2% (95% CI 25.0-55.4) and that of extensive cGVHD was 31% (95% CI 16.6-45.3%) [Table 2].

Relapse—Twenty-one patients relapsed/progressed after HCT – 9/15 in the low dose and 12/31 in the high dose group. One patient had recurrence of JAK2 positive clone by molecular analysis about 3 year post-HCT. This patient received DLI and remained alive in remission. The cumulative incidence of relapse was 39.1% (95% CI 24.8-53.4) at 3 years; 53.3% (95% CI 26.6-80.1) in the low dose arm and 32.3% (95% CI 15.4-49.1) in the high dose arm, p=0.05 [Table 2, Figure 2]. Similar findings were noted when the analysis was restricted to the trial patients [Table S1]. There was a trend towards a lower risk of relapse with high dose busulfan in both univariate (HR 0.41, 95% CI 0.17-0.99, p=0.05) [Table S2], and multivariate analyses (HR 0.44, 95% CI 0.18-1.07, p=0.07) [Table 3].

Survival—The 3-year EFS rate was 48% (95% CI 35-65); it was significantly better in the high dose group (58%, 95% CI 43-78) than in the low dose group (27%, 95% CI 12-62), p=0.03 [Table 2, Figure 3A]. Same trend was noted when the trial patients were analyzed, although without statistical significance likely due to fewer number of patients [Table S1]. In univariate analysis, patients with DIPSS-plus high risk disease had a significantly inferior EFS (HR 3.17, 95% CI 1.46-6.88; p=0.003) than intermediate-risk [Table S2, Figure 3B], and those who received high dose busulfan had a significantly superior EFS (HR 0.45, 95% CI 0.21-0.96, p=0.04) than the low dose group [Table S2]. In multivariate analysis, DIPSS-plus high risk disease was the only significant predictor of poor EFS (HR 2.69, 95% CI 1.19-6.05; p=0.02) [Table 3].

The 3 year probability of OS was 69% (95% CI 57-84); 74% (95% CI 60-91) in the high dose group versus 60% (95% CI 40-91) in the low dose group, p=0.25. [Table 2, Figure 3C] Findings remained unchanged when the analysis was restricted to the trial patients [Table S1]. In univariate analysis, increasing age (HR 1.08, 95% CI 1.01-1.14, p=0.02) and DIPSS-plus high risk disease (HR=7.12; 95% CI 2.53-20.01; p=0.0002) were associated with poor survival [Table S2, Figure 3D]. Similarly, in multivariate analysis, mortality risk increased with age and in those with high risk DIPSS-plus score [Table 3].

DISCUSSION

In this prospective phase II clinical trial, we show that both low dose and high dose Bu-Flu regimens were very well tolerated in patients with myelofibrosis. However, the high dose myeloablative reduced-toxicity regimen was associated with remarkable outcomes with 3 year OS of 74% while still retaining the benefits of low NRM (10% at 3 years) typically seen with RIC regimens. We initiated the trial with a low dose busulfan (median 6.5 mg/kg iv), but soon realized that although the regimen was non-toxic and had 0% NRM at day 100, it was associated with an exceedingly high risk of relapse (53% at 3 years). Consequently, we increased the busulfan dose with a hypothesis that higher dose would offer better disease control. The typical dose of busulfan in the traditional low dose Bu-Flu regimen where busulfan is given over 2 days (so called “FB2” regimen) is 6.4 mg/kg IV; and the dose of busulfan in the myeloablative so called “FB4” regimen, where busulfan is given over 4 days, is 12.8 mg/kg IV. In our study, patients in the high dose arm received a median busulfan dose of 10.8 mg/kg IV, which is about 15% lower than the full myeloablative dose. Although this was associated with a higher incidence of early toxicities within the first 100 days; yet, despite a substantial increase in the dose, there was no increase in NRM (10% at 3 year) as compared to the low dose RIC group (20% at 3 year). The NRM seen with our high dose regimen is substantially lower than what is reported with MAC regimens[1–3,26] and comparable to that of other RIC regimens.[8,9,11,13–15] [Table S5] More importantly, the high dose regimen showed considerably improved efficacy than the low dose regimen, and resulted in about 20% absolute reduction in the risk of relapse at 3 years (53% vs 32%, respectively) and more than doubled the EFS (58% vs 27%, respectively at 3 years). Similarly, in the multivariate analysis, high dose busulfan was not a predictor of NRM, but was associated with a 57% lower risk of relapse than the low dose busulfan, albeit with a borderline statistical significance. However, this analysis may have been limited as the study was not primarily designed or powered to compare the two regimens.

Our results compare favorably to two other prospective trials that were reported since the initiation of our trial[8,9] and several retrospective studies [7–15,27–29] that assessed the role of MAC or RIC regimens in patients with myelofibrosis [Table S5]. One of the largest retrospective studies (n=233) that included a variety of RIC regimens showed an OS of 47% and a NRM of 24% at 5 years.[13] In a prospective trial that used fludarabine and melphalan (Flu-Mel) RIC regimen, outcomes were influenced by the donor type.[9] With a median follow-up of 25 months, the matched sibling donor group had superior OS (75% vs 32%) and lower NRM (22% vs 59%) than the MUD group, respectively.[9] Another prospective trial that used Bu-Flu RIC regimen showed 5-year OS of 67% and 1 year NRM rate of 16%.[8] Similar to our study, this study found no difference in the outcomes of patients with related or unrelated donor. Busulfan in this study was given orally at 10 mg/kg (or equivalent IV) over 3 days without therapeutic drug monitoring.[8] Other regimens containing thiotepa have also shown promising efficacy.[30,31]

Pharmacokinetic monitoring of busulfan is critical as it allows standardization of the systemic exposure of the drug across the study population, and reduces regimen-related toxicity, as shown by us and others in patients with various hematologic malignancies.[1,27,32,33] This may explain why we did not see an increase in NRM with the high dose busulfan and yet achieved a lower risk of relapse than with the low dose busulfan.

In contrast to some other studies,[34,35] our study showed DIPSS-plus score to be an independent prognostic factor for both OS and EFS. The OS was significantly higher for patients with DIPSS-plus intermediate-risk (89% at 3-years; median not reached) than that in the high risk patients (39% at 3-years, median 18 months). Clearly, further work is needed to improve the outcomes of high risk patients, but in light of excellent outcomes seen in intermediate risk disease, HCT should be offered earlier in the natural history of the disease.

We acknowledge limitations of our study. First, the study was not designed to compare the two busulfan groups as the change of busulfan dose was unplanned, and the comparison was statistically limited by small number of patients and events in the low dose group. Nevertheless, the differences noted are clinically meaningful and are worthy of reporting, and merit further investigation. Next, how our results compare against pharmacokinetic-guided low dose busulfan, or other regimens is a matter of further investigation. One study compared Bu-Flu to Flu-Mel RIC regimens and noted higher risk of relapse with Bu-Flu (36% vs 4%) but lower NRM (32% vs 44%) than the Flu-Mel regimen, and similar OS (59% vs 52%).[11] Of note, the busulfan dose in that study was lower than what our high dose group received, and therapeutic drug monitoring was not performed. If there is a positive dose-response effect to reduce relapse risk as noted in our study, whether busulfan dose can be escalated further to target an AUC 5000 μmol.min daily requires additional evaluation. Also, because of the rarity of the study population, we included 5 patients in our analysis who were not enrolled on the trial due to insurance reasons, but were treated in a similar fashion and during the same time frame as the trial patients. Yet, separate analyses by including or excluding non-trial patients yielded similar findings. Although the role of alternative donor and graft sources has been assessed in other studies,[36] our study included PB as a predominant graft source from mostly HLA-matched related or unrelated donors. Next, our study was not designed to address quality of life assessment after transplantation, which has

been investigated by others.[37] Lastly, patients in our study were enrolled prior to the significance of mutations other than JAK2,[35] such as CALR, MPL, ASXL1 and SRSF2 was known, and thus, we could not assess the impact of these mutations and the myelofibrosis transplant score (MTSS)[38] on HCT outcomes.

To conclude, our prospective phase II trial with a long term follow-up of over 5-years confirms that HCT is a potentially curative option for patients with intermediate or high risk myelofibrosis. Even though the optimal regimen in patients with myelofibrosis is undefined, Bu-Flu conditioning in our study was very well tolerated and led to encouraging outcomes. For patients receiving Bu-Flu conditioning, our data support the use of high dose busulfan, especially with pharmacokinetic dose monitoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Myeloablative PK-guided IV busulfan is safe in older myelofibrosis patients
- It reduced relapse without increasing NRM even in older patients
- Intermediate 2 DIPSS-plus risk has better outcomes than high risk disease

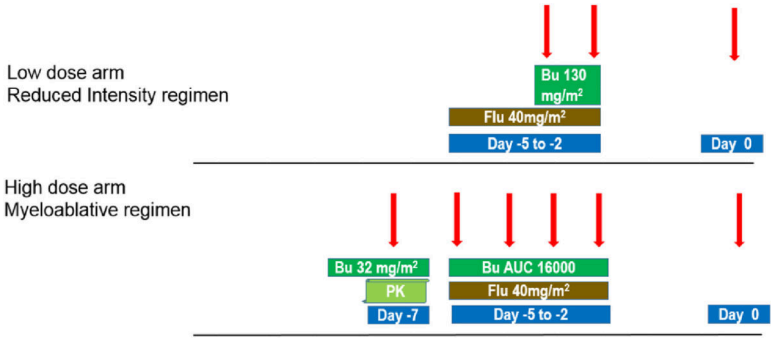

Figure 1: Study schema.

Abbreviations: Bu, busulfan; Flu, fludarabine, PK, pharmacokinetic analysis; AUC, area under the plasma drug concentration-time curve.

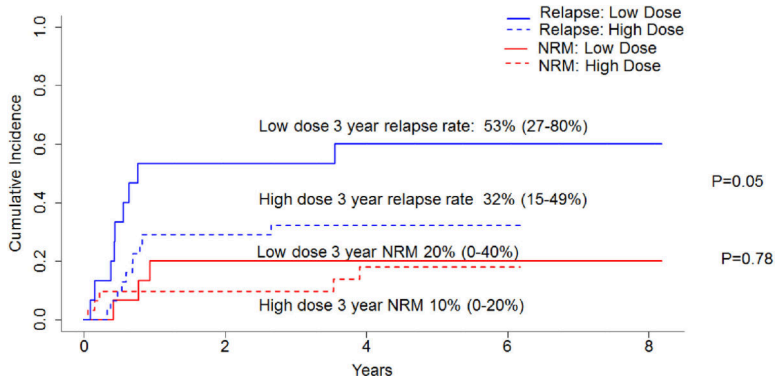

Figure 2:

Relapse and Non-relapse mortality (NRM) by busulfan dose.

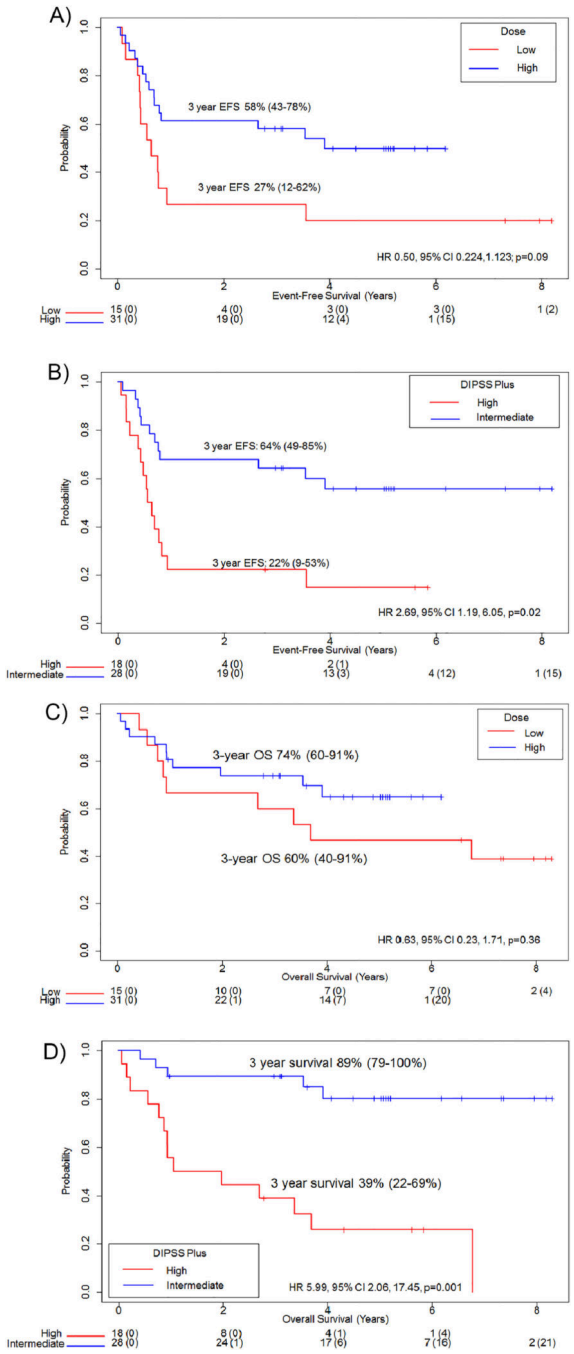

Figure 3:

Event-free survival (EFS) and overall survival (OS) by busulfan dose and DIPSS-plus score. EFS by (A) busulfan dose and (B) DIPSS-plus score, and OS by (C) busulfan dose and (D) DIPSS-plus score.

Table 1:

Baseline Characteristics

	All patients		Low dose Busulfan		High dose Busulfan		P value
	N=46	%, Range	N=15	%, Range	N=31	%, Range	
Gender: female	23	50	7	46.7	16	51.6	1.0
Median age at transplantation (years)	58	27–74	58	27–65	59	31–74	1.0
Age>/=60 years	17	37	4	26.7	13	41.9	0.35
Secondary myelofibrosis	18	39.1	8	53.3	10	32.3	0.20
Lille risk							1
Intermediate	24	52.1	8	53.3	16	51.6	
High	22	47.8	7	46.7	15	48.4	
DIPSS-plus risk							0.27
Intermediate-1	1	2.2	0	0	1	3.2	
Intermediate-2	27	58.7	7	46.7	20	64.5	
High	18	39.1	8	53.3	10	32.3	
JAK2 mutation present *	26	59.1	8	57.1	18	60.0	1.0
Graft source							1.0
Bone marrow	5	10.9	2	13.3	3	9.7	
Peripheral blood	41	89.1	13	86.7	28	90.3	
Donor type							0.191
Matched related	19	41.3	4	26.7	15	48.4	
Matched unrelated	23	50	8	53.3	15	48.4	
Mismatched unrelated	4	8.7	3	20	1	3.2	
Median duration from diagnosis to transplant (months)	23	2–392	23	5–235	23	2–392	1.0
HCT-CI							0.74
< 3	31	67.4%	11	73.3%	20	64.5%	
>= 3	15	32.6%	4	26.7%	11	35.5%	

* 2 missing; result not available

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; HCT-CI, hematopoietic cell transplantation comorbidity index; JAK2, Janus Kinase 2

Table 2.

Transplantation outcomes

	All patients (95% CI)	Low dose Busulfan (95% CI)	High dose Busulfan (95% CI)	P value *
Non-relapse mortality, cumulative incidence				
Day 100	6.5% (0–13.7%)	0% (0–0%)	9.7% (0–20.3%)	0.84
1 year	13% (3.2–22.9%)	20% (0–41.9%)	9.7% (0–20.3%)	
3 years	13% (3.2–22.9%)	20% (0–41.9%)	9.7% (0–20.3%)	
Relapse, cumulative incidence				
1 year	37% (22.8–51.1%)	53.3% (26.6–80.1%)	29% (12.7–45.4%)	0.05
3 years	39.1% (24.8–53.4%)	53.3% (26.6%–80.1%)	32.3% (15.4–49.1%)	
Acute GVHD at 100 day, cumulative incidence				
grade 2–4	22.3% (10–34.7%)	13.3% (0–31.3%)	26.7% (10.5–42.9%)	0.27
grade 3–4	6.8% (0–14.4%)	6.7% (0–19.8%)	6.9% (0–16.3%)	0.99
Chronic GVHD at 3 years, cumulative incidence				
Overall	40.2% (25–55.4%)	26.7% (2.8–50.5%)	46.4% (27.2–65.5%)	0.36
extensive	31% (16.6–45.3%)	20% (0–41.7%)	35.6% (17.3–54.0%)	0.37
3-year event free survival	48% (3565%)	27% (1262%)	58% (4378%)	0.03
3-year overall survival	69% (5784%)	60% (4091%)	74% (6091%)	0.25

* Note: p-values represent comparisons over entire curve over time, not at specific time points

Abbreviations: GVHD, graft versus host disease

Table 3

Multivariate Regression Models

		NRM		**Relapse**		**EFS**		**OS**	
Parameter	Level	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	Continuous, per year	1.101 (.975–1.243)	.12	1.006 (.956–1.059)	.83	1.047 (.995–1.100)	.08	1.079(1.008–1.155)	.03
Busulfan dose	Low	Ref	.70	Ref	.07	Ref	.09	Ref	.36
	High	.712 (.126–4.015)		.439 (.180–1.071)		.501(224–1.123)		.626 (.229–1.713)	
DIPSS-plus	Intermediate	Ref	.30	Ref	.21	Ref	.02	Ref	.001
	High	2.117 (.515–8.708)		1.756(730–4.220)	2.688(1.195–6.045)			5.993 (2.059–17.45)	
HCT-CI	<3	Ref							
	≥3	2.491 (.608–10.20)	.20						