

Post-Transplant Cyclophosphamide in HLA Matched and Haploidentical Transplant Recipients Receiving Myeloablative Fractionated Busulfan Conditioning Regimen: Results of a Phase II study

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Background

Fractionated busulfan/fludarabine (Bu-Flu) myeloablative conditioning yields low non-relapse mortality (NRM) in older patients and those with comorbidities, after matched sibling (MSD) or unrelated (MUD) donor transplant (HCT). [Popat *et al*, *Lancet Haematology* 2018].

Whether this regimen could be used safely with post-transplant cyclophosphamide (PTCy) and in the haploidentical setting is unknown.

Design & Objectives

Open-label, non-randomized, phase II trial

Age 12-75 yrs; any hematologic malignancy; HLA-matched (MUD or MSD) or haploidentical donor

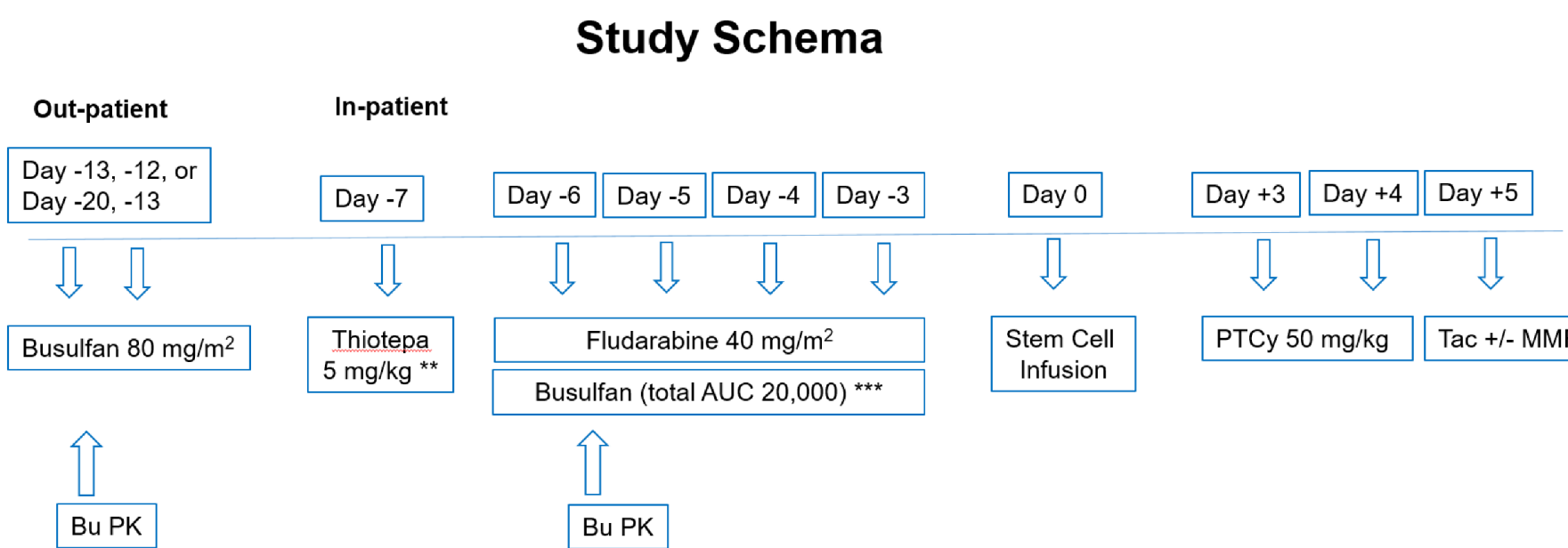
Exclusion: Prior allo HCT, CAD, HIV, active infection and prior inotuzumab or gemtuzumab

Objectives:

Primary: Day 100 NRM and grade >3 adverse events (AE).

Secondary: engraftment, GVHD, relapse, PFS, OS, & GFRS.

Post-hoc **exploratory analyses:** outcomes by donor type (matched vs haploidentical).



Baseline Characteristics

Characteristic		Characteristic	
No. of patients	55	No. of patients	55
Age, median (range), (IQR)	47 (15-65), (40-57)	Graft source	
Age group, n (%)		PBPC	33 (60)
< 50 years	30 (54.5)	BM	22 (40)
≥ 50 years	25 (45.5)	GVHD prophylaxis	
Sex, n (%)		PTCy + Tacrolimus	25 (45.5)
Male	34 (61.8)	PTCy + Tacrolimus+ MMF *	30 (54.5)
Female	21 (38.2)	DRI	
Race, n (%)		Low	5 (9.1)
Whites	32 (58.2)	Intermediate	36 (65.5)
Blacks	8 (14.6)	High	14 (25.4)
Other	15 (27.2)	HCT-CI	
Diagnosis, n (%)		0-2	33 (60)
AML/MDS	30 (54.5)	≥ 3	22 (40)
CML/MPD	9 (16.4)	KPS	
ALL	6 (10.9)	<90	26 (47.3)
Multiple Myeloma	5 (9.1)	90-100	29 (52.7)
Lymphoma	5 (9.1)	Follow-up in months; median (range)	37.6 (25.3-47.8)
Donor			
Haploidentical	26 (47.3)		
MUD	18 (32.7)		
MSD	11 (20)		

Safety Outcomes

Day 100 NRM was 16.4% (95% CI 6.5-26.3%)

47 patients (87%) had at least one grade ≥3 AE

Most common AE: culture-negative grade 3 neutropenic fever (n=32) at a median of 3 days post-HCT (IQR 2-4.5).

Thirty infection events occurred, mostly bacterial (n=15) or viral (n=14)

Overall 21 deaths –relapse (8), acute GVHD (4), infections (6- 2 bacterial, 3 viral, and 1 protozoal), DAH (1), SOS (1) and unidentified cause (1)

Engraftment and GVHD

No graft failure. The median time to neutrophil engraftment was 17 days (range, 13-39).

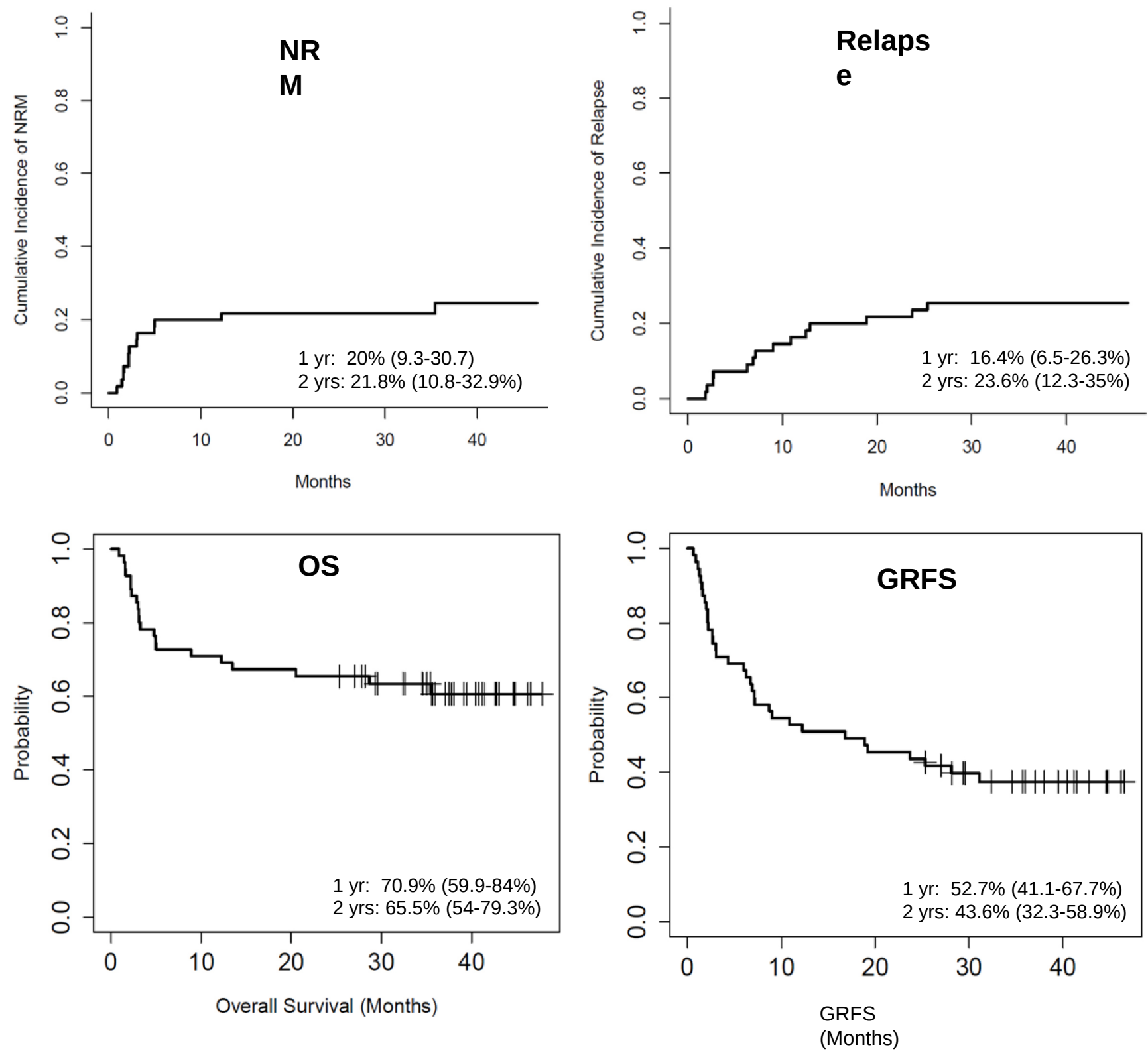
The median time to platelet engraftment (≥ 20K/μL, n=49) was 25 days (range, 11-167) and platelets (≥ 50K/μL, n=42) was 32 days (range, 15-296).

Chimerism: day 30, day 100, 6 months and 1-year post HCT: median donor 100% myeloid and 100% T cells

Day 100 grade II-IV acute GVHD: 38.2% (95% CI 25.2-51.2%) & grade III-IV acute GVHD: 9.1% (95% CI 1.4-16.8%).

Chronic GVHD (all extensive): 10.9% (95% CI 2.5-19.3%) at 2 years.

Other Outcomes



Outcomes by donor

	Haploidentical	HLA-matched
OS		
1 year	61.5% (45.4-83.4%)	79.3% (65.9-95.5%)
2 year	53.8% (37.7-76.9%)	75.9% (61.8-93.2%)
NRM		
1 year	30.8% (12.6-48.9%)	10.3% (0-21.7%)
2 year	34.6% (15.9%-53.4%)	10.3% (0-21.7%)
Relapse		
1 year	11.5% (0-24.2%)	20.7% (5.6-35.7%)
2 year	19.2% (3.6-34.9%)	27.6% (10.9-44.2%)
GRFS		
1 year	46.2% (30.5-69.9%)	58.6% (43.2-79.6%)
2 year	38.5% (23.7-62.5%)	48.3% (33.1-70.4%)

Conclusion

The fractionated myeloablative Bu-Flu conditioning regimen with PTCy is well-tolerated and leads to a low risk of acute and chronic GVHD, NRM and encouraging survival in patients with HLA-matched or haploidentical donors.

This myeloablative regimen is an option for patient undergoing haploidentical transplant and results are promising.

Modifications of the fractionated Bu-Flu regimen to further enhance its efficacy, such as with the addition of other chemotherapy/targeted therapies, and further lengthening the conditioning regimen over 3 weeks period are ongoing