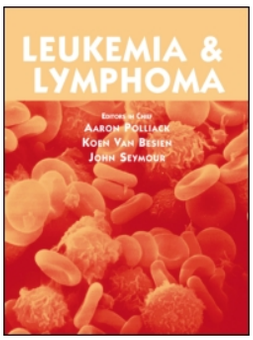

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COMMENTARY

Busulfan or melphalan: is there a better conditioning regimen for allogeneneic transplantation?

Jingmei Hsu[a], Koen Van Besien[a] and Frédéric Baron[b]

[a]Weill Cornell Medical Center/New York Presbyterian Hospital, Department of Medicine, Division of Hematology/Oncology, New York, NY, USA; [b]Laboratory of Hematology, University of Liege and CHU of Liège, Liège, Belgium

Conditioning regimens for allogeneic transplantation were initially thought to have two essential properties, namely immunosuppression and the creation of 'space', the so-called myeloablative properties which depended on high 'myeloablative' doses of busulfan or on total body irradiation. However, further studies and observations in the 1990s showed that engraftment could also be achieved without 'myeloablation' leading to the era of non-myeloablative transplants or reduced intensity conditioning (RIC) and many new conditioning regimens were created. Practically all of these included fludarabine or related nucleoside analogs, usually either melphalan, lower doses of busulfan, lower dose of total body irradiation or different combinations of these approaches. The distinction between myeloablative conditioning (MAC) and RIC and the definitions of RIC and MAC were then clearly defined and established in an empiric *post-hoc* fashion [1].

In 2017 after years of single institution studies and retrospective comparisons, Scott et al. in the phase III randomized BMT CTN 0901 trial, compared MAC and RIC for fit patients with acute myeloid leukemia and myelodysplasia (AML/MDS) [2]. Relapse was significantly higher in the RIC arm and MAC patients had a better relapse free survival (RFS), with a trend toward improved overall survival (OS) at 18 months. This was particularly true for patients with AML, but several RIC (fludarabine/busulfan (Flu/Bu) and fludarabine/melphalan (Flu/Mel)) and MAC (fludarabine/busulfan, busulfan/cyclophosphamide or cyclophosphamide/Total body irradiation) regimens were included in this prospective study. Whether the same conclusion holds true for each individual RIC or MAC regimen is still unclear (Table 1). Further examination of individual regimens and their dosing strength should provide more important information on the impact of these conditioning regimens on allogeneic stem cell transplant (alloSCT) clinical outcomes.

In this issue of *Leukemia and Lymphoma*, DiMaggio et al. compared RIC Flu/Mel with both MAC and RIC flu/bu (MAC Flu/Bu was defined as an area under the concentration curve target (AUC) 5300uM*L/min vs RIC busulfan with a target level of AUC 3500uM*L/min) for patients with AML/MDS treated with allo SCT from HLA-matched related or unrelated donors [3]. After a median follow-up of 3 years for all surviving patients, they showed that both RIC and MAC Flu/Bu regimens had a higher relapse rate compared to Flu/Mel, particularly in patients transplanted with active disease. Among patients transplanted in remission, relapse incidence was similar for patients receiving MAC flu/bu, but the relapse rate or RIC Flu/Bu was considerably higher.

DiMaggio's paper is one of a growing number of reports showing that Flu/Mel has superior antileukemic effects, compared to RIC Flu/Bu and is similar to MAC regimens. Kawamura et al. also compared Flu/Mel with RIC and MAC Flu/Bu in 1607 Japanese patients older than 50 years [4]. Relapse rates were lower for Flu/Mel than for either RIC or MAC Flu/Bu, and high-risk AML patients had a significant survival advantage with Flu/Mel. Eapen et al. [5] in a large retrospective study for CIBMTR and Baron et al. [6] for EBMT also found that Flu/Mel had similar outcomes to MAC regimens and a lower rate of disease recurrence than RIC Flu/Bu. Several other recent comparative studies also support the notion that Flu/Mel has a lower relapse rate and assures better disease control

CONTACT Jingmei Hsu jih9026@med.cornell.edu Starr Pavilion 520 East 70th Street 3rd Floor, New York, 10021, NY, USA
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Table 1. Studies Comparing MAC and RIC regimens in patients with AML/MDS.

Study	Disease	Donor	GVHD PPX		Patient # Age (range)	Conditioning Regimen*	NRM (%) Month	Relapse (%) Month	RFS/PFS (%) Month	OS (%) Month	GVHD	Conclusion
DiMaggio et al. [3] Retrospect 2020	AML MDS	MRD MUD	TAC/SIR TAC/MTX Others	MAC	*N* = 256 56yr (40-74)	$Flu_{30\text{-}40mg/m^2}$/ $Bu_{5300\ \mu M*L/min}$ (Flu/Bu)	24m 21%	24m 33%	24m 47%	24m 53%	D100 aGVHD 62% 24m cGVHD 65%	MAC and RIC regimens have comparable OS and RFS; Flu/Mel has lower relapse rate
				RIC	*N* = 150 66yr (41-76)	$Flu_{30\text{-}40mg/m^2}$/ $Bu_{3500\ \mu M*L/min}$ (Flu/Bu) $Flu_{30\text{-}40mg/m^2}$/Mel $140_{mg/m^2}$ (Flu/Mel)	24m Flu/Bu 21% Flu/Mel 32%	24m Flu/Bu 44% Flu/Mel 19%	24m Flu/Bu 37% Flu/Mel 47%	24m Flu/Bu 45% Flu/Mel 57%	D100 aGVHD Flu/Bu 57% Flu/Mel 56% 24m cGVHD Flu/Bu 65% Flu/Mel 56%	
Alatrash et al. [20] Retrospect 2019	AML MDS	MRD MUD	TAC/MTX/ATG	MAC	*N* = 56 53yr (NR)	$Flu_{120\text{-}180mg/m^2}$/ $Bu_{5\text{-}6000\mu M\ min}$ (Flu/Bu)	NR	NR	24m ~59%	24m ~62%	D100 aGVHD 45% ≥D100 cGVHD 54%	MAC and RIC Flu/Bu regimens have comparable NRM, relapse rate, PFS and OS
				RIC	*N* = 56 57yr (NR)	$Flu_{120\text{-}180mg/m^2}$/ $Bu_{4000\mu M\ min}$ (Flu/Bu)	NR	NR	24m ~50%	24m ~57%	D100 aGVHD 57% ≥D100 cGVHD 30%	
Eapen [5] Retrospect 2018	AML MDS	MRD MUD MMUD	TAC/MMF TAC/MTX CSA/MMF ATG	MAC	*N* = 1271 54yr (18- >60)	$Flu_{\ 120–180\,mg/m^2}$/ $Bu_{16\text{-}18\,mg\ PO;\ 10\text{-}13\,mg/kg\ IV}$ (Flu/Bu4 ± ATG) 59% $Bu_{16\text{-}18\,mg\ PO;\ 10\text{-}13\,mg/kg\ IV}$/ $Cy_{\ 120\,mg/kg}$ (Bu/Cy) 41%	36m Bu/Cy 27% Flu/Bu 27% Flu/Bu/ATG 23%	36m Bu/Cy 32% Flu/Bu 32% Flu/Bu/ATG 41%	36m Bu/Cy 44% Flu/Bu 44% Flu/Bu/ATG 38%	36m Bu/Cy 51% Flu/Bu 48% Flu/Bu/ATG 42%	D180 aGVHD GIII/IV Bu/Cy 21% Flu/Bu 19% Flu/Bu/ATG 15% 24m cGVHD Bu/Cy 62% Flu/Bu 60% Flu/Bu/AGT 42%	RIC Flu/Mel ± ATG and MAC Flu/Bu4 and Bu/Cy regimens have comparable RFS
				RIC	*N* = 938 63yr (18->60)	$Flu/Mel_{100\ -140\,mg\ /m2\ IV}$ (Flu/Mel ± ATG) 29% $Flu/Bu_{5\text{-}8\,mg/kg\ PO;\ 4\text{-}7\,mg/kg\ IV}$ (Flu/Bu2 ± ATG) 71%	36m Flu/Mel 27% Flu/Mel/ATG 27% Flu/Bu 18% Flu/Bu/AGT 18%	36m Flu/Mel 22% Flu/Mel/ATG 28% Flu/Bu 46% Flu/Bu/ATG 56%	36m Flu/Mel 52% Flu/Mel/ATG 44% Flu/Bu 38% Flu/Bu/ATG 31%	36m Flu/Mel 57% Flu/Mel/ATG 46% Flu/Bu 47% Flu/Bu/ATG 41%	D180 aGVHD GIII/IV Flu/Mel 19% Flu/Mel/ATG 26% Flu/Bu 16% Flu/Bu/ATG 14% 24m cGVHD Flu/Mel 56% Flu/Mel/ATG31% Flu/Bu 52% Flu/Bu/ATG 44%	RFS with Flu/Mel was superior to RFS with Flu/Bu2 ± ATG because of lower relapse rates

(*continued*)

Table 1. Continued.

Study	Disease	Donor	GVHD PPX		Patient # Age (range)	Conditioning Regimen*	NRM (%) Month	Relapse (%) Month	RFS/PFS (%) Month	OS (%) Month	GVHD	Conclusion
Kröger [21]	MDS	MRD	CSP/MTX	MAC	$N = 64$	$Bu_{16\ mg/kg\ PO;\ 12.8mg/kg\ IV}$/	12m	24m	24m	24m	D100	MAC Bu/Cy and RIC Flu/Bu
Phase III	sAML	MUD	ATG		50yr	$Cy_{120\ mg/kg}$ (Bu/Cy)	17%	17%	62%	76%	aGVHD 38%	regimens have comparable
2017		MMUD			(19-64)						24m	NRM, relapse rate, RFS
											cGVHD 65%	and OS
				RIC	$N = 65$	$Flu_{150\ mg/m2/}$	12m	24m	24m	24m	D100	
					51yr	$Bu_{8mg/\ kg\ PO;\ 6.4\ mg/kg\ IV}$	25%	15%	58%	63%	aGVHD 32%	
					(22-63)	(Flu/Bu)					24m	
											cGVHD 62%	
Dhere [11]	AML	MRD	TAC/MTX	MAC	$N = 73$	$Bu_{14.4\ mg/kg\ IV;\ 16mg/\ kg}$/	24m	24m	24m	24m	D100	MAC Bu/Cy and RIC Flu/Mel
Retrospect		MUD	ATG		39yr	$Cy_{120\ mg/kg}$ (Bu/Cy)	25%	22%	62%	65%	aGVHD 48%	regimen have comparable
2018					(NR)						cGVHD 48%	relapse rate, RFS and OS.
				RIC	$N = 83$	$Flu_{100\ mg/m^2}/Mel_{140\ mg\ /m^2}$	24m	24m	24m	24m	D100	Bu/Cy had a higher NRM
					59yr	(Flu/Mel)	20%	15%	50%	52%	aGVHD 59%	
					(NR)						cGVHD 49%	
Scott [2]	AML	MRD	TAC/MTX	MAC	$N = 131$	$Flu_{120\text{-}180mg/m^2}/Bu_{\ 12.8\text{-}16mg/kg}$	NR	18m	18m	18m	D100	MAC has superior RFS than RIC
Phase III	MDS	MUD	CSP/MTX		55yr	(Flu/Bu4) 64%		14%	68%	78%	aGVHD 45%	regimens and trend toward
2017			TAC/MMF		(22-66)	$Bu_{12.8\text{-}16mg/kg}/Cy_{120\ mg/kg}$		AML 16%	AML 65%	AML 76%	GIII/IV 14%	better OS
			CSP/MMF			(Bu/Cy) 30%		MDS 4%	MDS 78%	MDS 82%	18m	RIC (mostly Flu/Bu2) have
			SIR/TAC			$Cy_{120\ mg/kg}/TBI_{12-\ 14.2\ Gy}$ (Cy/TBI) 6%					cGVHD 64%	higher relapse and TRM
			ATG	RIC	$N = 132$	$Flu_{\ 120\text{-}180mg/m^2}$/	NR	18m	18m	18m	D100	compared to MAC
					55yr	$Bu_{\leq 8mg/kg}$ (Flu/Bu2) 81%		48%	47%	68%	aGVHD 32%	
					(22-66)	$Flu_{\ 120\text{-}180mg/m^2}$/		AML 51%	AML 45%	AML 63%	GIII/IV 4%	
						$Mel_{\ \leq 150mg/m^2}$ (Flu/Mel) 19%		MDS 37%	MDS 56%	MDS 85%	18m	
											cGVHD 47.6%	
Savani [22]	AML	MMUD	TAC/MMF	MAC	$N = 1041$	$TBI_{\ 10\text{-}15\ Gy}$-based 35%	24m	24m	24m	24m	D100	MAC and RIC regimens have
Retrospect			TAC/MMF ± MTX		43yr	$Bu_{16mg/kg\ po}/Cy_{120\ mg/kg}$	28%	30%	43%	45%	aGVHD 33%	comparable NRM, relapse,
2016					(18-72)	(Bu/Cy) 34%					24m	LFS and OS for patients <
						$Flu/Bu_{>8mg/kg}$ (Flu/Bu4) 14%					cGVHD 29%	50yr
						Flu/Mel 3%						RIC regimens have superior LFS,
						Others 13%						OS and decreased NRM for
				RIC	$N = 883$	TBI-based 31%	24m	24m	24m	24m	D100	patients ≥50yr.
					57yr	Flu/Bu2 35%	27%	33%	40%	45%	aGVHD 32%	
					(18-75)	Flu/Mel 20%					24m	
						Others 13%					cGVHD 34%	
Shimoni [23]	AML	MRD	CSP/MTX	MAC	$N = 701$	$Bu_{\geq 9.6\ mg/kg}/Cy$	120m	120m	120m	120m	120 m	MAC and RIC regimens have
Retrospect			ATG		54yr	$Mel_{>140\ mg/m^2}$	35%	34%	31%	33%	cGVHD 40%	comparable 10- year LFS,
2016			Alemtuzumab		(50-72)	$Treosulfan_{\geq 36g/m^2}$						GRFS and OS.
						$TBI_{\geq 10Gy}$						For patients >55yr, RIC has
				RIC	$N = 722$	$Flu/Bu_{< 9.6\ mg/kg}$	120m	120m	120m	120m	120m	superior LFS
					57yr	$Flu/TBI_{<8Gy}$	20%	48%	32%	35%	cGVHD 43%	MAC regimens have higher 10-
					(50-75)							year NRM and lower relapse

(*continued*)

Table 1. Continued.

Study	Disease	Donor	GVHD PPX		Patient # Age (range)	Conditioning Regimen*	NRM (%) Month	Relapse (%) Month	RFS/PFS (%) Month	OS (%) Month	GVHD	Conclusion
Baron [6] Retrospect 2016	AML	UCB	CSP ± MMF TAC ± MMF CSP/MTX CY-p ATG Others	MAC	*N* = 479 37yr (18-68)	Flu/Cy/TBI 18% Bu/Cy 9% Flu/Bu/Thio 37% TBI-other 17%	24m 19%	24m 23%	24m 40%	24m 46%	D100 aGVHD 26% 24m cGVHD 23%	MAC and RIC regimens have comparable LFS, GRFS and OS. RIC regimens have lower NRM and higher relapse rate
				RIC	*N* = 415 54yr (19-72)	Flu/Cy/$TBI_{<6Gy}$ 74% Flu/Mel 4% $TBI_{<6Gy}$ -other 7% Flu/$Bu_{\leq 8\ mg/kg}$/ Thio 5%	24m 36%	24m 41%	24m 41%	24m 43%	D100 aGVHD 35% 24m cGVHD 23%	
Bornhauser [24] Phase III 2012	AML	MRD MUD	CSP/MTX ATG	MAC	*N* = 90 45yr (18-60)	$Cy_{120\ mg/kg}$ /TBI_{12Gy} (Cy/TBI)	36m 18%	36m 26%	36m 56%	36m 57%	NR	MAC Cy/TBI and RIC Flu/TBI regimens have comparable NRM, relapse rate, LFS and OS. (TBI dose was higher in RIC than other studies)
				RIC	*N* = 94 44yr (18-60)	Flu_{150mg/m^2} /TBI_{8Gy} (Flu/TBI)	36m 13%	36m 28%	36m 58%	36m 61%	NR	
Sebert [25] Retrospect 2015	AML	MRD MUD	CSP/MTX CSP/MMF CSP ± CS ATG	MAC	*N* = 72 44yr (35-56)	$Cy_{120\ mg/kg}$ /TBI_{12Gy} (Cy/TBI) 17% $Bu_{16mg/Kg}$/ $Cy_{120\ mg/kg}$ (Bu/Cy) 69% Bu/Mel 10% Others	48m 28%	48m 33%	NR	48m 43%	47m aGVHD 61% 48m cGVHD 28%	MAC and RIC regimens have Comparable relapse rate and OS. RIC regimens have lower NRM
				RIC	*N* = 60 54yr (37-66)	Flu/Bu 57% Flu/Mel 15% Flu/TBI_{2Gy} 25% Others	48m 13%	48m 44%	NR	48m 50%	47m aGVHD 35% 48m cGVHD 37%	
Martino [26] Retrospect 2006	MDS tAML	MRD	CSP/MTX CSP +/-other ATG Alemtuzumab	MAC	*N* = 621 45yr (18-67)	Cy/$TBI_{\geq 8Gy}$ +Others 44% $Bu_{16\ mg/kg}$ /Cy (Bu/Cy) 34% $Bu_{16\ mg/kg}$ / $Cy_{\ 120\ mg/\ kg}$ +Others (Bu/Cy/ Others) 22%	36m 32%	36m 27%	36m 41%	36m 45%	D100 aGVHD 58% 12m cGVHD 52%	MAC and RIC regimens have comparable LFS and OS. RIC regimens have higher relapse and lower NRM
				RIC	*N* = 215 56yr (27-72)	Flu/TBI_{2-4Gy} (Flu/TBI) 6% Flu /$Bu_{\ 8-10mg/kg}$ (Flu/Bu) 28% Flu/$Mel_{\ 80\ -140mg/m^2}$ (Flu/Mel) 7% Flu/ Others 59%	36m 22%	36m 45%	36m 33%	36m 41%	D100 aGVHD 43% 12m cGVHD 45%	

ATG: Anti-thymocyte globulin; Bu: busulfan; CSP: cyclosporine; CS: corticosteroids; Cy: Cytoxan; Cy-p: post-transplant Cytoxan; Flu: fludarabine; GVHD: graft vs host disease; GRFS: graft vs host disease/relapse-free survival; MAC: myeloablative conditioning; MRD: matched-related donor; Mel: melphalan; MMF: mycophenolate mofetil; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; NR: not reported; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; PPX: prophylaxis; PT: patient; RFS: relapse-free survival; RIC: reduced intensity conditioning; sAML: secondary AML; tAML: therapy related AML; SIR: Sirolimus; TAC: tacrolimus; TBI: total body irradiation; Thio: thiotepa; UCB: umbilical cord blood.

*Doses are only shown when reported by the study. When multiple conditioning regimens were included in the MAC or RIC arms, percentage were shown for significant regimens.

than RIC Flu/Bu, even with survival advantages often apparent in high risk groups [4,5,7–11].

The cost of superior disease control, may however be a higher regimen related non-relapse mortality (NRM) with similar trends observed across studies. Baron et al. [12] for EBMT found higher NRM with Flu/Mel compared to RIC Flu/Bu (HR 1.6, $p = .1$), and Kawamura et al. [4] found a similar trend in AML patients (HR 1.35, $p = .15$) and a significant difference in MDS (HR 2.6, $p = .002$), while DiMaggio et al. [3] also report a non-significant trend (HR 1.4, $p = .2$). Identifying an optimal melphalan dose that allows for disease control and minimizes treatment related mortality will be the key for its wider usage. In this respect, Ciurea et al. [13] recently showed that older patients benefited from reduction of melphalan from 140 mg/m2 to 100 mg/m2 with an improvement in PFS (Flu/Mel 100 vs Flu/Mel 140 HR 1.2, $p = .04$) mainly because of reduction of NRM.

Interestingly for AML patients with detectable MRD prior to HSCT, intensity of the conditioning regimen does appear to play a role. In BMT CTN 0901, all patients were transplanted while in CR and the survival benefit MAC was apparent in those with detectable MRD at transplant. Those with molecular remission had similar outcomes with MAC and RIC [14], but 82% of patients in the RIC arm received RIC Flu/Bu. Whether the same conclusion holds true for patients receiving Flu/Mel for RIC HSCT remains to be seen. The last word has not been written as yet and as we continue to analyze outcomes with established conditioning regimens, innovation continues.

We and others have integrated low dose radiation into RIC regimens, with promising preliminary results [15,16]. MAC busulfan-based regimen over a longer period of 3 weeks for elderly patients appears to have favorable outcomes – with 1 yr OS and relapse rate of 82% and 14% [17] respectively. Treosulfan, a novel alkylator appears to be superior to busulfan [18]. With Apamistamab (α-CD45 ^{131}I) already in phase III trials designed for elderly patients with relapsed/refractory AML [19], other upcoming antibody-based conditioning regimens (α-CD117, α-CD123 *et al*) will undoubtedly play an important role in the future. The integration of modern MRD assessment with these new approaches will guide further development of conditioning regimens.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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