La ciclofosfamide post-trapianto è preferibile rispetto al siero antilinfocitario nella profilassi della GVHD acuta del trapianto da donatore HLA compatibile?

Le ragioni del si.

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Istituto di Ricovero e Cura a Carattere Scientifico

GITMO

ASU FC Azienda sanitaria universitaria Friuli Centrale

UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

CONVEGNO EDUCAZIONALE GITMO

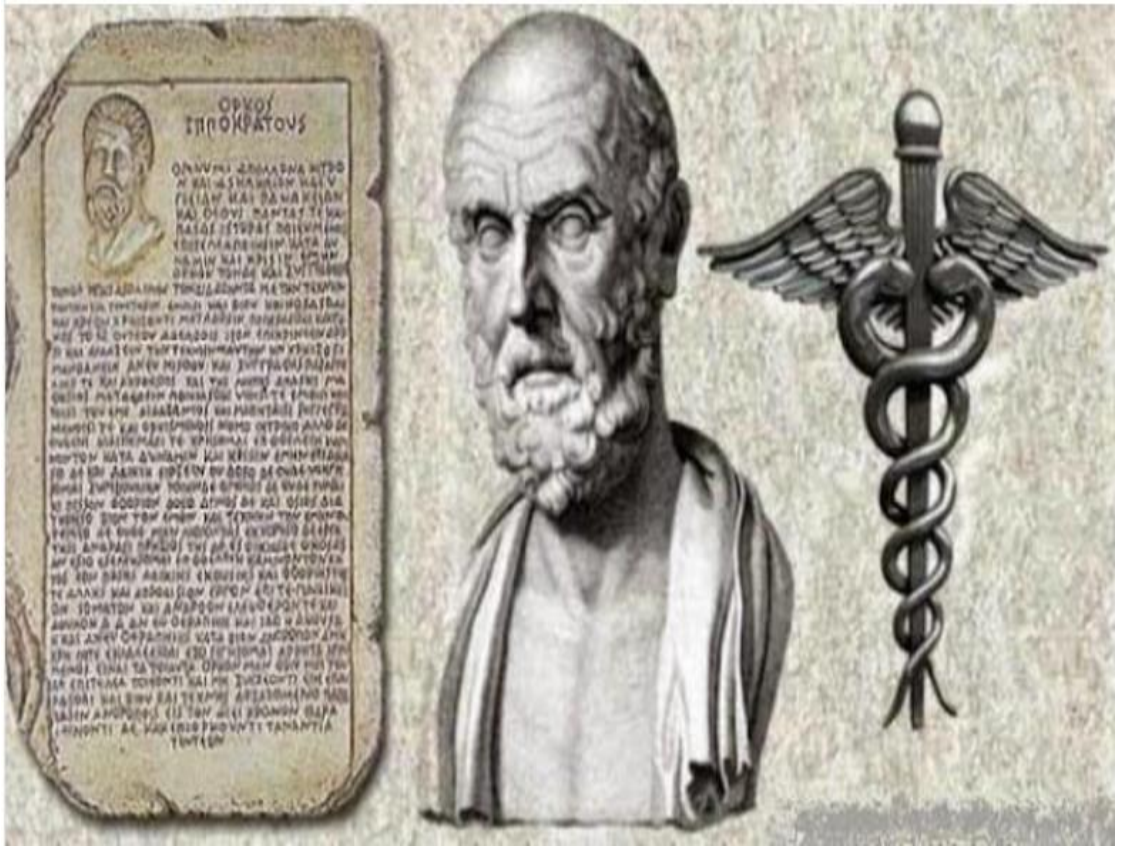
HOT QUESTIONS IN TRASPLANTATION AND CELLULAR THERAPIES

Udine
13-14 novembre 2023
Aula Polifunzionale - Ospedale di Udine

«La ragione e il torto non si dividono mai con un taglio così netto che ogni parte abbia soltanto dell'uno e dell'altra»

«I Promessi Sposi» cap.I

Esistono soltanto due cose: scienza ed opinione; la prima genera conoscenza, la seconda ignoranza.

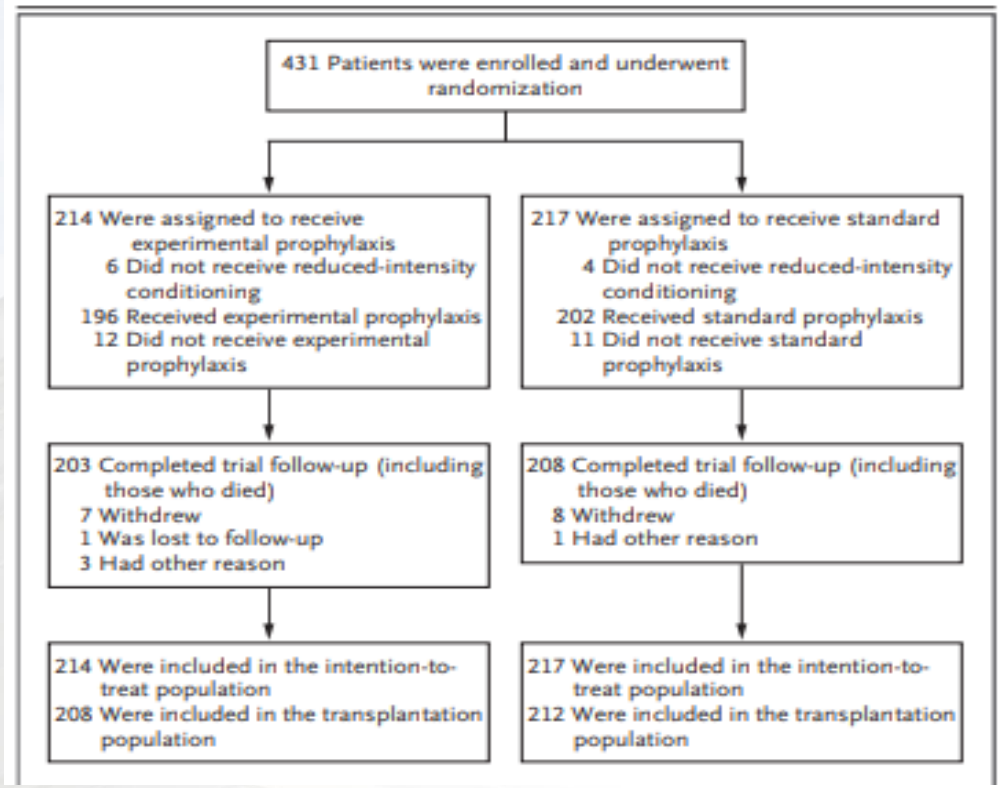


ORIGINAL ARTICLE

Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

J. Bolaños-Meade, M. Hamadani, J. Wu, M.M. Al Malki, M.J. Martens, L. Runaas, H. Elmariah, A.R. Rezvani, M. Gooptu, K.T. Larkin, B.C. Shaffer, N. El Jurdi, A.W. Loren, M. Solh, A.C. Hall, A.M. Alousi, O.H. Jamy, M.-A. Perales, J.M. Yao, K. Applegate, A.S. Bhatt, L.S. Kean, Y.A. Efebera, R. Reshef, W. Clark, N.L. DiFronzo, E. Leifer, M.M. Horowitz, R.J. Jones, and S.G. Holtan, for the BMT CTN 1703 Investigators*

2023



Multicenter phase 3 trial random (1:1)
Cyclophosphamide–tacrolimus–MMF(experimental)

Tacrolimus–methotrexate (standard).
The patients underwent HSCT from an HLA-is sibl.or a MUD or 7/8 misMUD, after RIC.

Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Experimental-Prophylaxis Group (N=214)	Standard-Prophylaxis Group (N=217)	All Patients (N=431)
Male sex — no. (%)	134 (62.6)	126 (58.1)	260 (60.3)
Age			
Mean — yr	64.2±8.5	64.5±8.9	64.3±8.7
≥65 yr — no. (%)	120 (56.1)	125 (57.6)	245 (56.8)
Karnofsky performance-status score ≥90 — no. (%)‡	106 (49.5)	108 (49.8)	214 (49.7)
Primary disease — no. (%)			
Acute lymphoblastic leukemia	12 (5.6)	27 (12.4)	39 (9.0)
Acute myeloid leukemia	107 (50.0)	100 (46.1)	207 (48.0)
Myelodysplastic syndrome	63 (29.4)	65 (30.0)	128 (29.7)
Other§	32 (15.0)	25 (11.5)	57 (13.2)
Donor type and HLA matching — no. (%)			
Related donor 6/6	60 (28.0)	68 (31.3)	128 (29.7)
Unrelated donor 7/8	7 (3.3)	8 (3.7)	15 (3.5)
Unrelated donor 8/8	147 (68.7)	141 (65.0)	288 (66.8)

GRFS: HR 0.64; P=0.001

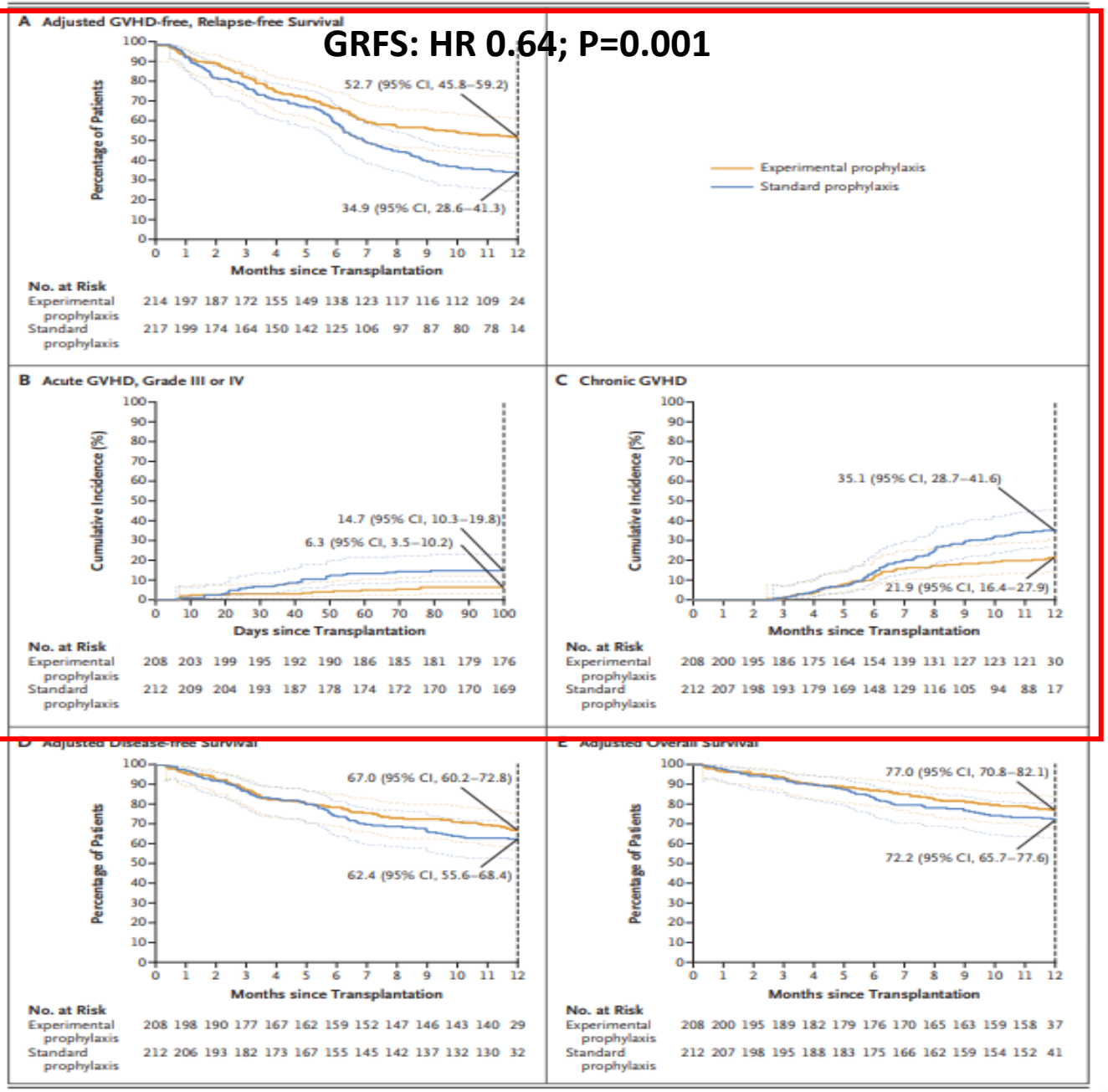


Table 2. Secondary End Points.*

End Point	Experimental-Prophylaxis Group	Standard-Prophylaxis Group
	percent (95% confidence interval)	
Adjusted 1-yr survival		
Overall	77.0 (70.8–82.1)	72.2 (65.7–77.6)
Disease-free	67.0 (60.2–72.8)	62.4 (55.6–68.4)
Cumulative incidence of 1-yr transplantation-related death	12.3 (8.2–17.2)	17.2 (12.4–22.6)
Cumulative incidence of 1-yr relapse and progression	20.8 (15.5–26.7)	20.2 (15.0–25.9)
Cumulative incidence of acute GVHD at day 100†		
Grade II to IV	53.8 (46.7–60.4)	51.9 (44.9–58.4)
Grade III or IV	6.3 (3.5–10.2)	14.7 (10.3–19.8)
Cumulative incidence of chronic GVHD at 1 yr	21.9 (16.4–27.9)	35.1 (28.7–41.6)
Cumulative incidence of neutrophil recovery at day 28	90.3 (85.3–93.6)	93.4 (89.0–96.1)
Cumulative incidence of platelet recovery to >20,000 platelets/microliter at day 100	90.3 (85.3–93.7)	92.8 (88.2–95.6)
Cumulative incidence of infections at 1 yr		
Grade 2 or 3	40.0 (33.2–46.7)	30.4 (24.3–36.7)
Grade 2	33.7 (27.3–40.2)	20.5 (15.3–26.2)
Grade 3	12.2 (8.2–17.1)	13.3 (9.1–18.3)
Cumulative incidence of CMV reactivation at day 100	7.3 (4.3–11.4)	7.1 (4.1–11.1)
Immunosuppression-free survival at 1 yr‡	50 (42.8–57.2)	39.7 (32.9–46.8)

No significative differences in:
relapse
engraftment and hematopoietic recovery
NRM
severe infections
OS

BUT WITHOUT ATG!!

Why ATG??

authors		aGVHD II-IV		aGVHD III -IV		cGVHD mod/ sev		cGVHD		NRM		RELAPSE		DFS		GRFS	
		ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO
Finke 2017 (ATG - F)	Pr MAC 202 PB 164 BM 37	33%	51% p=0.011	11%	24% p=0.054	14%	52% p<0·0001	30%	58% p<0·0001	21%	34% p=0·15	35%	30% p=0·15	44%	36% p=0·15	34%	13% p=0·0003
Kroger 2016 (ATG - F)	Pr HLA id PB MAC AL	10%	18% p=0·15	2%	8% p=0·15	10,8 %	46% p<0.001	32%	68% p<0.001	14%	12% p=0.6	32%	25% p=0·21	59%	64% p=0·21	36%	16% p=0.054
Soiffer 2017 JCO (ATG - F)	Pr MAC MUD 224 AML MDS	23%	40% p=0.004	4%	11% p=0·09	12%	33% p<0.001	16%	38% p<0.001	21%	13% p=0·5	32%	21% p=0·1	47%	65% p=0·04	48%	18% p=0·15
Walker 2020 Lancet oncol (Thymo)	Pr 203MUD MMUD(20%) MAC 70% PB 88%	50% I-IV	37% p=0·012	28%	28% p=1	13%	18% p=0·15	26%	41% p=0·06	21%	31% p=0.16	17%	16% p=0·73			45%	24% p=0·003

Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

Olaf Penack, Monia Marchetti, Tapani Ruutu, Mahmoud Aljurf, Andrea Bacigalupo, Francesca Bonifazi, Fabio Ciceri, Jan Cornelissen, Ram Malladi, Rafael F Duarte, Sebastian Giebel, Hildegard Greinix, Ernst Holler, Anita Lawitschka, Stephan Mielke, Mohamad Mohty, Mutlu Arat, Arnon Nagler, Jakob Passweg, Hélène Schoemans, Gerard Socié, Carlos Solano, Radovan Vrhovac, Robert Zeiser, Nicolaus Kröger, Grzegorz W Basak

Lancet Haematol 2020; 7: e157–67

RECOMMENDATIONS

rATG (Thymoglobulin [Sanofi, Paris, France] or Grafalon [Neovii, St Gallen, Switzerland]) is recommended for preventing GVHD in patients undergoing matched unrelated donor allogeneic stem-cell transplantation†	100	1
rATG can also be recommended for preventing GVHD in patients undergoing MRD allogeneic peripheral blood allogeneic stem-cell transplantation; rATG is recommended for patients who are at a high risk of GVHD	95	2B

Anti-thymocyte globulin as graft-*versus*-host disease prevention in the setting of allogeneic peripheral blood stem cell transplantation: a review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Haematologica 2017
Volume 102(2):224-234

Frédéric Baron,[1] Mohamad Mohty,[2-4] Didier Blaise,[5] Gérard Socié,[6] Myriam Labopin,[2-4] Jordi Esteve,[7] Fabio Ciceri,[8] Sebastian Giebel,[9] Norbert Claude Gorin,[2] Bipin N Savani,[10] Christoph Schmid[11] and Arnon Nagler[12,13]

Name	Type of antibodies	Lympho-depletion *in vivo*	GvHD prevention (total dose administered)
Antithymocyte globulin (ATG)			
ATGAM (ATG-h)	Polyclonal IgG from horses immunized with human thymocytes	+/-	–[28]*
ATG-Thymoglobuline (ATG-T)	Polyclonal IgG from rabbits immunized with human thymocytes	+	+ (2.5-10 mg/kg)
ATG-Fresenius / Neovii (ATG-F)	Polyclonal IgG from rabbits immunized with human Jurkat T leukemia cell line	+	+ (15-60 mg/kg)

Table 4. Proposed indications for immunoregulation with ATG in patients given PBSC from allogeneic donors.

	Recommendation for ATG	Dose and timing of ATG
Myeloablative PBSCT from matched sibling donors[58]	standard of care	ATG-F 10 mg/kg/day on days -3, -2 and -1.
Myeloablative PBSCT from HLA-matchedunrelated donors[56,60,57]	standard of care	ATG-F 20 mg/kg/day on days -3, -2 and -1*. ATG-T 0.5 mg/kg on day -2 and 2 mg/kg on days -1 and +1.
RIC-PBSCT fludarabine-busulfan[61]	recommended	ATG-T 2.5 mg/kg/day on days -2 and -1.
Non-myeloablative PBSCT	developmental	/
HLA-haplo-identical stem cell transplantation (Bejing approach)[58]	standard of care	ATG-T 2.5 mg/kg/day from days -5 to -2.

* some centers use smaller doses such as 15 mg/kg total dose.

Serum weaknesses

1) ATG formulations are not the same: there are not comparative head – to – head study.

	Polverelli et al., 2018, [25], (*n* = 77)		Oostenbrink et al., 2019, [26], (*n* = 58)		Liu et al., 2021, [27], (*n* = 214–Total, *n* = 67–Selected for ATG-T, ATG-G) *		Butera et al., 2021, [29], (*n* = 395)		Wang et al., 2023, [28], (*n* = 186)	
Type of ATG utilised	ATG-T	ATG-G	ATG-T	ATG-G	ATG-T	ATG-G	ATG-T	ATG-T	ATG-G	ATG-T
Number of patients	*n* = 31 (40%)	*n* = 46 (60%)	*n* = 42 (72%) High-dose *n* = 24, Low-dose *n* = 18	*n* = 16 (28%) High-dose *n* = 9 Low-dose *n* = 7	*n* = 44 (66%)	*n* = 23 (34%)	*n* = 197 (50%)	*n* = 198 (50%)	*n* = 107 (58%)	*n* = 79 (42%)
Age (years), median (range)	45 (17–61)	48 (18–66)	9 (1–18)	6 (1–17)	27 (6–50)	26 (3–52)	52.4 (20.7–69.4)	50.4 (20.7–66.8)	25 (3–59)	30 (3–65)
Sex, (%) Male Female	*n* = 23 (74%) *n* = 8 (26%)	*n* = 29 (63%) *n* = 19 (37%)	NR	NR	*n* = 27 (61.36%) *n* = 17 (38.64%)	*n* = 13 (56.52%) *n* = 10 (43.48%)	*n* = 99 (50%) *n* = 98 (50%)	*n* = 117 (59%) *n* = 81 (41%)	*n* = 63 (58.9%) *n* = 44 (41.1%)	*n* = 50 (63.3%) *n* = 29 (36.7%)
Dose of ATG (total, mg/kg)	7.5 mg/kg	30 mg/kg	High-dose 10 mg/kg Low-dose 6–8 mg/kg	High-dose 60 mg/kg Low-dose 45 mg/kg	MRD 12.5 mg/kg Haplo 10 mg/kg	MRD 25 mg/kg Haplo 20 mg/kg	5 mg/kg	6–7.5 mg/kg	20 mg/kg	10 mg/kg
Follow-up (days/months), median (range)	20 (1–88) months	22 (2–60) months	NR	NR	37.65 (0.50–186.78) months	44.34 (3.0–76.15) months	81.5 (50.2–119.3) months	81.5 (50.2–119.3) months	NR	NR
	Polverelli et al., 2018, [25], (*n* = 77)		Oostenbrink et al., 2019, [26], (*n* = 58)		Liu et al., 2021, [27], (*n* = 214–Total, *n* = 67–Selected for ATG-T, ATG-G) *		Butera et al., 2021, [29], (*n* = 395)		Wang et al., 2023, [28], (*n* = 186)	
Diagnosis	Acute leukaemia *n* = 17 (56%) MDS *n* = 1 (3%) MPNs *n* = 1 (3%) Lymphoproliferative neoplasms *n* = 11 (35%) Others *n* = 1 (3%)	Acute leukaemia *n* = 24 (52%) MDS *n* = 7 (15%) MPNs *n* = 2 (5%) Lymphoproliferative neoplasms *n* = 12 (26%) Others *n* = 1 (2%)	ALL *n* = 17 (40%) AML *n* = 25 (60%)	ALL *n* = 16 (100%)	Severe aplastic anaemia	Severe aplastic anaemia	ALL *n* = 23 (11.7%) AML/MDS *n* = 111 (56.3%) MPN *n* = 14 (7.1%) LPD *n* = 49 (24.9%)	ALL *n* = 29 (14.7%) AML/MDS *n* = 88 (44.4%) MPN *n* = 19 (9.6%) LPD *n* = 62 (31.3%)	ALAL *n* = 4 (3.7%) ALL *n* = 29 (27.1%) AML *n* = 42 (39.3%) CLL *n* = 1 (0.9%) CML *n* = 23 (21.5%) MDS *n* = 7 (6.5%) NHL *n* = 1 (0.9%)	ALAL *n* = 4 (5.1%) ALL *n* = 16 (20.3%) AML *n* = 43 (54.4%) CLL *n* = 0 (0%) CML *n* = 6 (7.6%) MDS *n* = 6 (7.6%) NHL *n* = 4 (5.1%)
Conditioning regimen	MAC *n* = 16 (52%) RIC *n* = 15 (48%)	MAC *n* = 22 (48%) RIC *n* = 24 (52%)	NR	NR	FLU + CY [5] *n* = 15 (34.01%) BU + CY [5] *n* = 29 (65.91%)	FLU + CY [5] *n* = 4 (17.39%) BU + CY [5] *n* = 19 (82.61%)	MAC *n* = 154 (78.2%) RIC *n* = 43 (21.8%)	MAC *n* = 107 (54%) RIC *n* = 91 (46%)	TBI/CY [1] *n* = 10 (9.3%) BU/CY [2] *n* = 60 (56.1%) Haplo [3] *n* = 30 (28.0%) FB3 [4] *n* = 6 (5.6%) Other *n* = 1 (0.9%)	TBI/CY [1] *n* = 3 (3.8%) BU/CY [2] *n* = 3 (3.8%) Haplo [3] *n* = 21 (26.6%) FB3 [4] *n* = 6 (7.6%) Other *n* = 0 (0%)
Stem cell source, (%) BM PBSC	BM *n* = 5 (16%) PBSC *n* = 26 (84%)	BM *n* = 5 (11%) PBSC *n* = 41 (89%)	BM *n* = 34 (81%) PBSC *n* = 8 (19%)	BM *n* = 14 (87%) PBSC *n* = 2 (13%)	BM + PBSC *n* = 28 (63.64%) BM *n* = 10 (22.73%) PBSC *n* = 6 (13.64%)	BM + PBSC *n* = 18 (78.26%) BM *n* = 2 (8.7%) PBSC *n* = 3 (13.04%)	BM *n* = 25 (12.7%) PBSC *n* = 172 (87.3%)	BM *n* = 30 (15.15%) PBSC *n* = 168 (84.85%)	NR	NR

ATG Formulation	Type of Antibodies	Recommended Dose for GvHD Prophylaxis (Total, mg/kg)
h-ATG	Polyclonal IgG from horses immunised with human thymocytes	-
ATG-T	Polyclonal IgG from rabbits immunised with human thymocytes	2.5–10
ATG-G	Polyclonal IgG from rabbits immunised with human Jurkat T leukaemia cell line	15–60

"It is important to know that antilymphocyte globulin is produced in rabbits after vaccination with the human Jurkat T-cell line, whereas antithymocyte globulin is produced after vaccination with human thymocytes. Because of the different immunologic properties of these distinct preparations and the lack of reliable comparative studies, the different brands and doses are not interchangeable and our results with antilymphocyte globulin may not be generalizable to antithymocyte globulin".

N. Kröger, C.Solano, F. Bonifazi NEJM 2016

High dose PT Cyclophosphamide as GVHD prophylaxis is a standard (drug, time , doses)

Annals of Hematology

Arcuri et al.

Table 1 Studies with matched-sibling and unrelated donors

Author	Year	Population	Graft	Conditioning	PTCy mg/kg	Other	*N*	aGVHD II-IV	aGVHD III-IV	cGVHD	cGVHD, ext/mod/sev	NRM	OS
Luznik [3] (P)	2022	HLA-matched	BM	MAC	100	-	109	38%	10%	NR	27%	16%	76% @2y
Zu [4] (P)	2022	URD	PBSC	MAC	40	ATG + CSA + MMF	53	25%	8%	14%	8%	13%	79% @2y
Bolaños-Meade [5] (P)	2019	MSD and URD	PBSC	RIC	100	TAC + MMF	92	27%	2%	28%	22%	11%	71% @1y
Kanakry [6] (P)	2014	HLA-matched	BM	MAC	100	-	92	51%	15%	14%	14%	16%	67% @2y
Moiseev [7] (P)	2016	URD	PBSC	MAC and RIC	100	TAC + MMF	86	19%	4%	NR	16%	16%	69% @2y
Gooptu [8] (CIBMTR)	2021	URD	88% PBSC	RIC	100	CSA/TAC + MMF	187	29%	4%	29%	NR	8%	67% @2y
Gooptu [8] (CIBMTR)	2021	URD	88% PBSC	MAC	100	CSA/TAC + MMF	97	32%	4%	25%	NR	15%	77% @1y
Brissot [9] (EBMT)	2020	URD	90% PBSC	MAC and RIC	100	NR	174	29%	9%	31%	19%	15%	63% @2y
Mehta [10] (R)	2022	MSD	99% PBSC	MAC and RIC	100	TAC ± MMF	140	44%	11%	19%	10%	11%	65% @3y
Mehta [10] (R)	2022	URD	77% PBSC	MAC and RIC	100	TAC ± MMF	246	52%	8%	18%	9%	13%	61% @3y
Berro [11] (R)	2020	URD	96% PBSC	80% MAC	100	TAC + MMF	28	25%	4%	NR	4%	25%	61% @2y
Cooper [12] (R)	2020	MSD and URD	94% PBSC	78% MAC	100	TAC + MMF	49	NR	6%	NR	21%	9%	82% @2y
Holtan [13] (P)	2022	MSD and URD	PBSC	RIC	100	TAC + MMF	214	NR	6%	22%	NR	NR	77% @1y
Broers [14] (P)	2022	HLA-matched	PBSC	RIC	100	CSA	99	33%	6%	25%	24%	10%	65% @3y
Brissot [15] (P)	2021	HLA-matched	PBSC	RIC	100	CSA	43	35%	9%	26%	NR	14%	79% @1y
Carnevale-Schianca [16] (P)	2021	HLA-matched	PBSC	NR	100	TAC + MMF	85	6%	NR	7%	7%	4%	82% @1y
Chevallier [17] (P)	2021	MSD and URD	PBSC	RIC	100	-	27	59%	19%	NR	23%	15%	81%@1y
Solomon [18] (P)	2014	HLA-matched	PBSC	RIC	100	SIR	26	46%	15%	31%	NR	4%	71% @2y
Greco [19] (R)	2016	MSD and URD	PBSC	MAC	100	SIR ± MMF	28	23%	4%	13%	4%	14%	64% @2y
Kunacheewa [20]	2020	MSD	PBSC	MAC	100	ATG	21	19%	10%	18%	0%	19%	52% @5y
Spyridonidis [21] (EBMT)	2022	URD	PBSC	MAC and RIC	100	ATG + Others	151	23%	8%	33%	10%	13%	67% @2y
Kwon [22] (R)	2019	MSD	86% PBSC	MAC and RIC	100	CSA + MMF30	57	23%	9%	34%	17%	9%	78% @2y
Shaw [23] (P)	2021	MMUD	BM	RIC	100	TAC + MMF	40	33%	0%	18%	NR	10%	79% @1y
Shaw [23] (P)	2021	MMUD	BM	MAC	100	TAC + MMF	40	43%	18%	36%	NR	8%	72% @1y
Battipaglia [24] (EBMT)	2019	MMUD	91% PBSC	MAC and RIC	NR	NR	93	30%	9%	39%	17%	16%	56% @2y
Jimenez Jimenez [25] (CIBMTR)	2022	MMUD	50% PBSC	MAC and RIC	100	TAC + MMF or SIR + MMF	82	NR	15%	9%	NR	19%	66% @2y
Modi [26] (R)	2021	MMUD	96% PBSC	MAC and RIC	100	TAC + MMF30	25	24%	NR	16%	NR	17%	70% @1y
Mehta [27] (R)	2022	HLA-matched	85% PBSC	MAC and RIC	100	TAC	242	38%	8%	14%	8%	10%	68% @2y
Koura [28] (P)	2021	HLA-matched	NR	MAC and RIC	100	Abatacept	10	NR	0%	NR	0%	NR	NR

2)Delayed immune reconstitution: higher incidence of infectious complications

ATG and infectious complications

authors		aGVHD II-IV		aGVHD III -IV		cGVHD mod/ sev		cGVHD		NRM		RELAPSE		DFS		GRFS	
		ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO	ATG	NO
Finke 2017 (ATG - F)	**Pr MAC 202 PB 164 BM 37**	**33%**	**51%** p=0.011	**11%**	**24%** p=0.054	**14%**	**52%** p<0·0001	**30%**	**58%** p<0·000	**21%**	**34%** p=0·15	**35%**	**30%** p=0·15	**44%**	**36%** p=0·15	**34%**	**13%** p=0·000
	In the ATG-F were more frequent: **HSV** inf. (25·5% vs1 5·8%), **CMV reactivation** OR: 2·22 (95% CI 1·41–3·49; p=0·0006)and **PTLD** (5 vs 1)																
Kroger 2016 (ATG - F)	**Pr HLA id PB MAC AL**	10%	18% p=0·15	2%	8% p=0·15	10,8 %	46% p<0.001	32%	68% p<0.001	14%	12% p=0.6	32%	25% p=0·21	59%	64% p=0·21	36%	16% p=0.054
	The rate of CMV and EBV reactivation and fungal infection was not different.																
Soiffer 2017 JCO (ATLG)	**Pr MAC MUD 224 AML MDS**	23%	40% p=0.004	4%	11% p=0·09	12%	33% p<0.001	16%	38% p<0.001	21%	13% p=0·5	32%	21% p=0·1	47%	65% p=0·04	48%	18% p=0·15
	1y. CI of CMV reactivation was 62 % vs 44% for ATLG and placebo (P=.03).																
Walker 2020 Lancet oncol (Thymo)	**Pr 203MUD MMUD(20%) MAC 70% PB 88%**	50% I-IV	37% p=0·012	28%	28% p=1	13%	18% p=0·15	26%	41% p=0·06	21%	31% p=0.16	17%	16% p=0·73			45%	24% p=0·003
	The incidence of serious infections did not differ between the treatment groups																

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

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[6] Primary Children's Hospital, Salt Lake City, UT, USA.
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[8] University of Kansas Medical Center, Department of Hematology/Oncology, Kansas City, Missouri, USA.
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[10] Vanderbilt University Medical Center, Department of Hematology/Oncology, Nashville, TN, USA.
[11] Texas Transplant Unit, San Antonio, Texas, USA.
[12] Fresenius Biotech, Lexington, MA, USA.
[13] BMT and Leukemia Program, Washington University School of Medicine, St. Louis, Missouri, USA.

Effect of Antihuman T Lymphocyte Globulin on Immune Recovery after Myeloablative Allogeneic Stem Cell Transplantation with Matched Unrelated Donors: Analysis of Immune Reconstitution in a Double-Blind Randomized Controlled Trial

M.Gooptu et al. 24(2018)2216-223

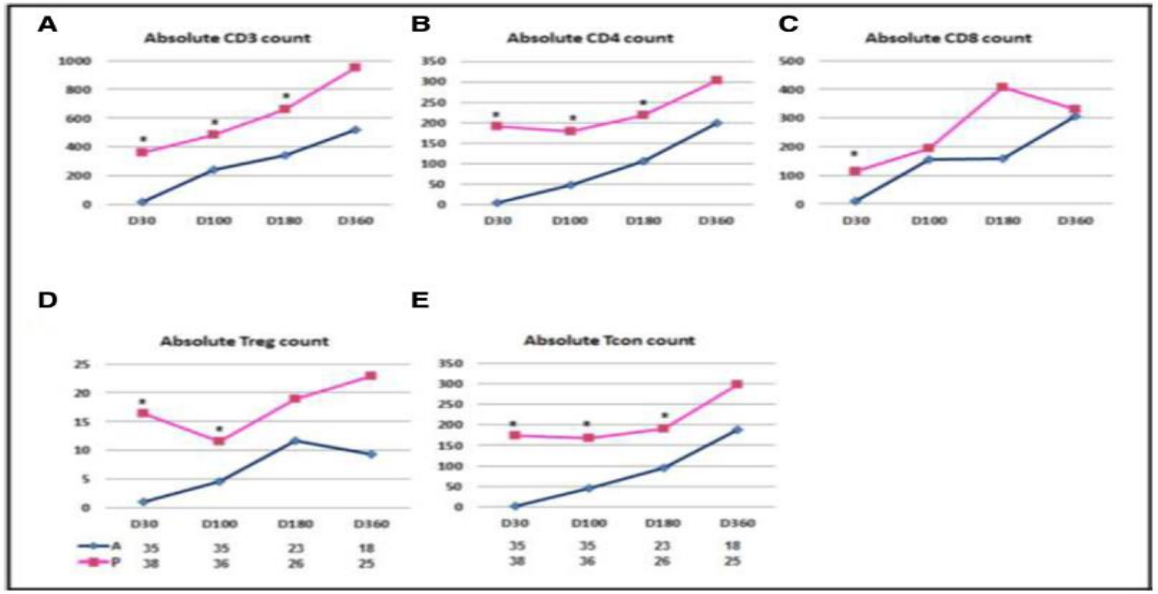

Figure 1. (A) Post-allogeneic transplant reconstitution of major T cell populations ($CD3^+$, $CD4^+$, $CD8^+$ $CD4^+25^+127^-$/Tregs, $CD4^+25\text{-}127^+$/Tconvs) by conditioning regimen at days 30, 100, 180, and 360. The median cell counts/μL for each population is represented at each time point. Significant *P* values are represented by an asterisk at each time point. Absolute $CD3^+$ and $CD4^+$ counts were significantly lower in the ATLG arm at days 30, 100, and 180 but not at day 360 (Figure 1A and 1)B. $CD8^+$ counts were significantly lower in the ATLG arm only at day 30 post-transplant (Figure 1C). Treg counts were significantly lower in the ATLG arm at days 30 and 100 but normalized thereafter (Figure 1D). Tconv counts were significantly lower in the ATLG arm at days 30, 100, and 180 but normalized at 1 year (Figure 1E).

Table 2
Multivariable Cox Regression Models for Clinical Outcomes, Treating Each Phenotypic Parameter as a Time-Dependent Variable (Tregs, Tconv, $CD19^+$ B-lymphocytes)

	aTreg*				aTconv*				aCD19+*			
Event	HR	95% CI		*P*	HR	95% CI		*P*	HR	95% CI		*p*
OS	.28	.11	.74	.0099	.14	.06	.31	<.0001	.59	.36	.96	.035
PFS	.34	.15	.78	.011	.22	.11	.46	<.0001	.83	.52	1.33	.44
NRM	.06	.01	.30	.0008	.01	.00	.10	<.0001	.50	.21	1.19	.12
Relapse	.52	.20	1.35	.18	.48	.22	1.04	.06	1.08	.64	1.86	.78
Moderate/severe GVHD-free survival	.49	.23	1.04	.06	.36	.20	.65	.0007	.70	.46	1.06	.09
cGVHD	1.45	.43	5.39	.56	2.84	.82	10.57	.10	1.21	.63	2.44	.59
Moderate/severe cGVHD	1.41	.39	5.71	.62	2.79	.74	11.35	.13	.95	.48	2.00	.90

All absolute cell counts were $\log_{10}$ transformed (*a) before modeling. HR reflects relative risk for unit change on the $\log_{10}$ scale. Each phenotypic parameter was treated as a time-dependent variable in the models. HR indicates hazard ratio; CI, confidence interval.

Conclusions: ATLG severely compromises the generation of naive CD4+ cells (Treg and Tconv), potentially affecting the diversity of the TCR repertoire and T cell responses against malignancy and infection.

frontiers in Immunology

REVIEW
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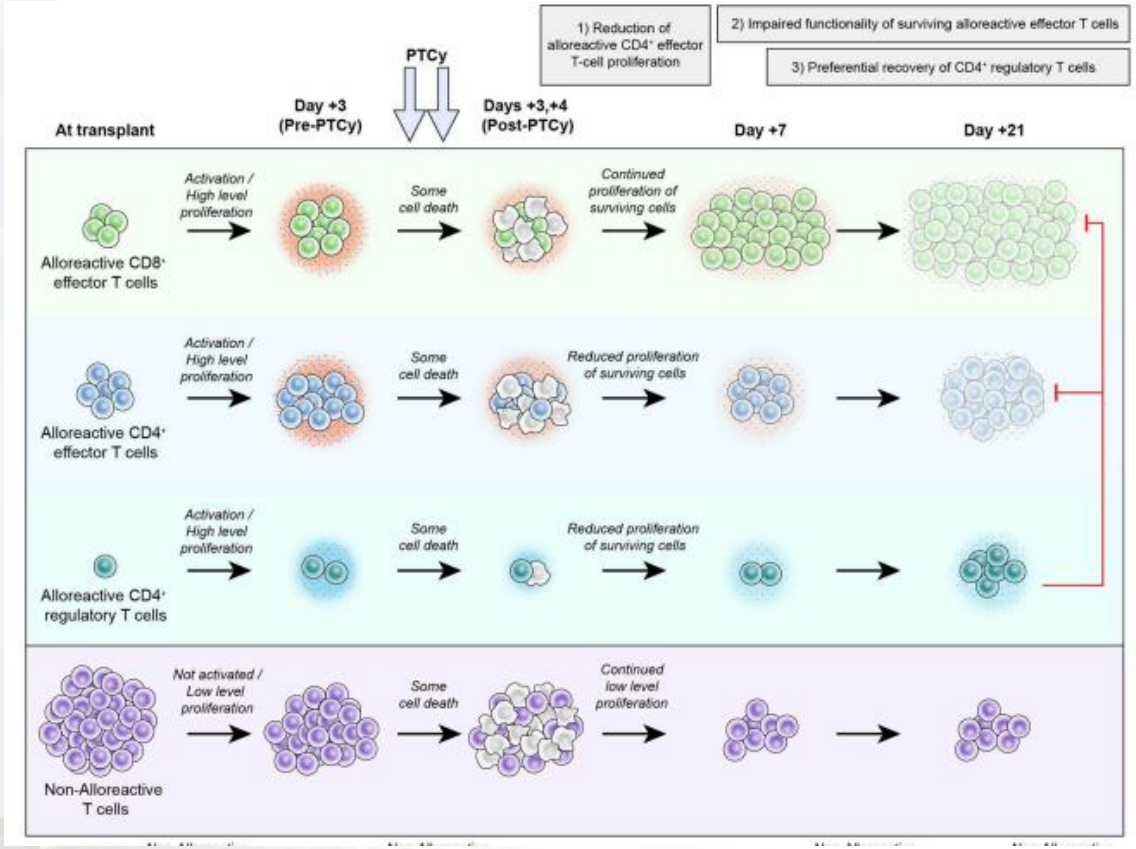
doi: 10.3389/fimmu.2019.02668

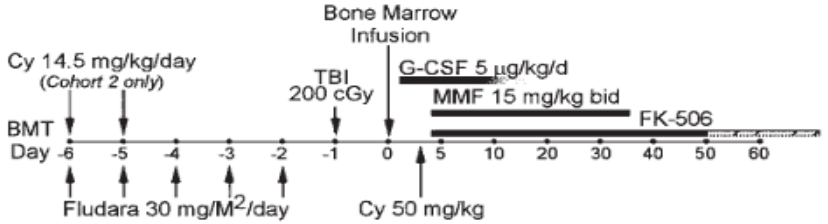
Mechanisms of Graft-versus-Host Disease Prevention by Post-transplantation Cyclophosphamide: An Evolving Understanding

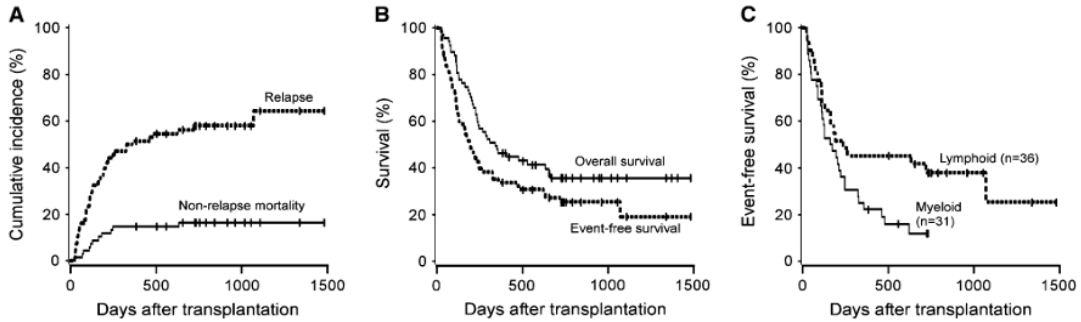
*Natalia S. Nunes and Christopher G. Kanakry**



Nonmyeloablative Bone Marrow Transplantation from Partially HLA-Mismatched Related Donors Using Posttransplantation Cyclophosphamide

P. V. O'Donnell, L. Luznik, R. J. Jones, G. B. Vogelsang, M. S. Leffell, M. Phelps, P. Rhubart, K. Cowan, S. Piantadosi, E. J. Fuchs





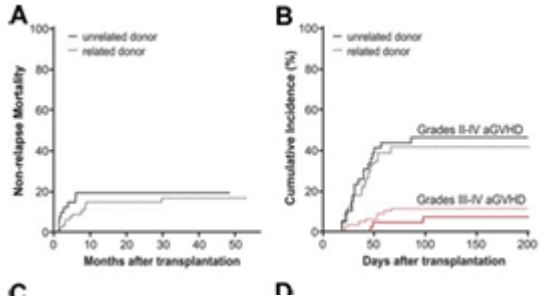
2008

PTCy as GVHD prophylaxis after HLA matched transplant

High-dose cyclophosphamide as single-agent, short-course prophylaxis of graft-versus-host disease

Leo Luznik,[1] Javier Bolaños-Meade,[1] Marianna Zahurak,[2] Allen R. Chen,[3] B. Douglas Smith,[1] Robert Brodsky,[1] Carol Ann Huff,[1] Ivan Borrello,[1] William Matsui,[1] Jonathan D. Powell,[1] Yvette Kasamon,[1] Steven N. Goodman,[2] Allan Hess,[1] Hyam I. Levitsky,[1] Richard F. Ambinder,[1] Richard J. Jones,[1] and Ephraim J. Fuchs[1]

Blood 2010

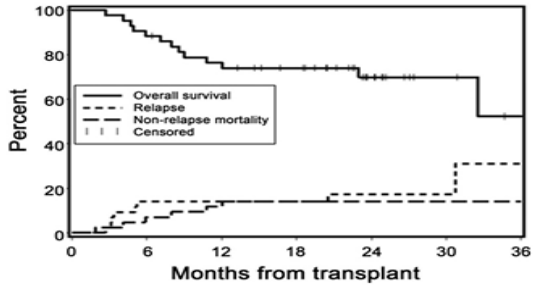


MAC

Posttransplantation cyclophosphamide for prevention of graft-versus-host disease after HLA-matched mobilized blood cell transplantation

Marco Mielcarek,[1,2] Terry Furlong,[1] Paul V. O'Donnell,[1,2] Barry E. Storer,[1,3] Jeannine S. McCune,[1,4] Rainer Storb,[1,2] Paul A. Carpenter,[1,5] Mary E. D. Flowers,[1,2] Frederick R. Appelbaum,[1,2] and Paul J. Martin[1,2]

Blood 2016

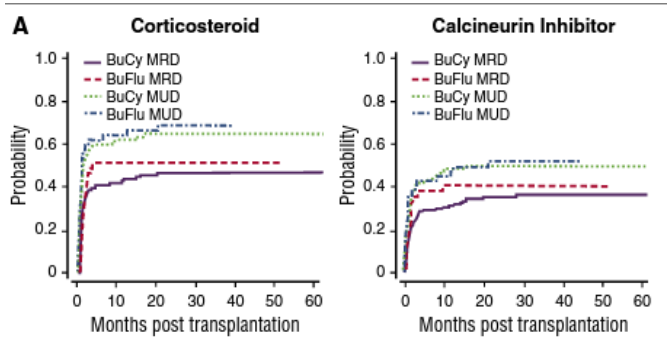


MAC

Low immunosuppressive burden after HLA-matched related or unrelated BMT using posttransplantation cyclophosphamide

Christopher G. Kanakry,[1] Javier Bolaños-Meade,[1] Yvette L. Kasamon,[1] Marianna Zahurak,[1] Nadira Durakovic,[1] Terry Furlong,[2] Marco Mielcarek,[2] Marta Medeot,[1] Ivana Gojo,[1] B. Douglas Smith,[1] Jennifer A. Kanakry,[1] Ivan M. Borrello,[1] Robert A. Brodsky,[1] Douglas E. Gladstone,[1] Carol Ann Huff,[1] William H. Matsui,[1] Lode J. Swinnen,[1] Kenneth R. Cooke,[1] Richard F. Ambinder,[1] Ephraim J. Fuchs,[1] Marcos J. de Lima,[3] Borje S. Andersson,[3] Ravi Varadhan,[1] Paul V. O'Donnell,[2] Richard J. Jones,[1] and Leo Luznik[1]

Blood 2017



Post-transplantation Cyclophosphamide Versus Antithymocyte Globulin in Patients with Acute Myeloid Leukemia Undergoing Allogeneic Stem Cell Transplantation From HLA-Identical Sibling Donors: A Retrospective Analysis From the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Inclusion criteria

Age ≥ 18 years
Diagnosis of AML in CR1
Transplant from HLA identical sibling
EBMT registry
ATG vs PTCy as
Transplant performed between 2008-2018

N. patients

ATG	PTCy
n=1913	n=197

Battipaglia et al Cancer 2021

Post-transplant cyclophosphamide versus antithymocyte globulin in patients with acute myeloid leukemia in first complete remission undergoing allogeneic stem cell transplantation from 10/10 HLA-matched unrelated donors

Inclusion criteria

Age ≥ 18 years
Diagnosis of AML in CR1
Transplant from 10/10 MUD HR
EBMT registry
ATG (Thymoglobuline 5 mg/kg) vs PTCy as
Transplant performed between 2010-2017

N. patients

ATG	PTCy
n=1452	n=174

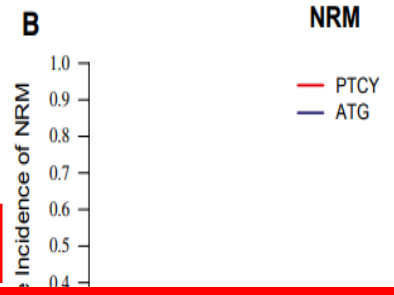
Journal of Hematology & Oncology

Brissot 2020

Results

TABLE 2. Cumulative Incidence (95% CI) of GVHD and 2-Year Survival Outcomes

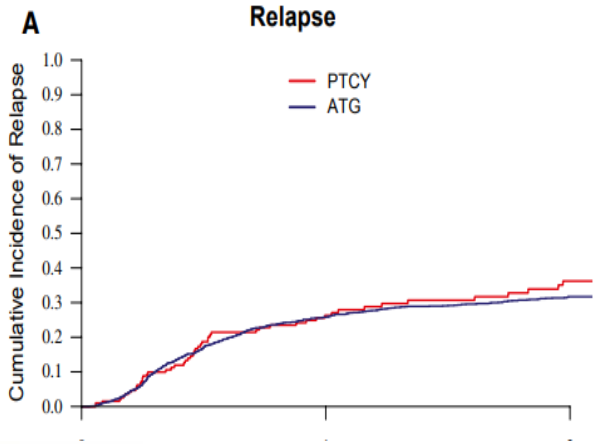
	ATG	PTCY	*P*
GVHD			
100-d grade II-IV aGVHD	17 (16-19)	19 (13-25)	.81
100-d grade III-IV aGVHD	6 (5-7)	6 (3-10)	.96
2-y cGVHD, any grade	30 (28-32)	37 (29-46)	.02
2-y cGVHD, extensive	12 (10-14)	16 (11-23)	<.01
2-year survival outcomes			
LFS			
OS			
GRFS			
RI			
NRM			



cGVHD at 2 years, was significantly lower in the ATG group compared with the PTCY group (P < .02).

TABLE 3. Mu

ATG vs PTCY	HR (95% CI)	*P*
LFS	1.00 (0.77-1.31)	.99
OS	0.97 (0.72-1.32)	.86
GRFS	0.85 (0.67-1.03)	.16
RI	0.97 (0.72-1.31)	.85
NRM	1.15 (0.63-2.11)	.65
Grade II-IV acute GVHD	0.96 (0.66-1.41)	.84
Grade III/IV acute GVHD	0.82 (0.43-1.58)	.56
Chronic GVHD, all grades	0.71 (0.52-0.97)	<.04
Extensive chronic GVHD	0.60 (0.38-0.93)	<.03



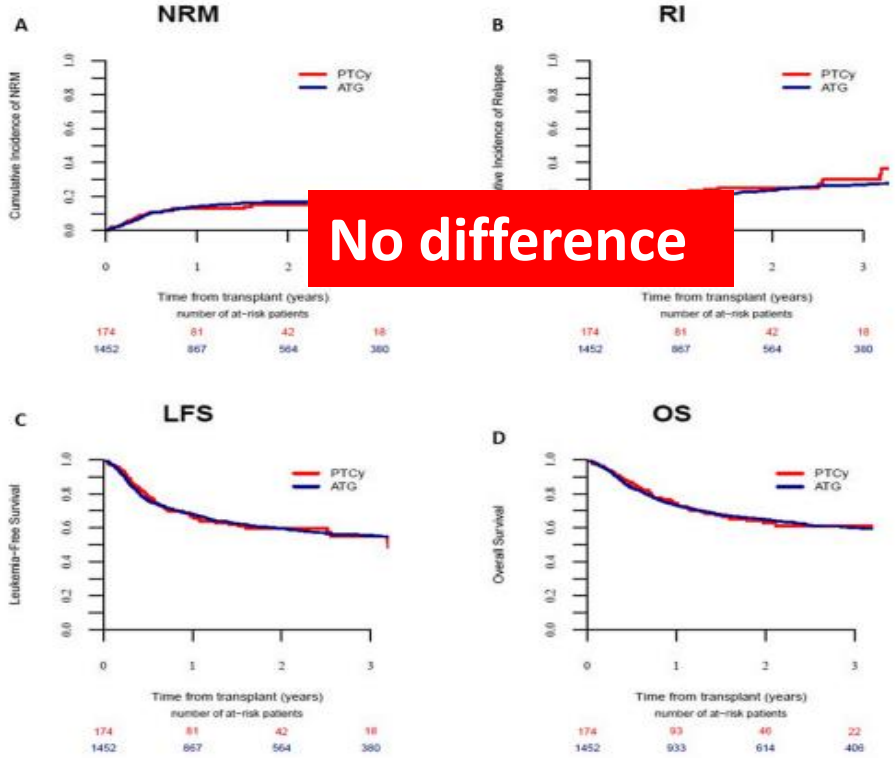
Battipaglia et al Cancer 2021

Results

Table 2 Cumulative incidence of GVHD

	180-day acute GVHD II–IV	180-day acute GVHD III–IV	2-year chronic GVHD	2-year ext. chronic GVHD
PTCY	28.8% [22.2–35.7]	8.8% [5.1–13.7]	31.4% [23.3–39.8]	18.5% [12–26.1]
ATG	29.2% [26.8–31.6]	9% [7.6–10.6]	33.6% [31–36.2]	13.1% [11.2–15]
***p* value**	0.68	0.89	0.43	0.11

Abbreviations: *ATG* antithymocyte globulin, *Ext* extensive, *GVHD* graft-versus host disease, *PTCY* post-transplantation cyclophosphamide



No difference

Journal of Hematology & Oncology

Brissot 2020

ATG versus PTCy in matched unrelated donor haematopoietic stem cell transplantations with non-myeloablative conditioning

Mesire Aydin[1] | David C. de Leeuw[2] | Caroline E. Rutten[1] | Otto J. Visser[3] | Man Wai Tang[1] | Cinthy van Roessel[2] | Jeroen J. W. Janssen[2] | Bart J. Biemond[1] | Arjan A. van de Loosdrecht[2] | Mette D. Hazenberg[1] | Ellen Meijer[2] | Erfan Nur[1,4]

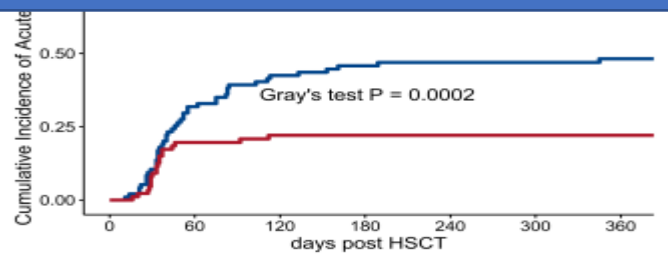
BJHaem 2023

Inclusion criteria

All hematological malig
10/10 MUD
2 centres from Netherl
NMAC regimen
PBSC in 99% of patient
ATG (total dose 8 mg/k
Transplant performed

Results

	Acute GvHD II–IV		Chronic GvHD mod/sev		OS		GRFS		Relapse incidence		NRM	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
ATG vs. PTCy	0.40 (0.23–0.68)	0.001	1.07 (0.57–2.00)	0.84	0.78 (0.49–1.20)	0.29	0.85 (0.57–1.30)	0.43	1.06 (0.64–1.70)	0.83	0.46 (0.20–1.10)	0.072
Age (≤40, >40)	0.99 (0.45–2.19)	0.98	1.85 (0.57–6.00)	0.31	1.78 (0.81–3.90)	0.15	1.43 (0.74–2.80)	0.289	0.82 (0.41–1.70)	0.59	4.46 (0.58–34.0)	0.15
Disease risk (non-adverse vs. adverse)	1.17 (0.64–2.15)	0.61	1.38 (0.62–3.10)	0.43	1.64 (0.91–3.00)	0.099	1.83 (1.09–3.10)	0.023	3.46 (1.73–6.90)	0.001	0.95 (0.36–2.50)	0.91
Disease response (CR1 vs. other)	1.21 (0.69–2.14)	0.51	0.67 (0.32–1.40)	0.29	1.26 (0.74–2.20)	0.39	1.11 (0.69–1.80)	0.67	1.15 (0.63–2.10)	0.64	1.28 (0.53–3.10)	0.58
Diagnosis (AML/MDS vs. other)	1.19 (0.63–2.23)	0.60	1.76 (0.80–3.90)	0.16	0.85 (0.46–1.60)	0.60	1.11 (0.66–1.90)	0.70	1.47 (0.76–2.80)	0.26	0.67 (0.25–1.80)	0.43



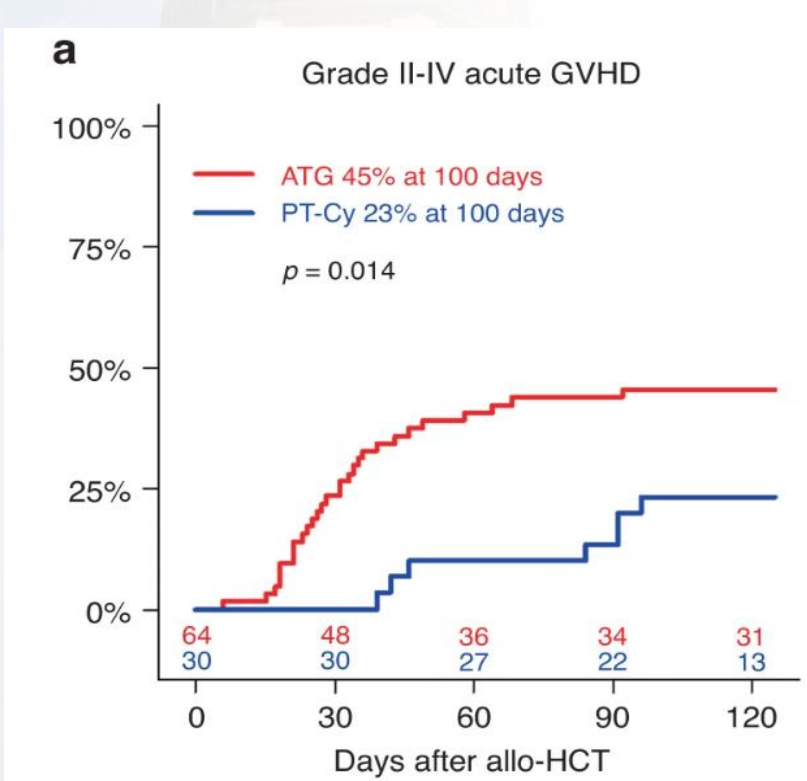
GVHD prophylaxis with post-transplant cyclophosphamide results in lower incidence of GVHD and allows faster immunosuppressive treatment reduction compared to antithymocyte globulin in 10/10 HLA-matched unrelated allogeneic hematopoietic cell transplantation

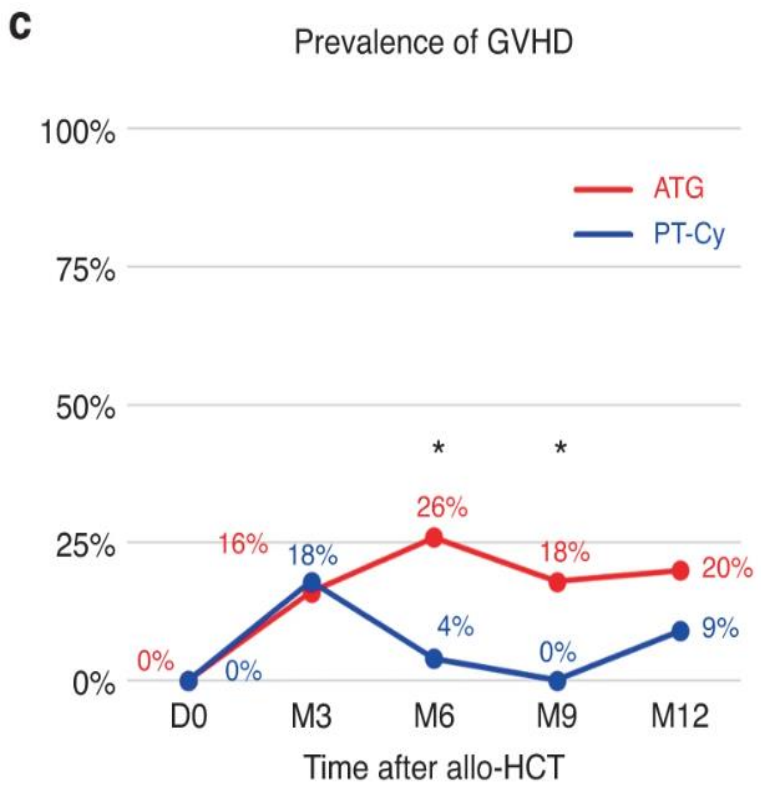
François Dachy[1], Sabine Furst[1], Boris Calmels[2,3], Thomas Pagliardini[1], Samia Harbi[1], Benjamin Bouchacourt[1], Anne Calleja[1], Claude Lemarie[2,3], Aude Collignon[1], Guillaume Morel[1], Faezeh Legrand[1], Elena Bekrieva[1], Angela Granata[1], Pierre Jean Weiller[1], Christian Chabannon[2,3,4], Jean Marc Schiano[1], Norbert Vey[1,4], Didier Blaise[1,5] and Raynier Devillier[1,4]✉

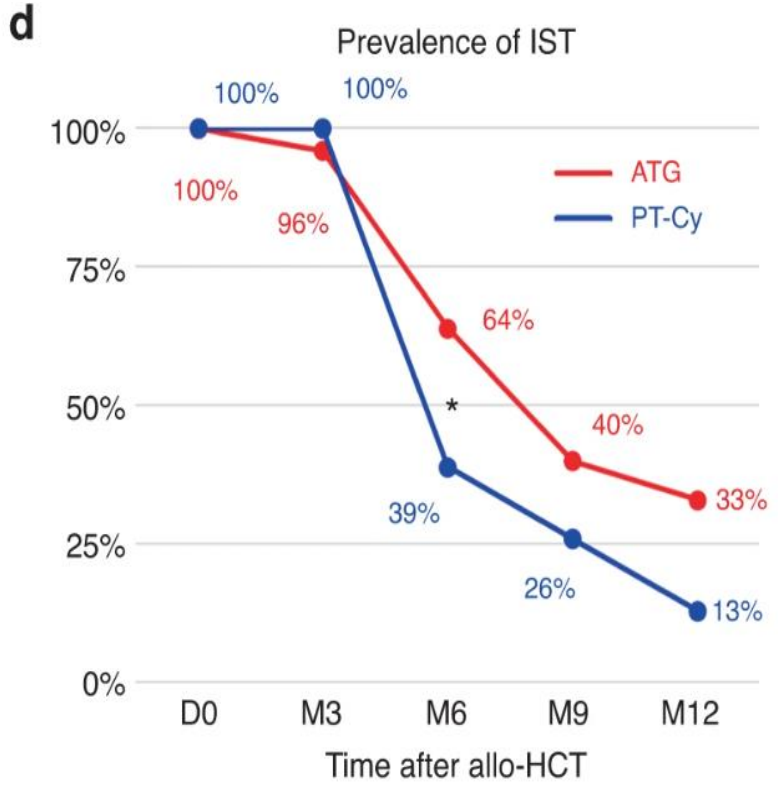
BMT 2023

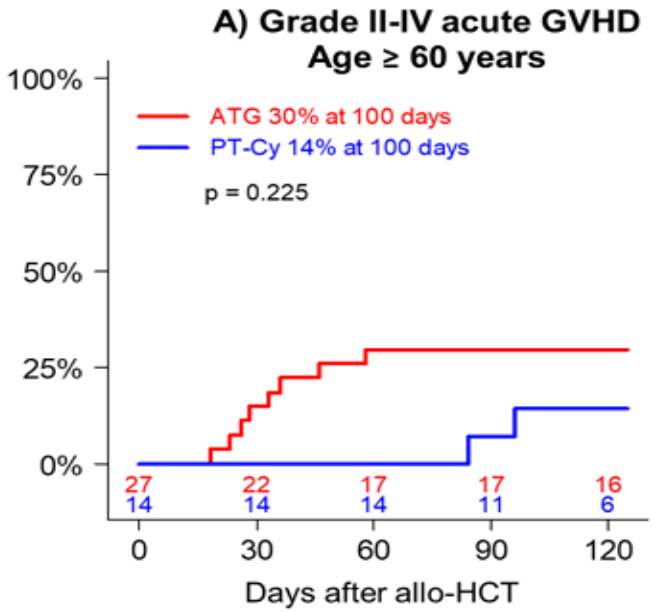
Single center experience/ retrospective study
ATG vs HD PTCy GVHD prophylaxis.

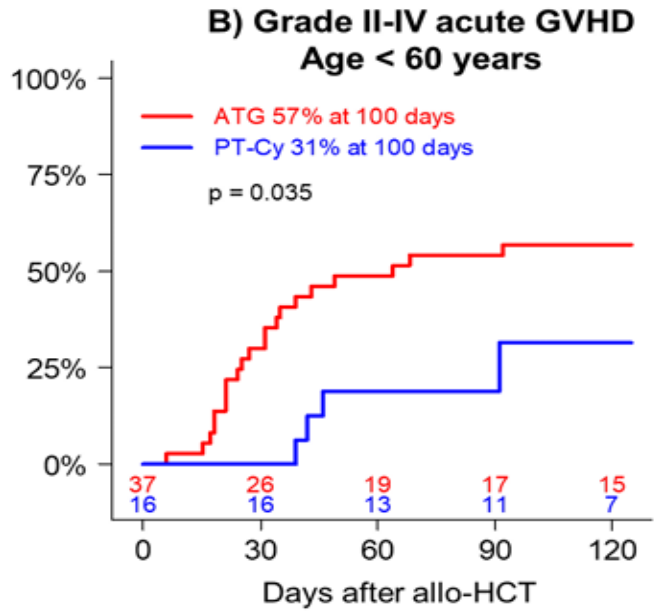
	ATG group (n = 64)		PT-Cy group (n = 30)		p
	n	%	n	%	
Age, median (range)	55	(22-70)	59	(18-75)	0.629
Conditioning					
TBF-MAC	0	0%	4	13%	< 0.001
TBF-RIC	0	0%	5	17%	
FB2	64	100%	0	0%	
CyFluTBI2	0	0%	21	70%	

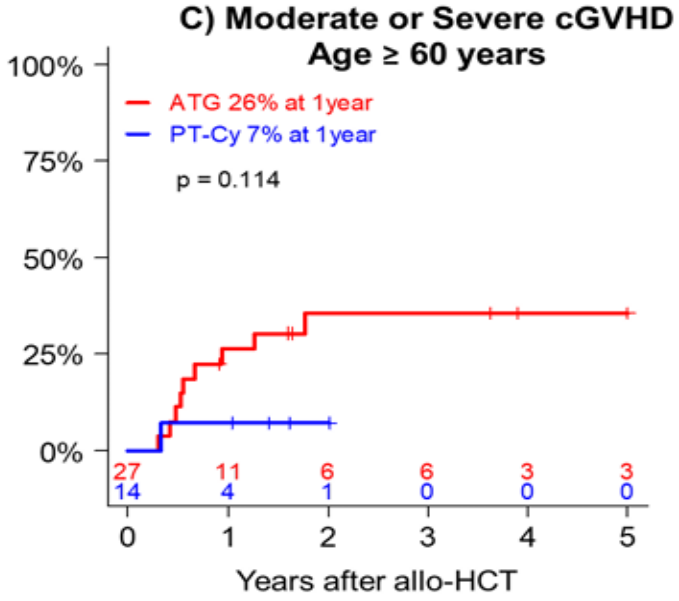


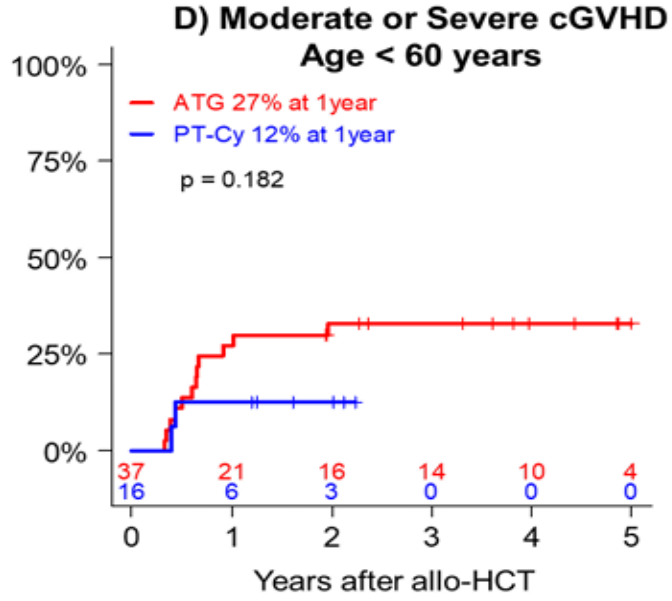












All patients engrafted.

	PT Cy	ATG
neutrophil recovery (>0.5 G/L)	+19	+17 ($p = 0.049$)
platelet recovery (>20 G/L)	+ 26	+ 10 ($p < 0.001$)

Supplemental Table 3: Multivariate analysis, with a focus on the impact of PT-Cy versus ATG as GVHD prophylaxis (Reference arm is ATG HR=1)

	HR	95% CI	*p*
Acute GVHD			
Grade 2-4	0.42	(0.18 - 0.97)	0.043
Grade 3-4	0.94	(0.28 - 3.13)	0.915
Chronic GVHD			
All grades	0.58	(0.20 - 1.67)	0.310
Moderate to severe	0.54	(0.16 - 1.84)	0.327
Relapse	0.91	(0.32 - 2.56)	0.860
NRM	0.23	(0.03 - 1.92)	0.175
PFS	0.64	(0.26 - 1.56)	0.324
OS	0.51	(0.17 - 1.54)	0.231

"The samples sizes does not allow firm conclusions, notably in case of non-significant difference that should not be interpreted as an equivalence".

PTCy would seem less GVHD ……..then more relapse???

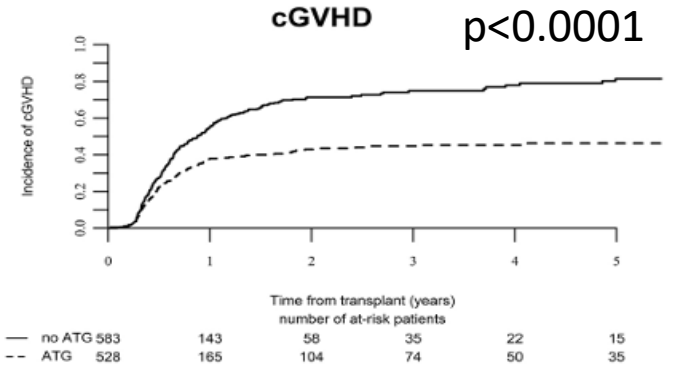
Impact of anti-thymocyte globulin on results of allogeneic peripheral blood stem cell transplantation for patients with Philadelphia-positive acute lymphoblastic leukaemia: An analysis by the Acute Leukemia Working Party of the EBMT

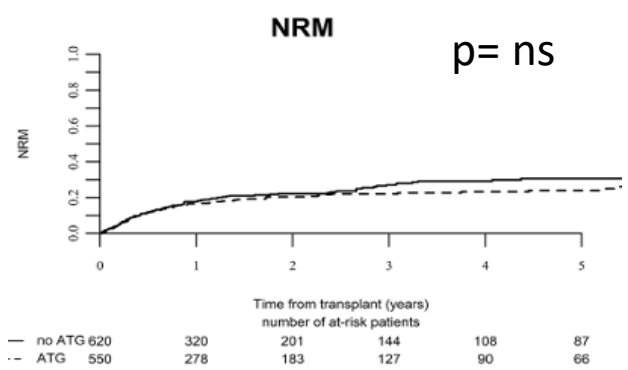
S. Giebel et al. / European Journal of Cancer 106 (2019) 212–219

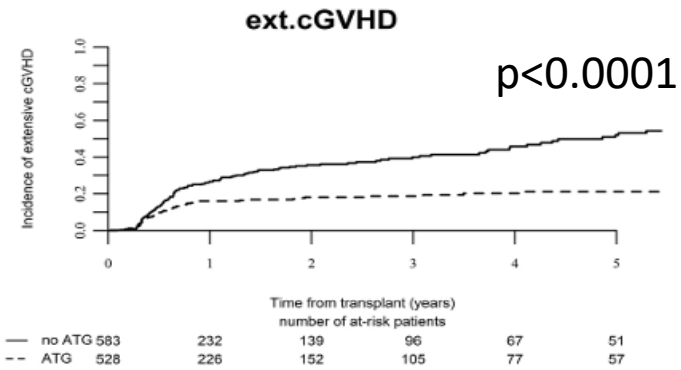
Inclusion criteria

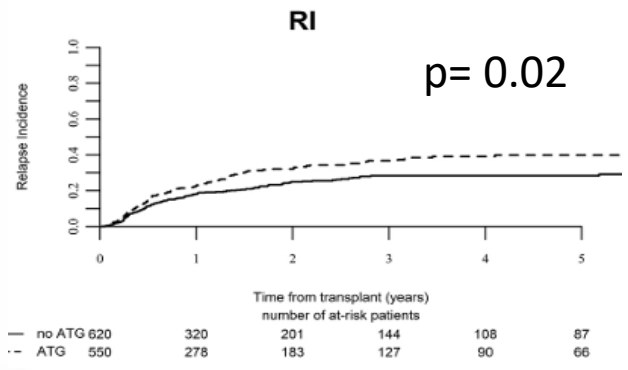
Age ≥ 18 years
Diagnosis of ALL Ph+ in CR1
Transplant from MSD or10/10 MUD HR
PBSC
EBMT registry
Transplant performed between 2007-2016

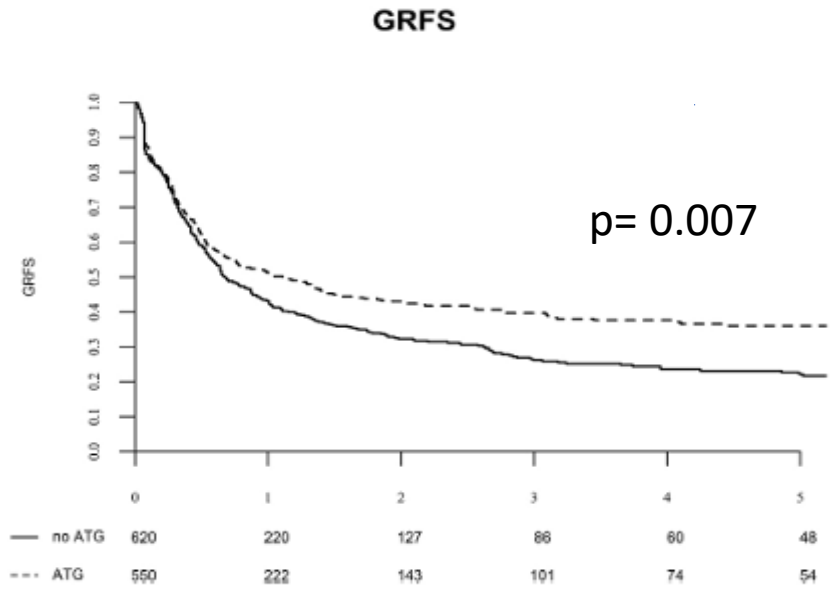
ATG	NO
n= 620	n= 550











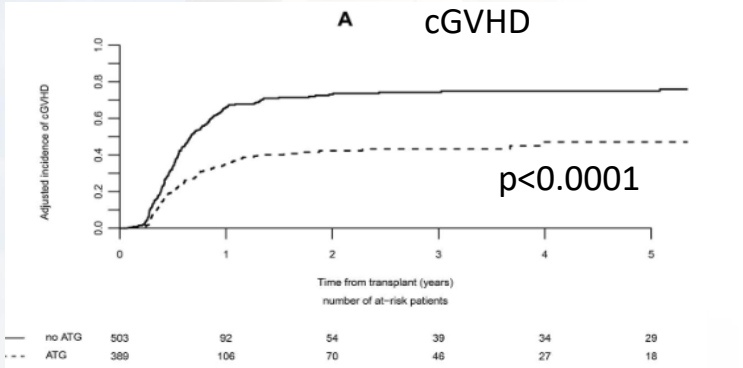
Anti-Thymocyte Globulin Improves Survival Free From Relapse and Graft-Versus-Host Disease After Allogeneic Peripheral Blood Stem Cell Transplantation in Patients With Philadelphia-Negative Acute Lymphoblastic Leukemia: An Analysis by the Acute Leukemia Working Party of the EBMT

Czrew et al. Cancer 2018

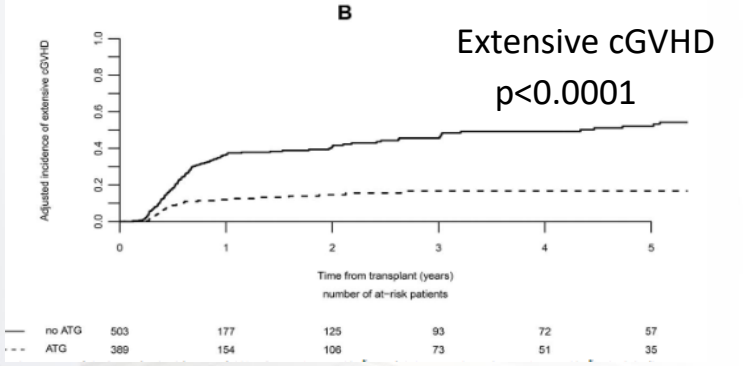
Inclusion criteria

Age ≥ 18 years
Diagnosis of ALL Ph- in CR1
Transplant from MSD or10/10 MUD HR
PBSC
EBMT registry
Transplant performed between 2007-2016

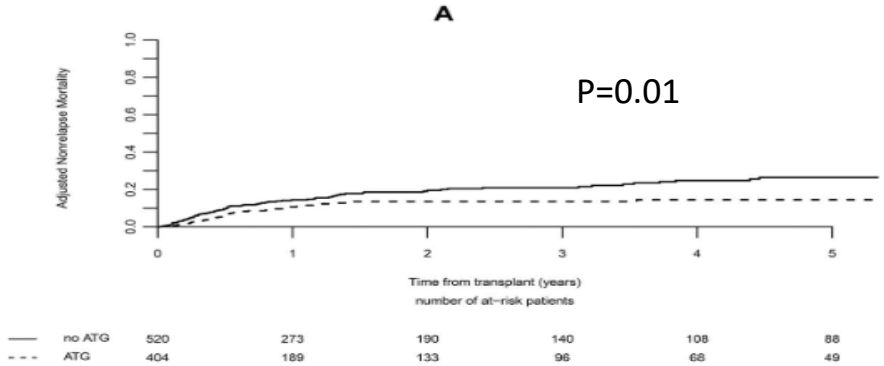
cGVHD



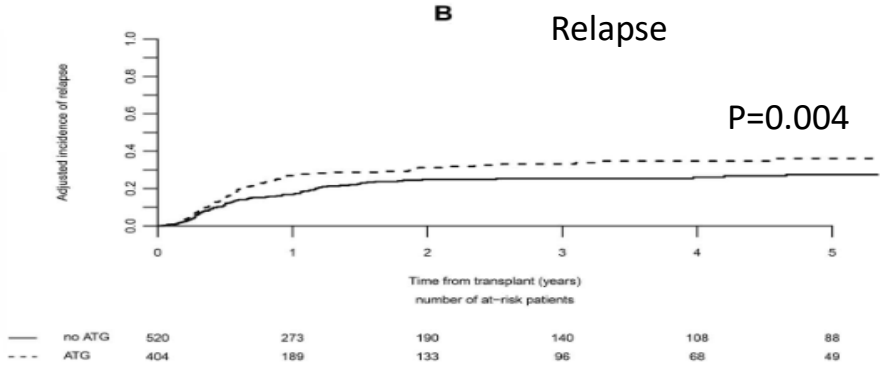
Extensive cGVHD



NRM



Relapse

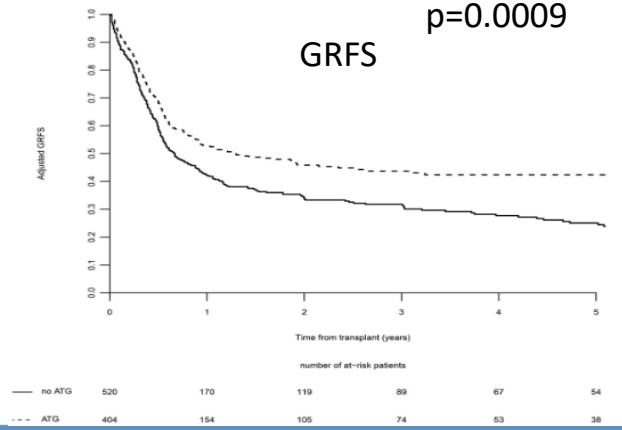


ATG n= 420

NO n= 520

GRFS

p=0.0009



GVHD occurrence does not reduce AML relapse following PTCy-based haploidentical transplantation: a study from the ALWP of the EBMT

Journal of Hematology & Oncology 2023

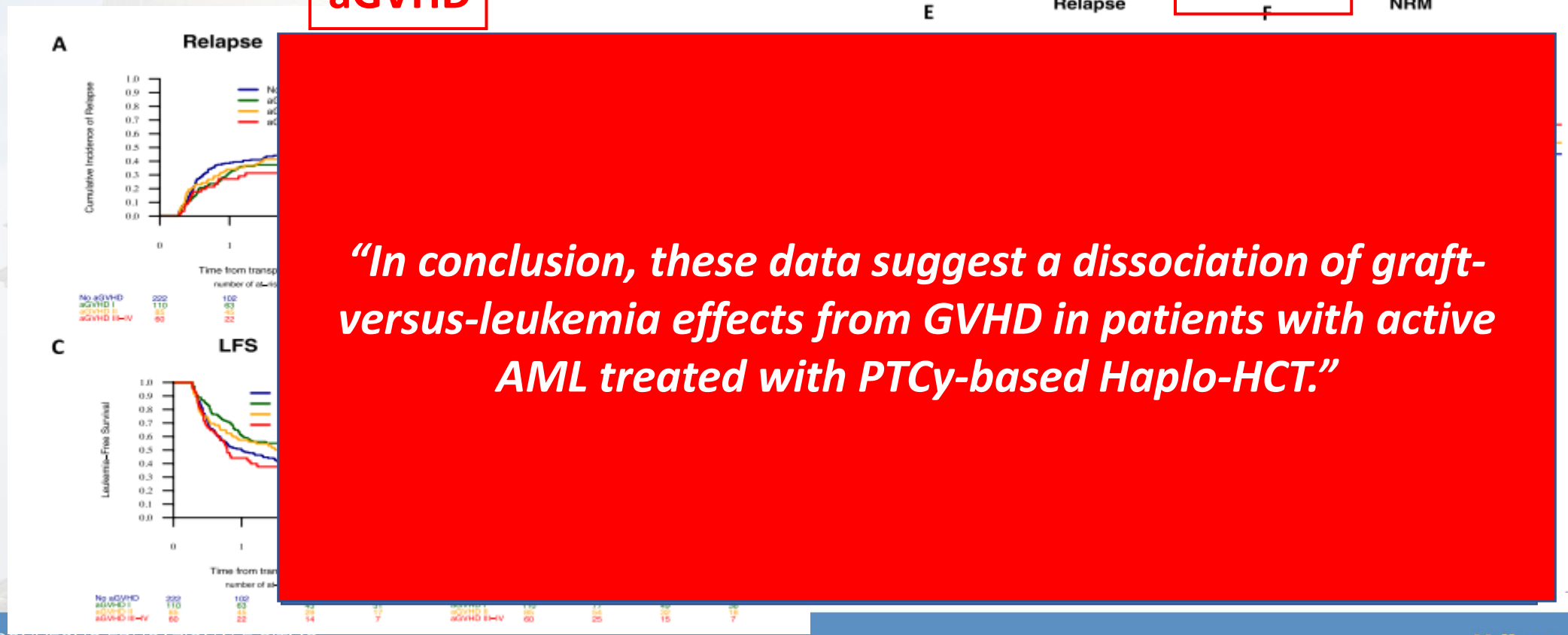
Frédéric Baron[1*], Myriam Labopin[2,3,4,5], Johanna Tischer[6], Anna Maria Raiola[7], Jan Vydra[8], Didier Blaise[9], Patrizia Chiusolo[10], Friedrich Stölzel[11,12], Renato Fanin[13], Patrice Chevallier[14], Arnon Nagler[15], Fabio Ciceri[16†] and Mohamad Mohty[2,3,4,5†]

Inclusion criteria

Diagnosis of AML, PIF or relapsed
Transplant from HAPLO
EBMT registry
PTCy as GVHD prophylaxis
Transplant performed between 2010-2020

aGVHD

cGVHD



"In conclusion, these data suggest a dissociation of graft-versus-leukemia effects from GVHD in patients with active AML treated with PTCy-based Haplo-HCT."

n.= 670

Article

Post-transplant cyclophosphamide prevents xenogeneic graft-versus-host disease while depleting proliferating regulatory T cells

Caroline Ritacco,[1] Murat Cem Köse,[1] Justine Courtois,[1] Lorenzo Canti,[1] Charline Beguin,[1] Sophie Dubois,[1] Benoît Vandenhove,[1] Sophie Servais,[1,2] Jo Caers,[1,2] Yves Beguin,[1,2] Grégory Ehx,[1,3,*] and Frédéric Baron[1,2,3,4,*]

iScience 26, March 17, 2023

GVHD ≠ GVL

Signatures of GVHD and relapse after posttransplant cyclophosphamide revealed by immune profiling and machine learning

Shannon R. McCurdy, Vedran Radojcic, [...], and Leo Luznik

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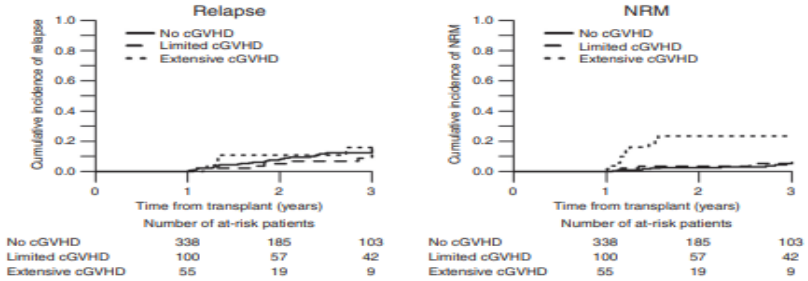
2022

ARTICLE

Check for updates

The association of graft-versus-leukemia effect and graft-versus host disease in haploidentical transplantation with post-transplant cyclophosphamide for AML

Avichai Shimoni[1]✉, Myriam Labopin[2], Emanuele Angelucci[3], Didier Blaise[4], Fabio Ciceri[5], Yener Koc[6], Zafer Gülbas[7], J. L. Diez-Martin[8], Benedetto Bruno[9], Luca Castagna[10], Massimo Martino[11], Montserrat Rovira[12], Mohamad Mohty[2,13] and Arnon Nagler[1,2]



BMT (2022) 57:384 – 39

Posttransplant cyclophosphamide versus antithymocyte globulin in patients with acute lymphoblastic leukemia treated with allogeneic hematopoietic cell transplantation from matched unrelated donors: A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

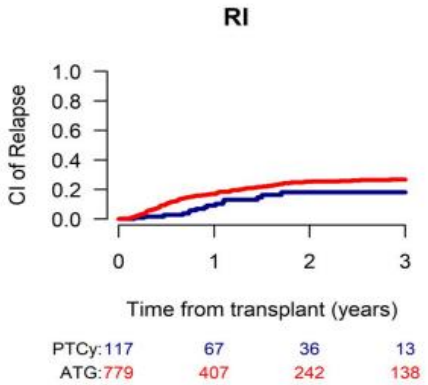
Giebel et al. Cancer. 2023;129:3735–3745.

Inclusion criteria

Age ≥ 18 years
Diagnosis of ALL in CR1
Transplant from 10/10 MUD HR
EBMT registry
ATG vs PTCy as GVHD prophylaxis
Transplant performed between 2015-2020

N. patients

ATG	PTCy
n= 779	n=197



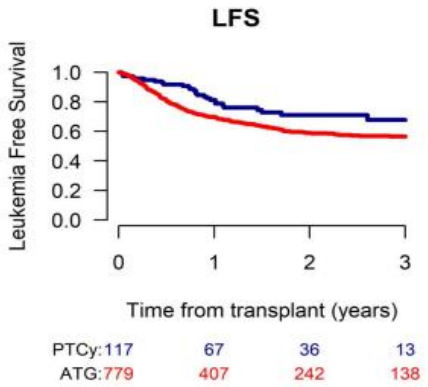


TABLE 2 Univariate comparison of posttransplant cyclophosphamide and antithymocyte globulin.

Variable	PTCY, *n* = 117	ATG, *n* = 779	*p*
Relapse incidence	18.0% (10.0%–27.5%)	25.0% (22.0%–29.0%)	.046
Nonrelapse mortality	11.0% (6.0%–18.0%)	16.0% (13.0%–19.0%)	.29
Leukemia-free survival	71.0% (60.0%–69.5%)	59.0% (55.0%–63.0%)	.01

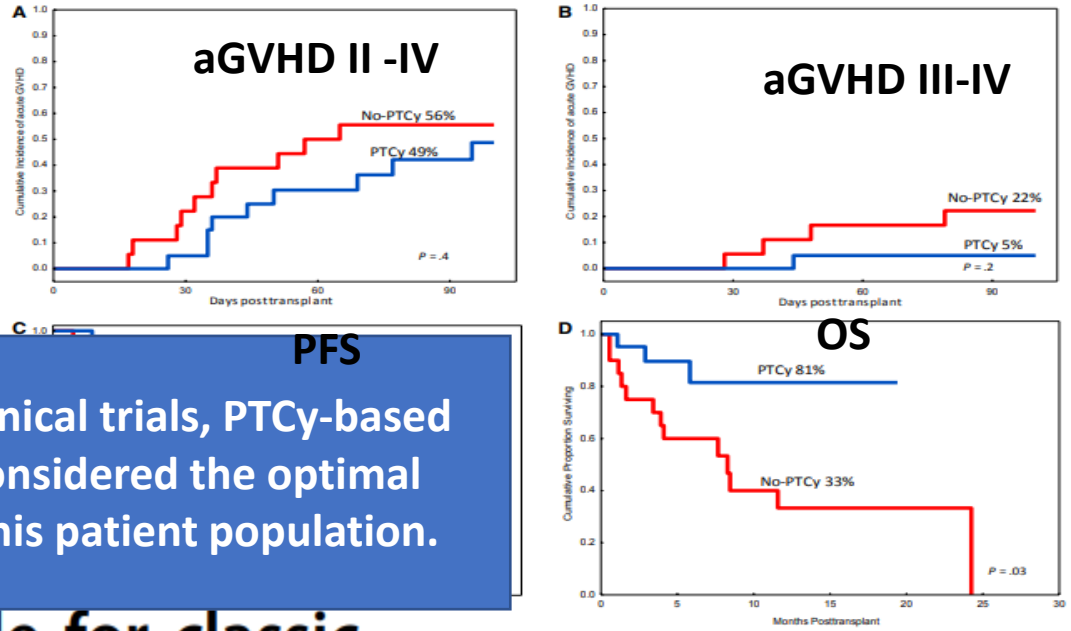
Multivariate analysis

	RI		NRM		LFS	
Factor	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Immunosuppression: ATG vs. PTCY	1.54 (0.88–2.68)	.13	1.62 (0.78–3.36)	.19	1.57 (1.01–2.45)[a]	.045[a]
Diagnosis						
Ph-negative BCP-ALL	1.00		1.00		1.00	
Ph-positive BCP-ALL	0.87 (0.61–1.25)	.46	0.89 (0.58–1.36)	.58	0.87 (0.66–1.15)	.33
TCP-ALL	0.79 (0.51–1.22)	.28	0.59 (0.32–1.08)	.085	0.71 (0.5–1.01)	.06
Patient age per 10 years	0.97 (0.85–1.1)	.59	1.24 (1.06–1.46)[a]	.009[a]	1.07 (0.96–1.18)	.22
Karnofsky score: ≥90 vs. <90	0.94 (0.63–1.39)	.74	1.2 (0.72–2.01)	.48	1.03 (0.75–1.4)	.87
Patient sex: Female vs. male	0.83 (0.6–1.15)	.26	0.73 (0.49–1.09)	.12	0.79 (0.61–1.01)	.06
Donor sex: Female vs. male	0.59 (0.4–0.87)[a]	.008[a]	0.71 (0.44–1.14)	.16	0.64 (0.47–0.86)[a]	.003[a]
Conditioning: RIC vs. MAC	1.37 (0.88–2.14)	.17	0.71 (0.41–1.25)	.24	1.05 (0.74–1.49)	.76
Conditioning: TBI vs. CHT	0.78 (0.55–1.11)	.16	0.83 (0.54–1.27)	.39	0.8 (0.61–1.05)	.11
Source of stem cells: PB vs. BM	0.51 (0.32–0.8)[a]	.004[a]	1.33 (0.58–3.07)	.5	0.69 (0.46–1.02)	.065

Posttransplantation Cyclophosphamide Improves Transplantation Outcomes in Patients With AML/MDS Who Are Treated With Checkpoint Inhibitors

Betül Oran, MD, MS [1]; Guillermo Garcia-Manero, MD [2]; Rima M. Saliba, PhD[1]; Mansour Alfayez, MD[2]; Gheath Al-Atrash, DO, PhD[1]; Stefan O. Ciurea, MD [1]; Elias J. Jabbour, MD [2]; Rohtesh S. Mehta, MD [1]; Uday R. Popat, MBA, MD [1]; Farhad Ravandi, MD[2]; Amin M. Alousi, MD[1]; Tapan M. Kadia, MD [2]; Marina Konopleva, MD, PhD[2]; Courtney D. DiNardo, MD [2]; Ka
Padmanee Sharma, MD, PhD[3]; Hagop M. Kantarjian, MD [2]; Ric

Cancer May 15, 2020



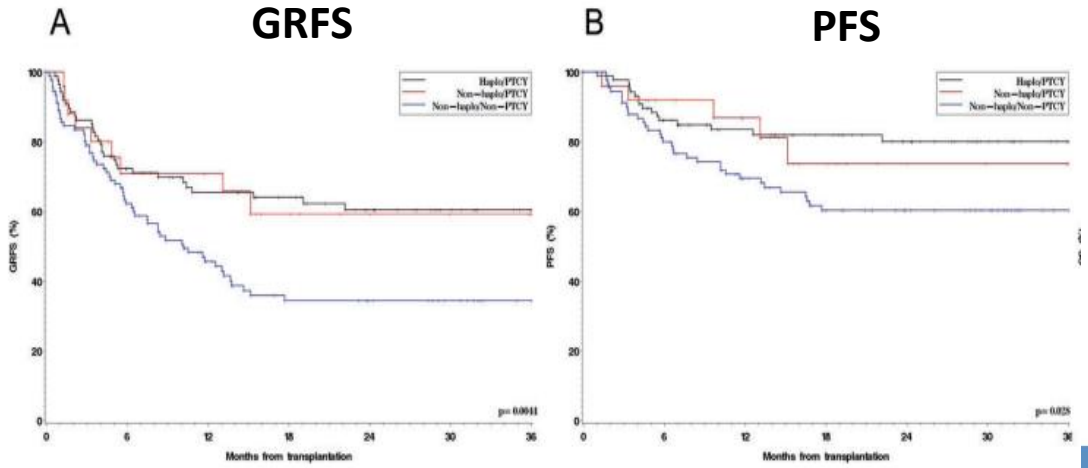
While awaiting prospective clinical trials, PTCy-based GVHD prophylaxis may be considered the optimal transplantation strategy for this patient population.

Allogeneic transplantation after PD-1 blockade for classic Hodgkin lymphoma

Merryman et al. Leukemia (2021) 35:2672–2683

Table 3 Multivariable analysis for CIR, NRM, and GVHD.

Variable	CIR		NRM		G2–4 aGVHD		cGVHD	
	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Age								
≤50 ($n = 187$)								
>50 ($n = 22$)	1.9	0.26	2.5	0.069				
Remission status at allo								
Non-CR ($n = 88$)								
CR ($n = 121$)	0.4	**0.018**	0.7	0.38				
Intervening salvage								
No ($n = 109$)								
Yes ($n = 100$)	2.9	**0.003**	0.7	0.34				
Haplo/PTCY								
No/No ($n = 91$)								
Yes/Yes ($n = 87$)	0.2	**0.006**	0.7	0.4	0.7	0.12	0.5	**0.026**
No/Yes ($n = 25$)	0.7	0.53	0.2	0.056	0.5	0.07	0.2	**0.011**
ATG								
No ($n = 163$)								
Yes ($n = 46$)	0.9	0.78	0.5	0.25	0.5	0.058	0.8	0.42



GS2-2 POST-TRANSPLANTATION CYCLOPHOSPHAMIDE VERSUS ANTITHYMOCYTE GLOBULIN AFTER RIC REGIMEN ALLO-HCT: FIRST ANALYSIS OF A PROSPECTIVE RANDOMIZED MULTICENTER TRIAL IN RECIPIENTS OF 10/10 MATCHED DONORS

Eolia Brissot (France)

All diagnosis
Transplant from MSD MUD 10/10
PTCy vs Thymoglobulin (5 mg/kg) as GVHD prophylaxis
Conditioning regimen of FB2
The stem cell source was PB.

ATG	PTCy
n= 37	n 43

	Cy PT	ATG	p
aGVHD II - IV	34,9%	24,3%	n.s.
aGVHD III - IV	9,3%	2,7%	n.s.
1y cGVHD	26%	30%	n.s.
1y.PFS	68,5%	67,1%	n.s.
1y PFS	78,9%	80,4%	n.s.
NRM	14%	22,1%	n.s.
GRFS	52,2	42,2%	n.s.

Conclusions: the use of PTCY for GVHD prophylaxis resulted in similar outcomes to ATG

NCT02876679

La ciclofosfamide post-trapianto è preferibile rispetto al siero antilinfocitario nella profilassi della GVHD acuta del trapianto da donatore HLA compatibile?

Le ragioni del si.

1) **PT Cy: strategia consolidata, standardizzata e riproducibile.**

2) **In alcuni lavori**

3) **Nessuno studi** **i ATG.**

4) **E' possibile che** **GVL.**

Mancano studi prospettici randomizzati di confronto

5) **In alcuni casi potrebbe la profilassi con PT Cy potrebbe essere vantaggiosa.**

Grazie per l'attenzione