La ciclofosfamide post-trapianto è preferibile rispetto al siero antilinfocitario nella profilassi della GVHD acuta del trapianto da donatore HLA compatibile?
Le ragioni del No

NICOLA MORDINI SC EMATOLOGIA CUNEO

To believe is very dull.
To doubt is intensely engrossing

O wilde : De profundis

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

www.thelancet.com/haematology Vol 7 February 2020

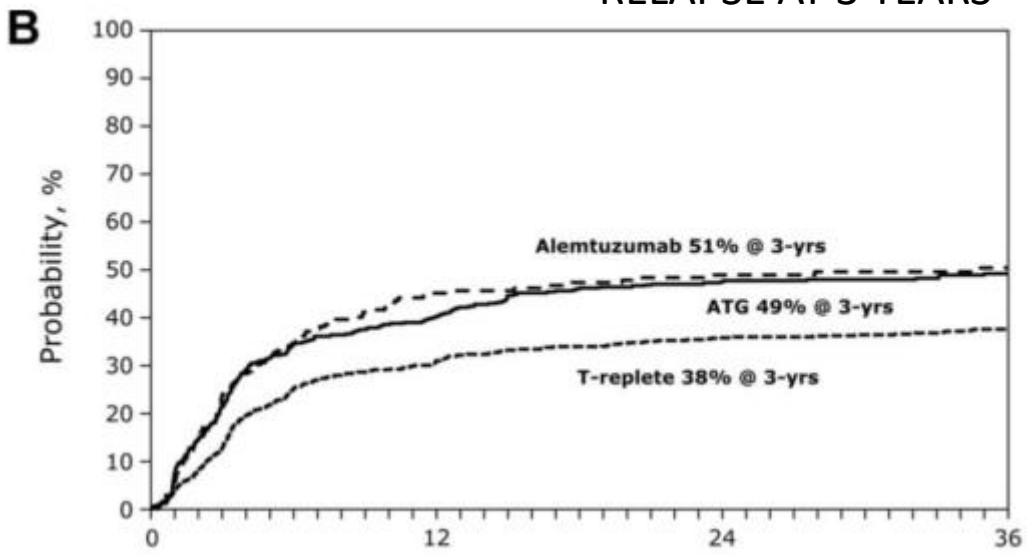
Certezze

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	The incidence and severity of chronic GVHD was reduced in clinical trials in allogeneic stem-cell transplant recipients treated with rATG or Grafalon as part of the conditioning regimen[7–9]
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	Reduction of chronic GVHD in randomised studies and retrospective analyses[9,24–26]

The recommended total dose of rATG Grafalon (Neovii, St Gallen, Switzerland) in adults is 30 mg/kg for matched related donor and 60 mg/kg for matched unrelated donor transplants; however, use of lower doses (15–30 mg/kg) has been shown to be effective in non-randomised studies.	95	2B	Clinical studies assessing the efficacy of ATG as GVHD prophylaxis have not addressed optimal dosing. Therefore, the dosing recommendations are largely based on expert opinions;[7,8,24,25,38] however, the optimal dosing has not been addressed in those studies
The recommended total dose of rATG Thymoglobulin (Sanofi, Paris, France) ranges from 2·5 to 5 mg/kg in matched related donor and 4·5 to 6 mg/kg in matched unrelated donor transplants: higher doses are associated with a higher risk of infectious complications	100	2A	This recommendation is based on evidence from randomised[9] and non-randomised studies[38,39]

Dubbio : Incremento relapse?

RELAPSE AT 3 YEARS



TRANSPLANTATION

Impact of immune modulation with anti–T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies

Robert J. Soiffer,[1] Jennifer LeRademacher,[2] Vincent Ho,[1] Fangyu Kan,[3] Andrew Artz,[4] Richard E. Champlin,[5] Steven Devine,[6] Luis Isola,[7] Hillard M. Lazarus,[8] David I. Marks,[9] David L. Porter,[10] Edmund K. Waller,[11] Mary M. Horowitz,[2] and Mary Eapen[2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI; [3]National Marrow Donor Program, Minneapolis, MN; [4]University of Chicago Medical Center, Chicago, IL; [5]M. D. Anderson Cancer Center, Houston, TX; [6]The Ohio State University, Columbus, OH; [7]Mount Sinai Hospital, New York, NY; [8]Case Western Reserve University, Cleveland, OH; [9]United Bristol Health Care Trust, Bristol, United Kingdom; [10]University of Pennsylvania, Philadelphia, PA; and [11]Emory University, Atlanta, GA

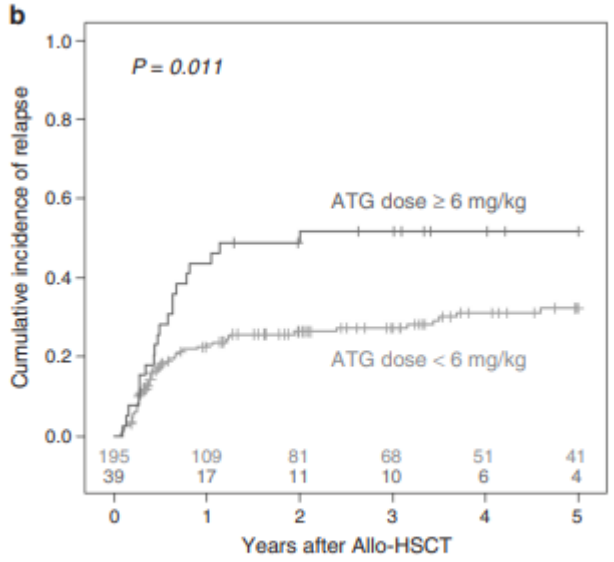


Fig. 2 NRM (a) and CIR (b) according to the ATG dose group (Color figure online)

Bone Marrow Transplantation (2018) 53:431–437
https://doi.org/10.1038/s41409-017-0043-y

ARTICLE

Impact of antithymocyte globulin doses in reduced intensity conditioning before allogeneic transplantation from matched sibling donor for patients with acute myeloid leukemia: a report from the acute leukemia working party of European group of Bone Marrow Transplantation

Raynier Devillier[1,2] · Myriam Labopin[3,4] · Patrice Chevallier[5] · Marie-Pierre Ledoux[6] · Gérard Socié[7] · Anne Huynh[8] · Jean-Henri Bourhis[9] · Jean-Yves Cahn[10] · Gabrielle Roth-Guepin[11] · Ghulam Mufti[12] · Déborah Desmier[13] · Mauricette Michallet[14] · Nathalie Fegueux[15] · Fabio Ciceri[16] · Fréderic Baron[17] · Didier Blaise[1,2] · Arnon Nagler[4,18] · Mohamad Mohty[3,4]

Certezze : evidenze prospettiche

Table 1. Summary of 3 randomized trials

	GITMO[6,7] 12/1995-07/2000		Finke[8,9] 05/2003-02/2007		Kröger[10] 12/2006-02/2012		Total			
	ATG	noATG	ATG	noATG	ATG	noATG	ATG	noATG	RR	*P*
Patients, n	56	53	103	98	83	72	242	223	–	–
aGVHD II-IV, %	50%	70%	33%	51%	11%	18%	31%	46%	1.47	.001
aGVHD III-IV, %	23%	43%	11%	24%	2%	8%	12%	25%	2.08	.0003
cGVHD, %	37%	60%	26%	50%	22%	46%	28%	52%	1.83	.00001
ext cGVHD, %	15%	41%	12%	45%	5%	24%	11%	37%	3.43	.00001
NRM, %	39%	47%	19%	33%	14%	12%	24%	31%	1.27	.1
Relapse, %	23%	21%	33%	28%	32%	25%	29%	25%	0.84	.2
Survival, %	55%	56%	55%	43%	74%	77%	61%	59%	1.04	.6

ext, extensive; GITMO, Italian Cooperative Transplant Group; NRM, non-relapse mortality; RR, relative risk of patients not receiving ATG as compared with ATG.

A Bacigalupo Blood Advances 2017

Table 2. Clinical Outcomes and Complications After HCT

Outcome or Complication	Univariable Analysis [Median % (Range)] Placebo	ATLG	*P*
Fatal graft failure, %	0.80	3.40	.029
Days to engraftment			
ANC ≥ 500/μL	19 (8-41)	24 (5-45)	< .001
Platelet count ≥ 20,000/μL	19 (5-45)	28 (6-205)	< .001
Day 30 ANC engraftment*	95 (89-97)	85 (77-90)	<.001
Day 100 platelet engraftment*	94 (89-97)	79 (71-86)	< .001
One-year CMV reactivation, %*	44	62	.030
[illegible]			
Acute GVHD within 180 days after HCT*			
Grade 2 to 4	40 (32-49)	23 (16-31)	.004
Grade 3 to 4	11 (6.4-17)	4.3 (1.6-9)	.090
cGVHD*			
All grades	38 (29-47)	16 (9.7-24)	< .001
Moderate-severe	33 (25-42)	12 (6.7-19)	< .001
[illegible] cGVHD-free survival			
[illegible]			
Two-year cGRFS	39 (30-48)	38 (29-47)	.730
Two-year OS	74 (65-81)	59 (48-69)	.034
Two-year PFS	65 (56-73)	47 (37-56)	.040
[illegible]			
Two-year relapse*	21 (14-29)	32 (23-41)	.100

	Multivariable Analysis [HR (95% CI)]	*P*
ATLG *v* placebo		
cGVHD-free survival	0.86 (0.60 to 1.22)	.390
OS	1.74 (1.12 to 2.71)	.010
PFS	1.55 (1.05 to 2.28)	.026

VOLUME 35 · NUMBER 36 · DECEMBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Prospective, Randomized, Double-Blind, Phase III Clinical Trial of Anti–T-Lymphocyte Globulin to Assess Impact on Chronic Graft-Versus-Host Disease–Free Survival in Patients Undergoing HLA-Matched Unrelated Myeloablative Hematopoietic Cell Transplantation

Robert J. Soiffer, Haesook T. Kim, Joseph McGuirk, Mitchell E. Horwitz, Laura Johnston, Mrinal M. Patnaik, Witold Rybka, Andrew Artz, David L. Porter, Thomas C. Shea, Michael W. Boyer, Richard T. Maziarz, Paul J. Shaughnessy, Usama Gergis, Hana Safah, Ran Reshef, John F. DiPersio, Patrick J. Stiff, Madhuri Vusirikala, Jeff Szer, Jennifer Holter, James D. Levine, Paul J. Martin, Joseph A. Pidala, Ian D. Lewis, Vincent T. Ho, Edwin P. Alyea, Jerome Ritz, Frank Glavin, Peter Westervelt, Madan H. Jagasia, and Yi-Bin Chen

Conditioning			.36
Cy-TBI	37 (28.9)	31 (24.6)	
Bu-Cy	37 (28.9)	47 (37.3)	
Bu-Flu	54 (42.2)	48 (38.1)	

Correspondingly, among TBI recipients, ATLG was associated with inferior PFS (HR, 2.65; 95% CI, 1.29 to 5.45; $P = .008$) and OS (HR, 3.47; 95% CI, 1.43 to 8.36; $P = .006$), whereas no difference was noted in patients who received Bu-based conditioning (Appendix

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

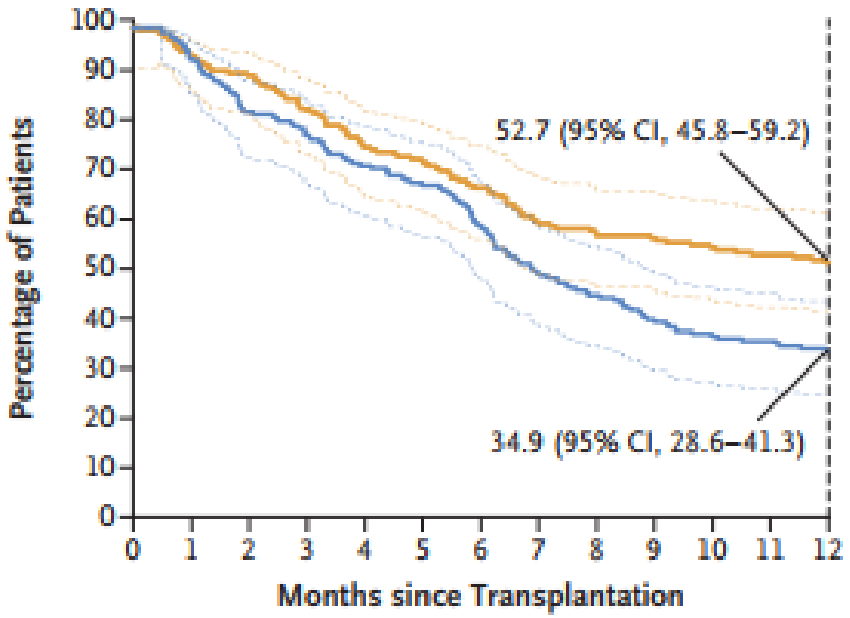
Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

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*

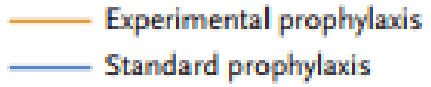
N ENGL J MED 388;25 NEJM.ORG JUNE 22, 2023

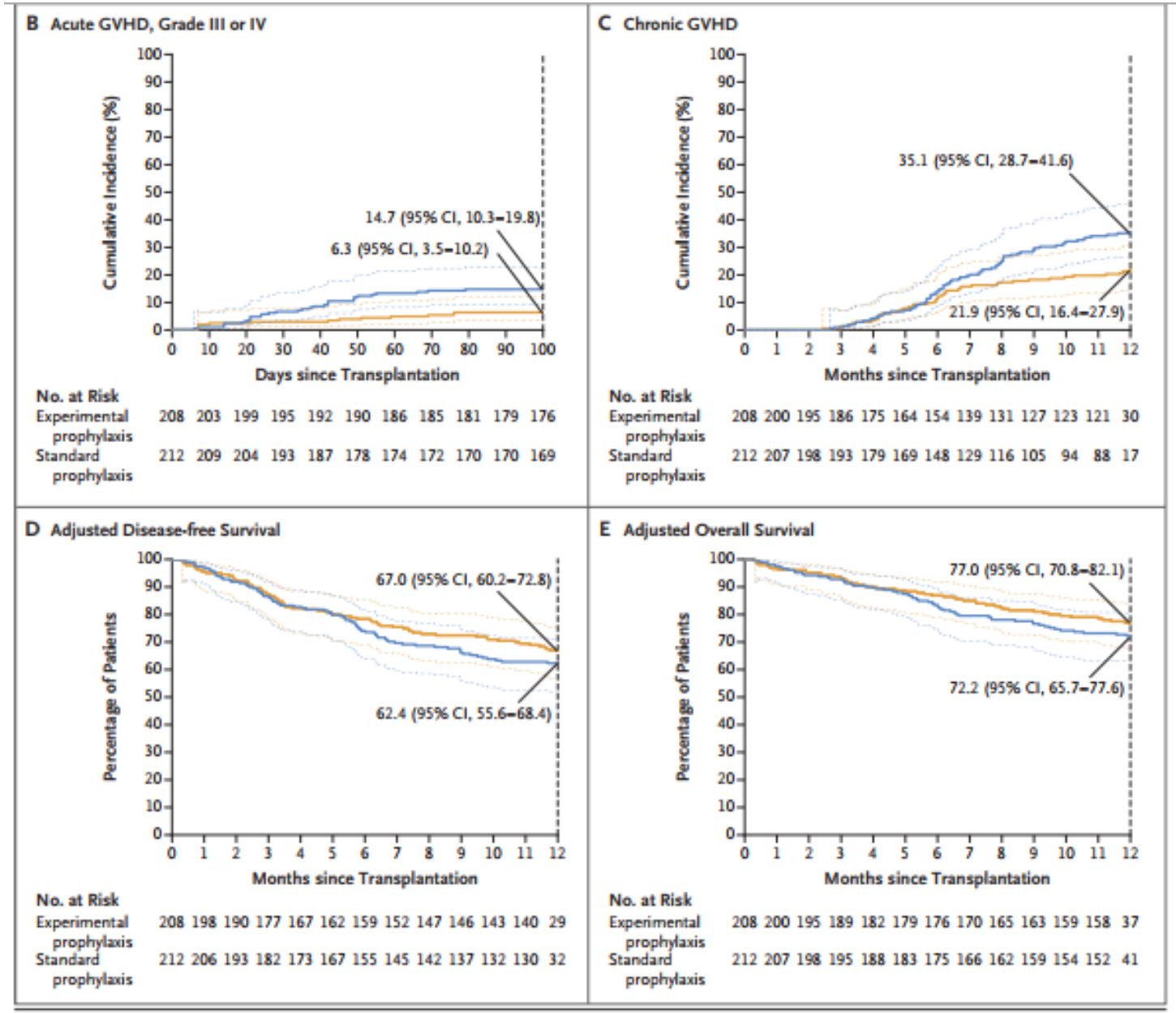
REDUCED INTENSITY
431 PAZ (CTX POST VS TAC/MTX NO ATG
ANCHE MMSM 1 AG (SOLO 15PT)

A Adjusted GVHD-free, Relapse-free Survival



No. at Risk													
Experimental prophylaxis	214	197	187	172	155	149	138	123	117	116	112	109	24
Standard prophylaxis	217	199	174	164	150	142	125	106	97	87	80	78	14




B Acute GVHD, Grade III or IV
Cumulative Incidence (%)
14.7 (95% CI, 10.3–19.8)
6.3 (95% CI, 3.5–10.2)
Days since Transplantation
No. at Risk
Experimental prophylaxis 208 203 199 195 192 190 186 185 181 179 176
Standard prophylaxis 212 209 204 193 187 178 174 172 170 170 169
C Chronic GVHD
Cumulative Incidence (%)
35.1 (95% CI, 28.7–41.6)
21.9 (95% CI, 16.4–27.9)
Months since Transplantation
No. at Risk
Experimental prophylaxis 208 200 195 186 175 164 154 139 131 127 123 121 30
Standard prophylaxis 212 207 198 193 179 169 148 129 116 105 94 88 17
D Adjusted Disease-free Survival
Percentage of Patients
67.0 (95% CI, 60.2–72.8)
62.4 (95% CI, 55.6–68.4)
Months since Transplantation
No. at Risk
Experimental prophylaxis 208 198 190 177 167 162 159 152 147 146 143 140 29
Standard prophylaxis 212 206 193 182 173 167 155 145 142 137 132 130 32
E Adjusted Overall Survival
Percentage of Patients
77.0 (95% CI, 70.8–82.1)
72.2 (95% CI, 65.7–77.6)
Months since Transplantation
No. at Risk
Experimental prophylaxis 208 200 195 189 182 179 176 170 165 163 159 158 37
Standard prophylaxis 212 207 198 195 188 183 175 166 162 159 154 152 41

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[1], *Myriam Lapobin*[2], *Hélène Labussière*[3], *Patrice Chevallier*[4], *Didier Blaise*[5], *Ibrahim Yakoub-Agha*[6], *Claude-Eric Bulabois*[7], *Anne Huynh*[8], *Sylvain Chantepie*[9], *Anne-Lise Menard*[10], *Marie-Thérèse Rubio*[11], *Patrice Ceballos*[12], *Mohamad Mohty*[1]

EBMT 2021

Method

Results: In total, 80 pts were randomized (43 in PTCy arm and 37 in ATG arm) between 2017-2019. Median age was 64.4y (range: 21-71), 56 pts (70%) were male. 47.5% pts were transplanted for acute myeloid leukemia,

Conclusions: The use of PTCY for GVHD prophylaxis resulted in similar outcomes to those seen with ATG for patients who underwent an FB2 RIC regimen allo-HCT with a 10/10 HLA-matched donor.

[95% CI: 0.2-12.3] respectively (p=0.24). The one-year CI of cGVHD was 26.0 [95% CI: 13.8-40] in PTCY recipients versus 30.2 [95% CI: 16.1-45.5] in CsA recipients (p=0.56). The one-year estimated PFS was 68.5% [95%CI: 51.6-80.5] and 67.1% [95% CI: 49.4-79.8] in the PTCy group and ATG groups, respectively (p=0.68). The one-year estimated OS was 78.9% [95% CI: 63.4-88.4] in the PTCy group and 80.4% [95% CI: 63.1-90.2] in the ATG group (p=0.93). NRM was 14% [95% CI: 5.6-26.1] in PTCy recipients versus 22.1% [95% CI: 10.2-36.8] in ATG recipients (p=0.49). The one-year estimated GRFS in the PTCy and ATG groups was 52.2% [95% CI: 36-66.2] and 42.2% [95% CI: 26.1-57.5], respectively (p=0.28).

Certezze (?): evidenze retrospettive di registro

Brissot et al. Journal of Hematology & Oncology (2020) 13:87
https://doi.org/10.1186/s13045-020-00923-0

RESEARCH Open Access

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

Eolia Brissot[1,2*], Myriam Labopin[3], Ian Moiseev[4], J. J. Cornelissen[5], Ellen Meijer[6], Gwendolyn Van Gorkom[7], Montserrat Rovira[8], Fabio Ciceri[9,10], Laimonas Griskevicius[11], Didier Blaise[12], Edouard Forcade[13], Martin Mistrik[14], Stephan Mielke[15], Claude Eric Bulabois[16], Riitta Niittyvuopio[17], Eric Deconinck[18], Annalisa Ruggeri[9,10], Jaime Sanz[19,20], Alexandros Spyridonidis[21], Bipin Savani[22], Sebastian Giebel[23], Arnon Nagler[24] and Mohamad Mohty[1,2]

Table 1 Baseline characteristics of patients

N	ATG	PTCY	Test *p* value
	1452	174	
Kanofsky performance score			
< 90	331 (24.68%)	29 (16.76%)	0.02
≥ 90	1010 (75.32%)	144 (83.24%)	
Missing	111	1	
Patient sex			
Male	759 (52.27%)	98 (56.32%)	0.31
Female	693 (47.73%)	76 (43.68%)	
Female donor-male recipient	165 (11.41%)	26 (14.94%)	0.17
Patient CMV serostatus			
Negative	499 (34.92%)	43 (25.15%)	0.011
Positive	930 (65.08%)	128 (74.85%)	
Missing	23	3	
Engraftement			
Graft failure	12 (0.83%)	2 (1.16%)	0.65
Engrafted	1432 (99.17%)	170 (98.84%)	
Missing	8	2	
Gaft cell type			
BM	143 (9.85%)	18 (10.34%)	0.84
PBSC	1309 (90.15%)	156 (89.66%)	

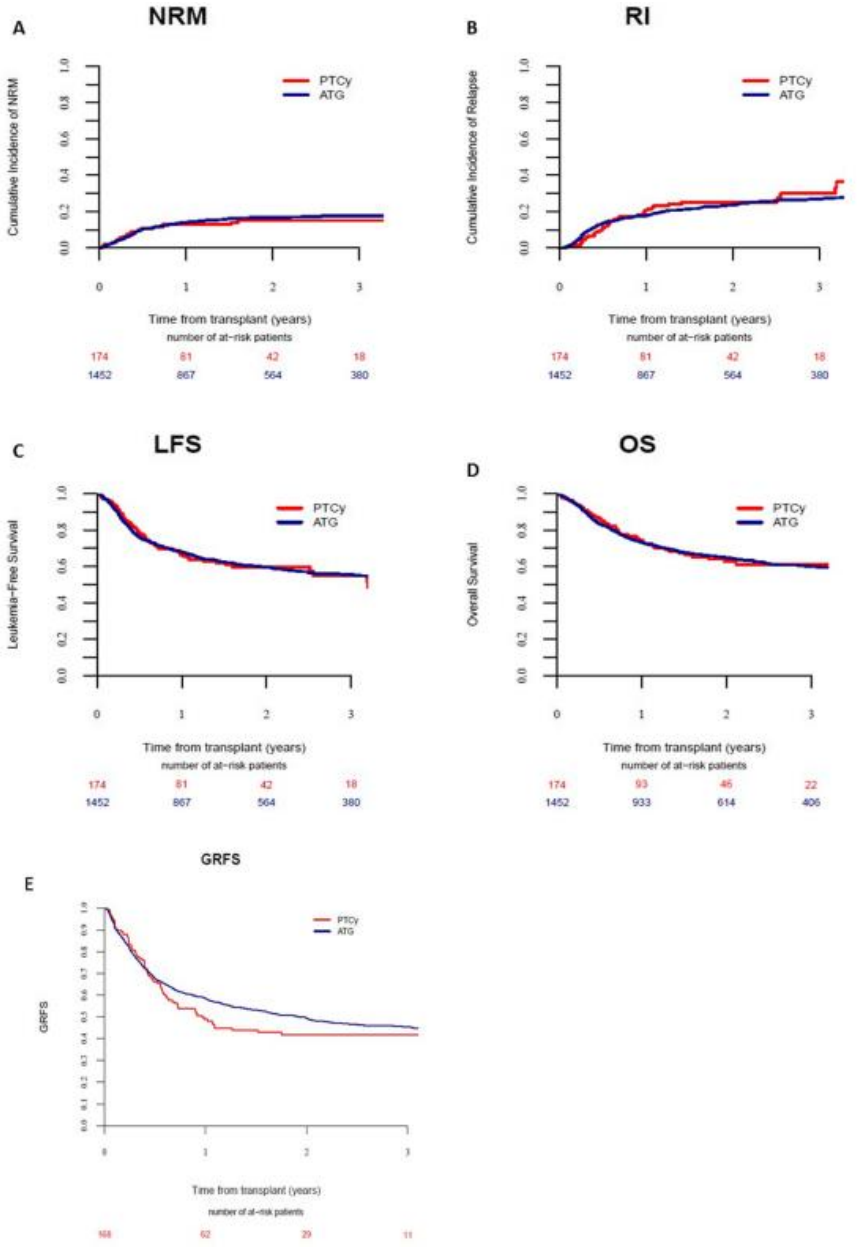
NB

Trapianto fra 2010 e 2017

Solo Thymoglobulin 5 mg/kg

circa 50% RIC

Circa 90% PBSC


A
NRM
Cumulative Incidence of NRM
PTCy
ATG
Time from transplant (years)
number of at−risk patients
174 81 42 18
1452 867 564 380
B
RI
Cumulative Incidence of Relapse
PTCy
ATG
Time from transplant (years)
number of at−risk patients
174 81 42 18
1452 867 564 380
C
LFS
Leukemia−Free Survival
PTCy
ATG
Time from transplant (years)
number of at−risk patients
174 81 42 18
1452 867 564 380
D
OS
Overall Survival
PTCy
ATG
Time from transplant (years)
number of at−risk patients
174 93 46 22
1452 933 614 406
E
GRFS
GRFS
PTCy
ATG
Time from transplant (years)
number of at−risk patients

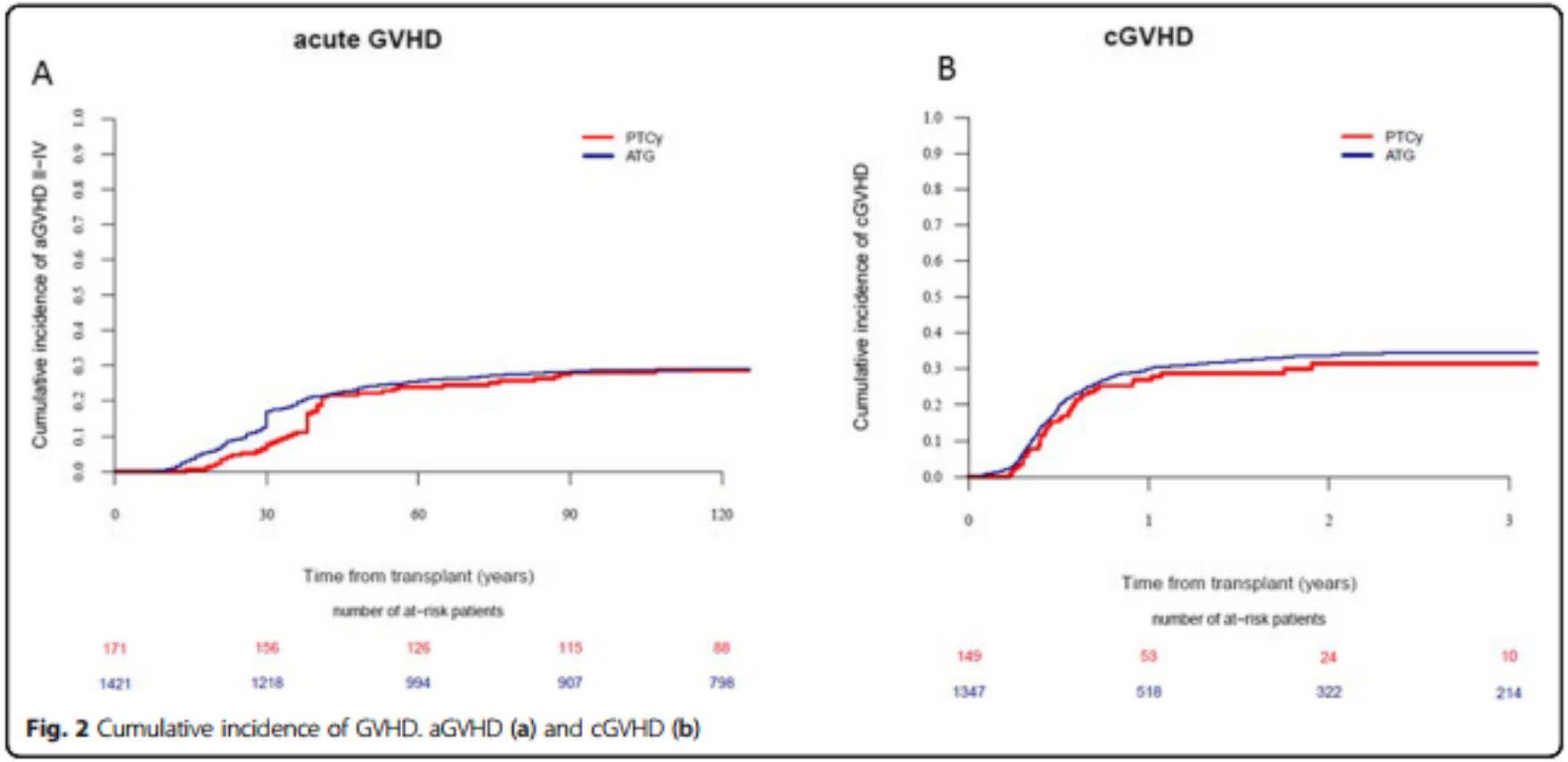


Fig. 2 Cumulative incidence of GVHD. aGVHD **(a)** and cGVHD **(b)**

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

Our results do, however, provide further proof that both ATG and PTCY are valid GVHD prophylactic strategies for transplants from 10/10 HLA-MUD.

One hypothesis is that the degree of disparity between a recipient with a 10/10 HLA matched unrelated donor is low and the effect of PTCY of minimizing other HLA major or minor histocompatibility mismatches is not needed in this situation

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

Giorgia Battipaglia, MD, PhD [1,2]; Myriam Labopin, MD[1,3,4]; Rose-Marie Hamladji, MD[5]; Didier Blaise, MD[6]; Patrice Chevallier, MD [7]; Eolia Brissot, MD, PhD[1,4]; Armin Gerbitz, MD[8]; Gerard Socié, MD[9]; Boris Afanasyev, MD[10]; Fabio Ciceri, MD, PhD[11]; Ellen Meijer, MD[12]; Yener Koc, MD[13]; Jan J. Cornelissen, MD[14]; Anne Huynh, MD[15]; Hakan Ozdogu, MD[16]; Johan Maertens, MD[17]; Franciane Paul, MD[18]; Hélène Labussière-Wallet, MD[19]; Annalisa Ruggeri, MD, PhD [11]; Mahmoud Aljurf, MD[20]; Ali Bazarbachi, MD[21]; Bipin Savani, MD [22]; Arnon Nagler, MD, PhD[3,23]; and Mohamad Mohty, MD, PhD[1,3,4]

Cancer January 15, 2021

TABLE 1. Patient, Disease, and Transplantation Characteristics

Characteristic	ATG (n = 1913)	PTCY (n = 197)	*P*
Age at allo-HCT, y, median (range)	54 (18-72)	47 (18-74)	<.01
Sex			.55
Men	1012 (53)	88 (55)	
Women	893 (47)	88 (45)	
Female donor into male recipient	456 (24)	51 (26)	.55
Secondary AML	318 (17)	31 (16)	.75
Cytogenetic risk			.51
Good	67 (3)	8 (4)	
Intermediate	869 (45)	87 (44)	
Poor	347 (19)	29 (15)	
NA/Failed	630 (33)	73 (37)	
Karnofsky performance status <90%	443 (24)	41 (21)	.39
Patient CMV serology			<.01
Positive	1330 (70)	152 (80)	
Negative	564 (30)	39 (20)	
Donor CMV serology			.07
Positive	1205 (64)	130 (71)	
Negative	674 (36)	54 (29)	
Interval from diagnosis to allo-HSCT, mo (range)	4.8 (1-18)	4.3 (1-17)	<.01
Year of allo-HSCT (range)	2014 (2008-2018)	2015 (2009-2018)	<.01
Conditioning regimen			<.01
Myeloablative	924 (48)	116 (59)	
Reduced intensity	989 (52)	81 (41)	
Source of stem cells			<.01
Bone marrow	91 (5)	58 (30)	
PBSC	1822 (95)	139 (70)	
Associated immunosuppressive agents			
Cyclosporine	539 (28)	44 (23)	
Cyclosporine + mycophenolate mofetil	553 (29)	23 (12)	
Cyclosporine + methotrexate	649 (34)	14 (7)	
Tacrolimus + mycophenolate mofetil	47 (2)	8 (4)	
PTCY alone	—	32 (16)	
Other	125 (7)	76 (38)	
Follow-up, mo, median (range)	28 (12-54)	19 (5-34)	<.01

Aa 2008-2018, Thymoglobulin 74%

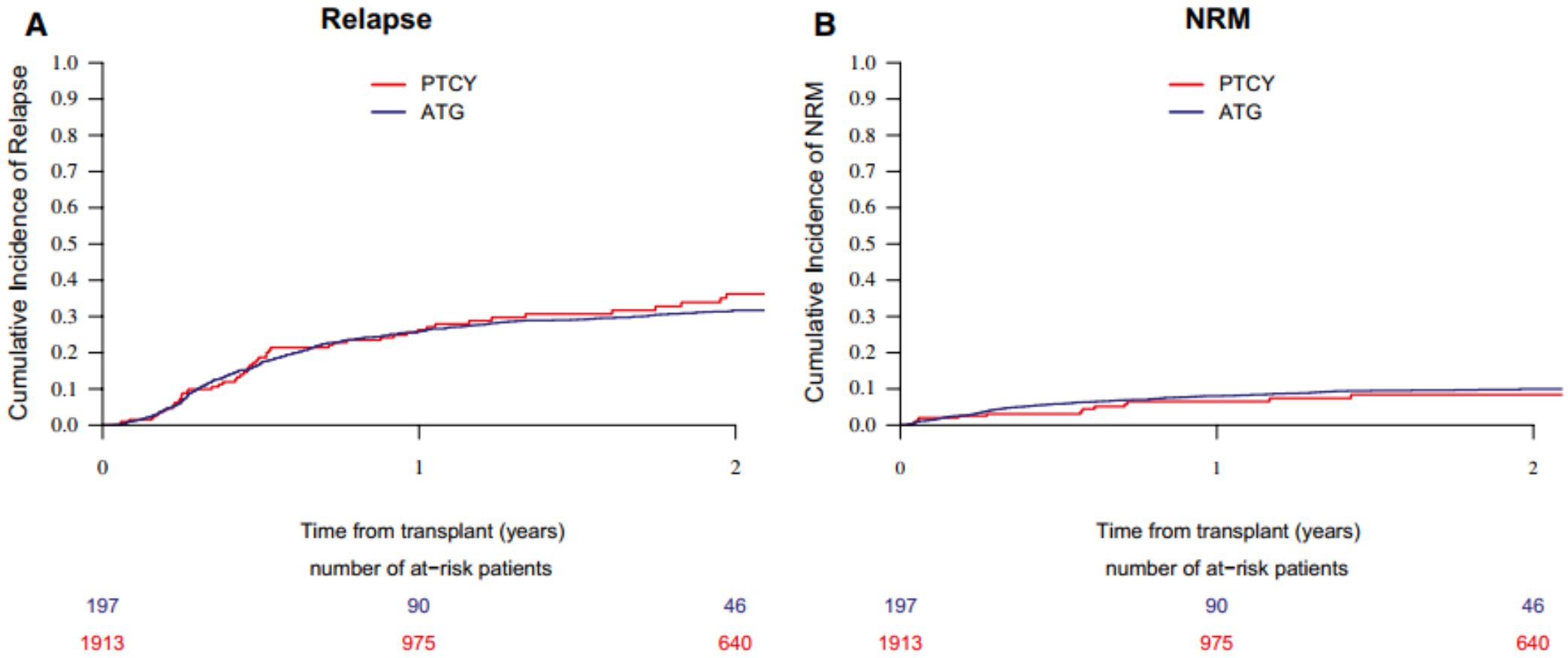
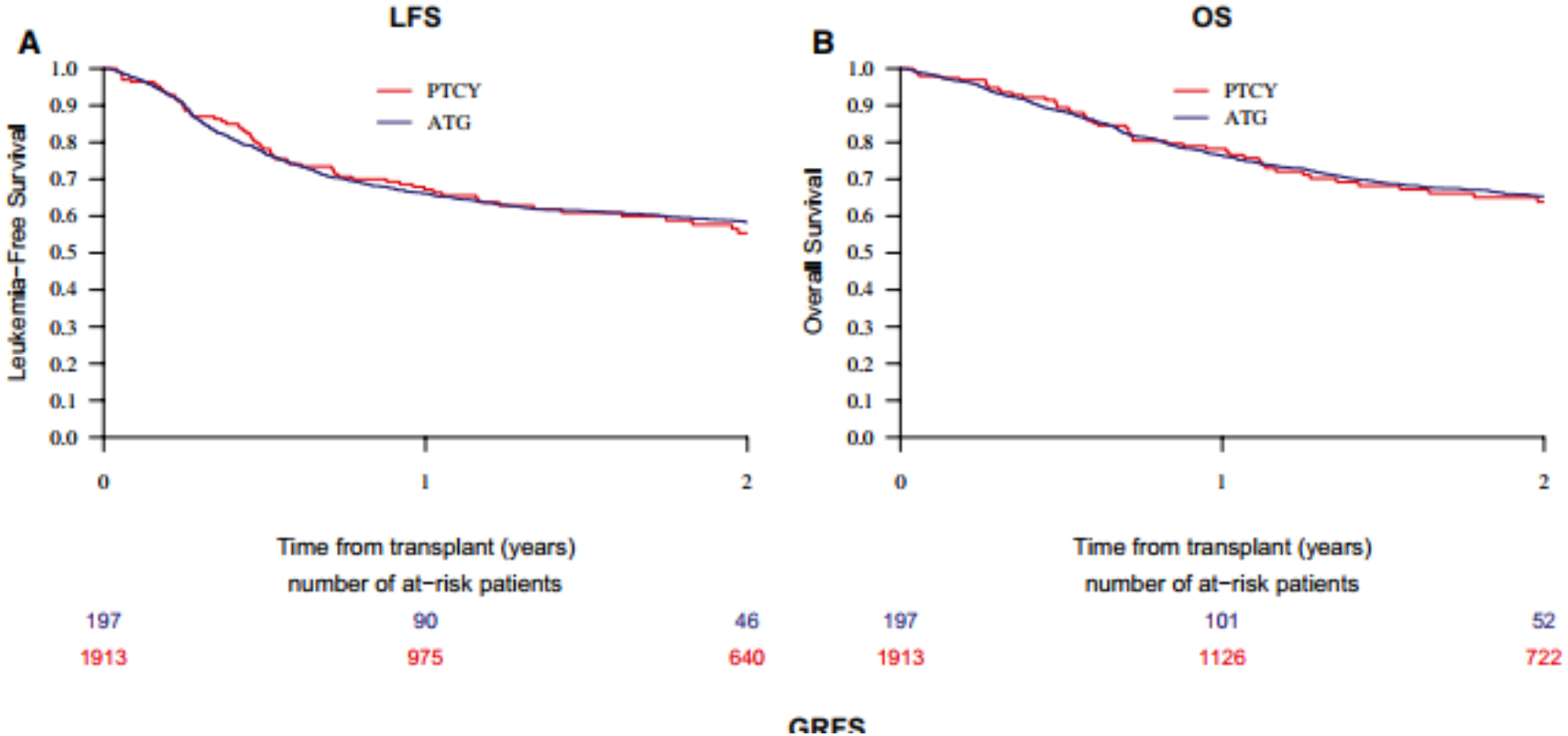
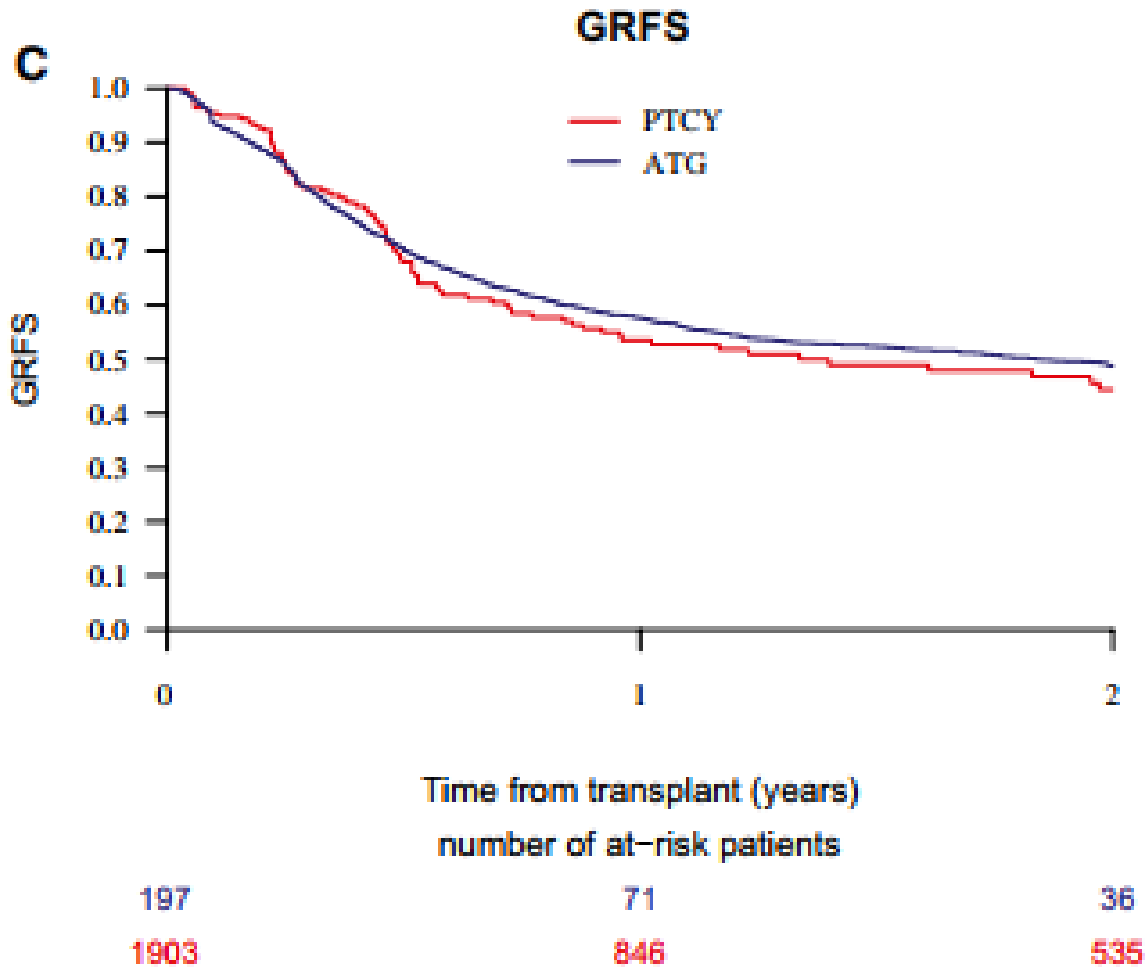


Figure 2. Cumulative incidences of (a) relapse incidence and (b) nonrelapse mortality at 2 years according to the use of Post-transplantation Cyclophosphamide or antithymocyte globulin. ATG, antithymocyte globulin; NRM, nonrelapse mortality; PTCY, Post-transplantation Cyclophosphamide.


A
LFS
Leukemia−Free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
PTCY
ATG
0
1
2
Time from transplant (years)
number of at−risk patients
197
90
46
1913
975
640
B
OS
Overall Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
PTCY
ATG
0
1
2
Time from transplant (years)
number of at−risk patients
197
101
52
1913
1126
722

GRFS


C
GRFS
PTCY
ATG
GRFS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
Time from transplant (years)
number of at−risk patients
197
71
36
1903
846
535

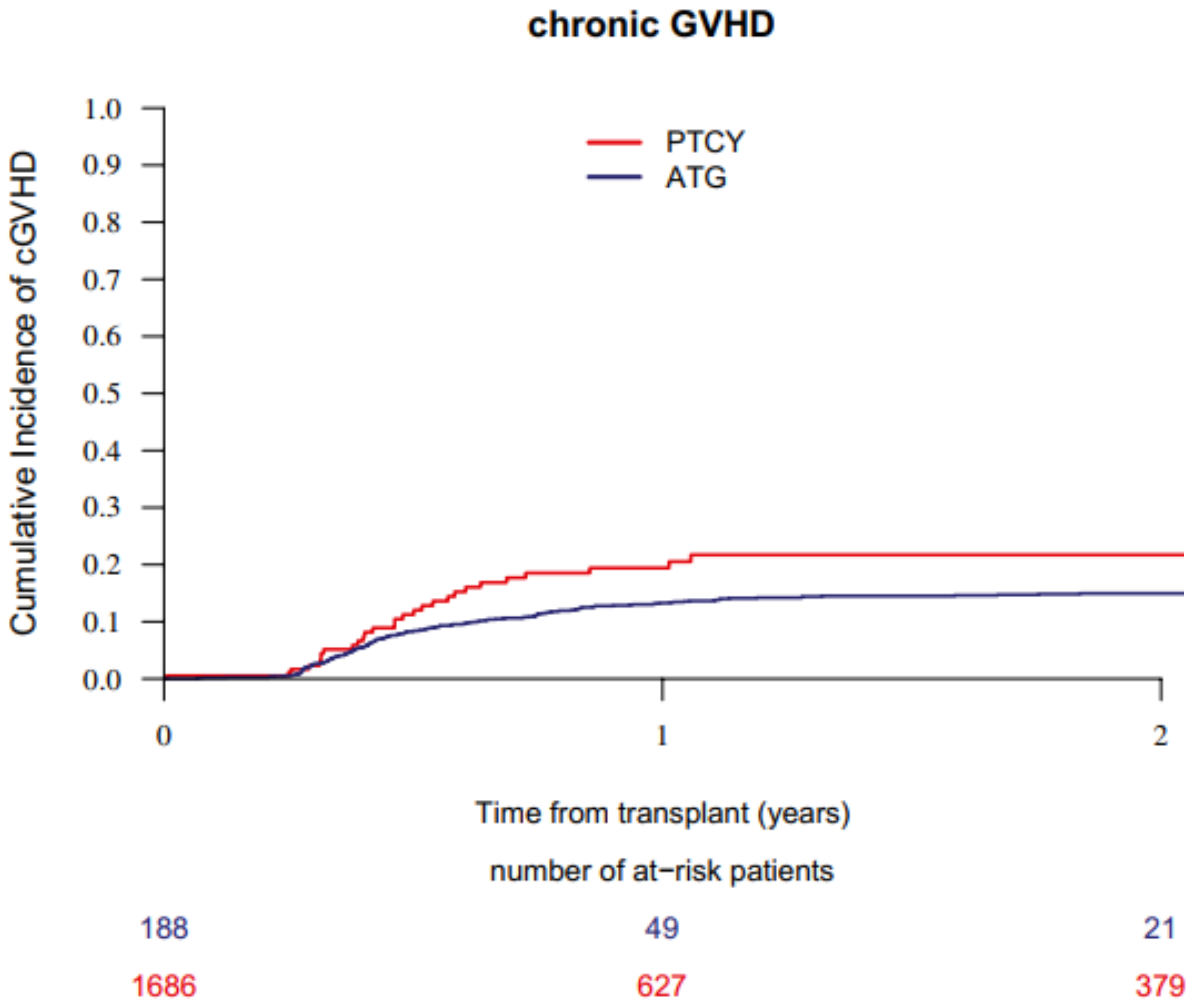


TABLE 3. Multivariate Analysis

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

Abbreviations: ATG, antithymocyte globulin; GRFS, graft-versus-host disease/relapse-free survival; GVHD, graft-versus-host disease; HR, hazard ratio; LFS, leukemia-free survival; NRM, nonrelapse mortality; OS, overall survival; PTCY, posttransplant cyclophosphamide; RI, relapse incidence.

PTCY was also explored. While the lower risk of chronic GVHD with ATG was confirmed in patients receiving 1 associated immunosuppressive agent, the same was not true when considering patients receiving 2 or 3 drugs in association with either ATG or PTCY, with similar rates of chronic GVHD (Supporting Table 4).

However, our results provide further proof that both ATG and PTCY represent valid GVHD prophylactic strategies in transplantations from HLA-identical siblings, with more favorable results than those obtained with standard immunosuppressive agents in terms of GVHD and similar survival outcomes, thus deserving consideration as GVHD prophylaxis strategies in routine clinical practice.

Received: 11 December 2022 | Revised: 26 February 2023 | Accepted: 28 February 2023

DOI: 10.1002/cncr.35004

ORIGINAL ARTICLE

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

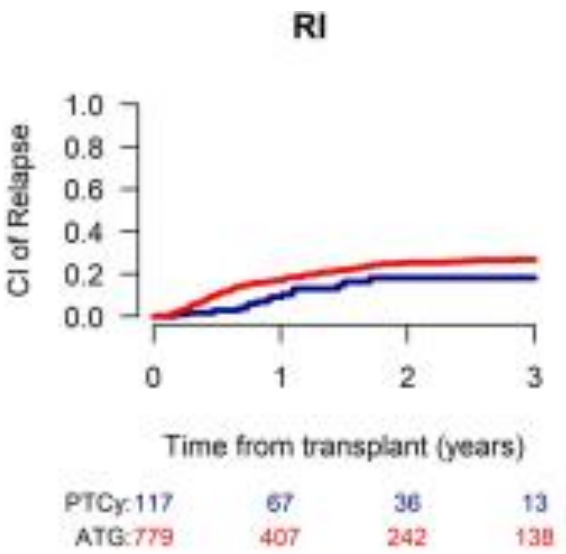
Sebastian Giebel MD[1] | Myriam Labopin MD[2,3] | Urpu Salmenniemi MD[4] | Gerard Socié MD[5] | Sergey Bondarenko MD[6] | Didier Blaise MD[7] | Nicolaus Kröger MD[8] | Jan Vydra MD[9] | Anna Grassi MD[10] | Francesca Bonifazi MD[11] | Tomasz Czerw MD[1] | Achilles Anagnostopoulos MD[12] | Bruno Lioure MD[13] | Annalisa Ruggeri MD[14] | Bipin Savani MD[15] | Alexandros Spyridonidis MD[16] | Jaime Sanz MD[17] | Zinaida Peric MD[18] | Arnon Nagler MD[19] | Fabio Ciceri MD[14] | Mohamad Mohty MD[2,3]

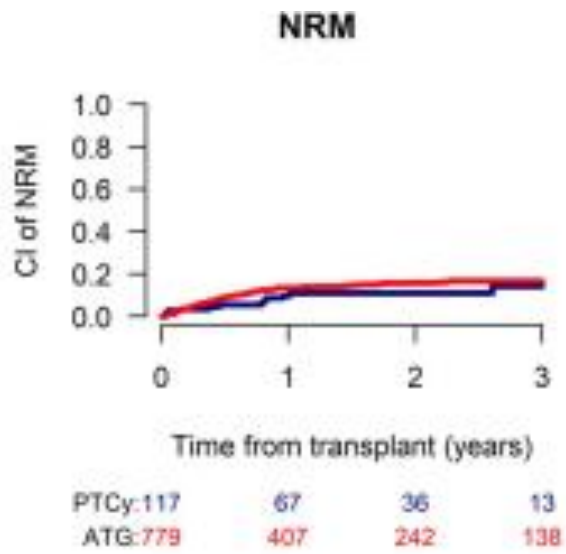
TABLE 1 Patient, donor, and transplantation characteristics.

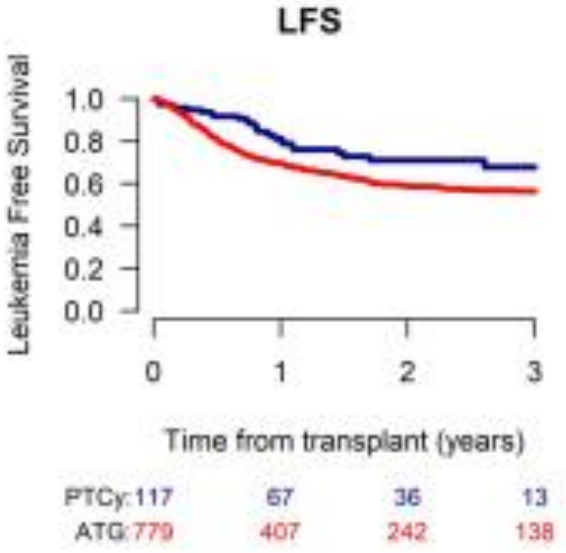
Characteristic	PTCY, *n* = 117	ATG, *n* = 779	*p*
Patient CMV serologic status: No. (%)			
Positive	75 (65)	491 (64)	.74
Negative	40 (35)	281 (36)	
Missing	2	7	
Donor CMV serologic status: No. (%)			
Positive	52 (45)	341 (44)	.86
Negative	63 (55)	428 (56)	
Missing	2	10	
Source of stem cells: No. (%)			
Peripheral blood	112 (96)	714 (92)	.13
Bone marrow	5 (4)	65 (8)	
Conditioning intensity: No. (%)			
Myeloablative	90 (77)	634 (81.5)	.24
>2	18 (17)	112 (18)	
Missing	12	155	
Patient sex: No. (%)			
Male	71 (61)	445 (57)	.41
Female	45 (39)	334 (43)	
Missing	1	–	
Donor sex: No. (%)			
Male	87 (75)	561 (73)	.63
Female	29 (25)	209 (27)	
Missing	1	9	
Donor/patient sex: No. (%)			
Female/male	21 (18)	102 (13)	.15
Other combinations	95 (82)	672 (87)	
Missing	1	5	

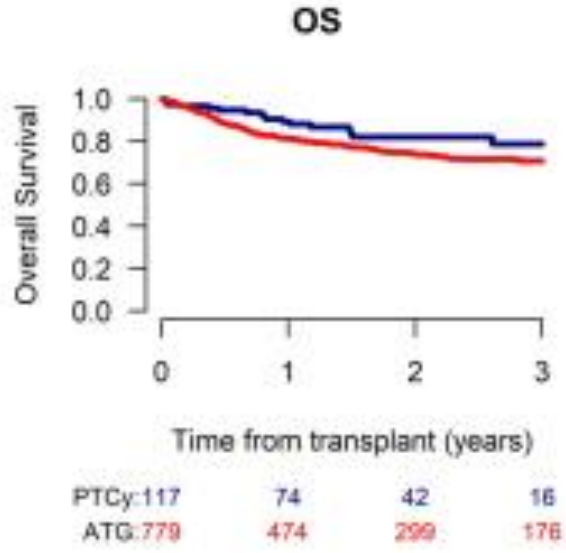
Aa 2015-2020
Studio di registro
117 PTCy e 779 ATG
Differenze statisticamemte significative :
Eta’ (40 vs 43 anni),
anno del trapianto (2018 vs 2017)
PS K score inferiore a 90 ((30% vs 20%)

Immunosuppression: No. (%)	
Cyclosporin A + MTX	–
Cyclosporin A + MMF	32 (27)
Cyclosporin A alone	14 (12)
Tacrolimus + MMF	43 (37)
Tacrolimus + MTX	–
Tacrolimus alone	12 (10)
Sirolimus + MMF	10 (9)
Cyclosporin A + MTX + MMF	–
Other	6 (5)









We conclude that the use of ATG compared with PTCY, despite a reduced risk of extensive chronic GVHD, is associated with inferior LFS in adults with ALL in CR1 undergoing allo-HCT from 10/10 HLA-MUDs. The effect is probably multifactorial but mainly is related to the risk of disease recurrence. Our findings warrant verification in prospective trials.

Mancano dati sul brand, sulle dosi e sul timing dell'infusione dell'ATG

Mancano i dati sulla MRD al trapianto

Manca dato sul criterio di scelta ATG-CTX

Certezze (?): evidenze retrospettive mono o pluricentriche

Received: 15 April 2023Accepted: 31 July 2023

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ORIGINAL PAPER

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

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Aa 2014-2021

lab. The NMC regimen in the ATG group consisted of ATG rabbit 2 mg/kg on days −8 to −5, fludarabine 30 mg/m^2 on days −4 to −2 and total body irradiation (TBI) 2 Gy on day −1. The standard GvHD prophylaxis in the ATG group consisted of ciclosporin starting from day −3 with a target level of 200–300 ng/mL and mycophenolate mofetil 15 mg/kg/8 h day 0–84. Ciclosporin was tapered after 100 days post-transplantation in the absence of GvHD. The main NMC regimen (96%) in the PTCy group consisted of cyclophosphamide 14.5 mg/kg on days −6 and −5, fludarabine 30 mg/m^2 on days −6 to −2, and TBI 2 Gy on day −1. Three patients (4%) received fludarabine 50 mg/m^2 on days −5 to −3 and TBI 2 Gy on day −2. All patients in the PTCy group received intravenous cyclophosphamide 50 mg/kg on days +3 and +4 and cyclosporine (target level of 200–300 ng/mL) from day +5 to +70 as GvHD prophylaxis. Graft source was unmanipulated peripheral blood stem cells in most patients (99%).

TABLE 1 Baseline characteristics.

	ATG ($n=95$)	PTCy ($n=90$)	p-Value
Age, median IQR	60 (52–66)	57 (48–66)	0.43
Disease risk,[a] n (%)			0.29
Non-adverse risk	38 (40)	43 (48)	
Adverse risk	57 (60)	47 (52)	
Diagnosis, n (%)			0.71
AML	47 (50)	39 (43)	
ALL	6 (6)	11 (12)	
MDS	15 (16)	15 (17)	
CLL/HL/NHL	24 (25)	22 (24)	
CML/CMML	3 (3)	3 (3)	
Disease response at HSCT, n (%)			0.78
CR1	54 (57)	58 (64)	
≥CR2	25 (26)	20 (22)	
PR	7 (7)	4 (5)	
SD/Upfront	9 (10)	8 (9)	

Lines of therapy, *n* (%)			0.35
1	57 (60)	60 (67)	
≥2	38 (40)	30 (33)	
WHO performance score, *n* (%)			0.11
0–1	93 (98)	83 (92)	
2	2 (2)	7 (8)	
HCT-CI, *n* (%)			0.11
0–1	41 (43)	50 (56)	
≥2	54 (57)	40 (44)	
CMV serostatus R/D			0.22
+/+	43 (45)	35 (39)	
+/–	8 (9)	17 (19)	
–/+	7 (7)	6 (7)	
–/–	37 (39)	32 (35)	
CD34+ cell dose, median (IQR)	7.0 (5.7–8.9)	7.1 (5.6–9.5)	0.53
CD3+ cell dose, median (IQR)	259 (201–335)	258 (188–329)	0.65
Follow-up in months, median (range)	46 (15–103)	36 (12–92)	
Engraftment			
Cumulative incidence of neutropenia (neutrophils $<0.5 \times 10^9$/L), (95% CI)	60% (49–69)	96% (88–98)	<0.001
Median neutrophil engraftment days, IQR	20 (15–24)	22 (19–26)	0.036
Cumulative incidence of thrombocytopenia (platelets $<20 \times 10^9$/L), (95% CI)	32% (22–41)	83% (74–90)	<0.001
Median platelet engraftment days, IQR	19 (15–22)	22 (16–33)	0.07

TABLE 2 Transplantation outcomes.

	ATG ($n=95$) (95% CI)	PTCy ($n=90$) (95% CI)	p-Value
Cumulative incidence of GvHD			
Acute GvHD II–IV (1 year)	48% (37–58)	21% (13–30)	0.0002
Acute GvHD III–IV (1 year)	19% (12–28)	2% (1–7)	0.0002
Chronic GvHD mod/sev (3 years)	27% (17–38)	27% (17–37)	0.69
Chronic GVHD severe (3 years)	4% (1–11)	11% (1–19)	0.26

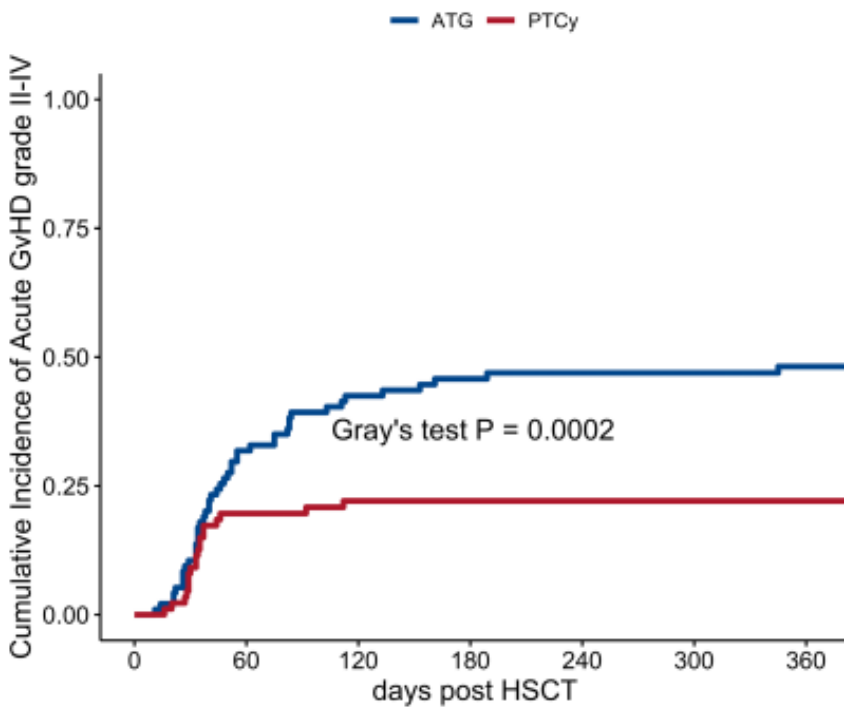


FIGURE 1 Cumulative incidence of acute GvHD grade II–IV.

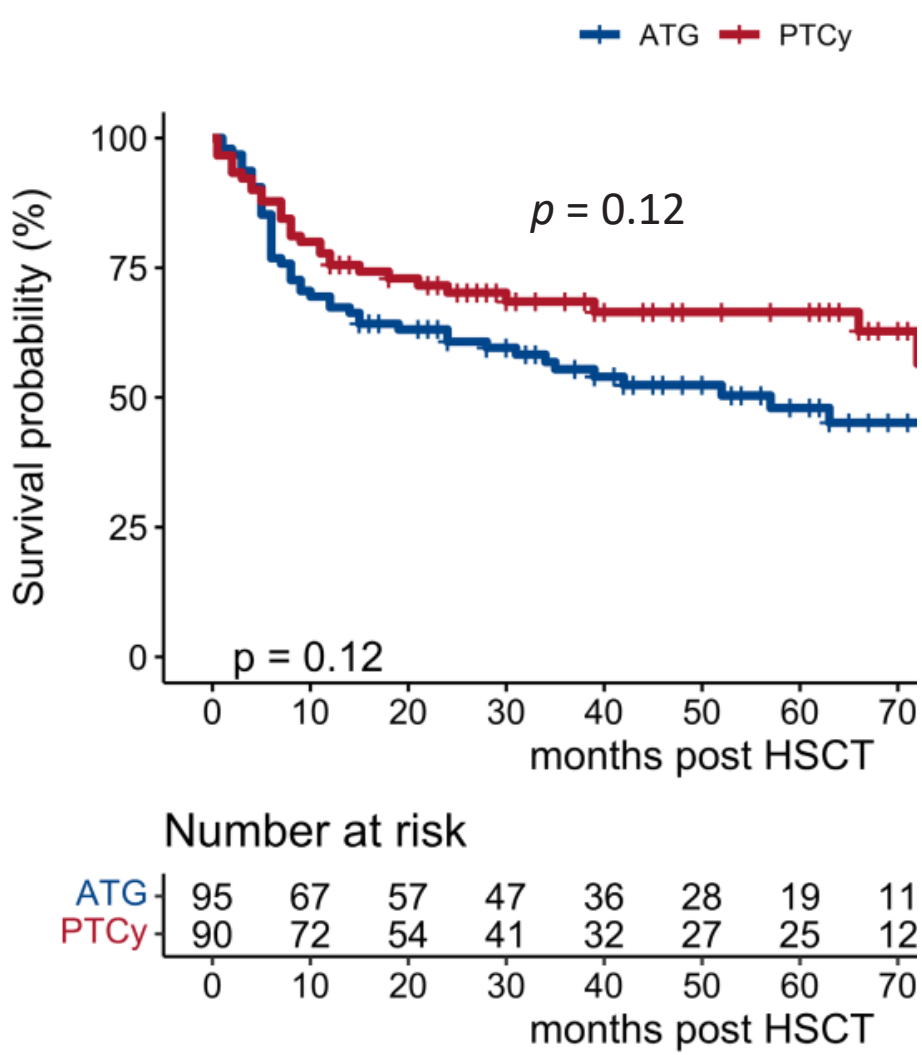


FIGURE 2 Overall survival probability for both t

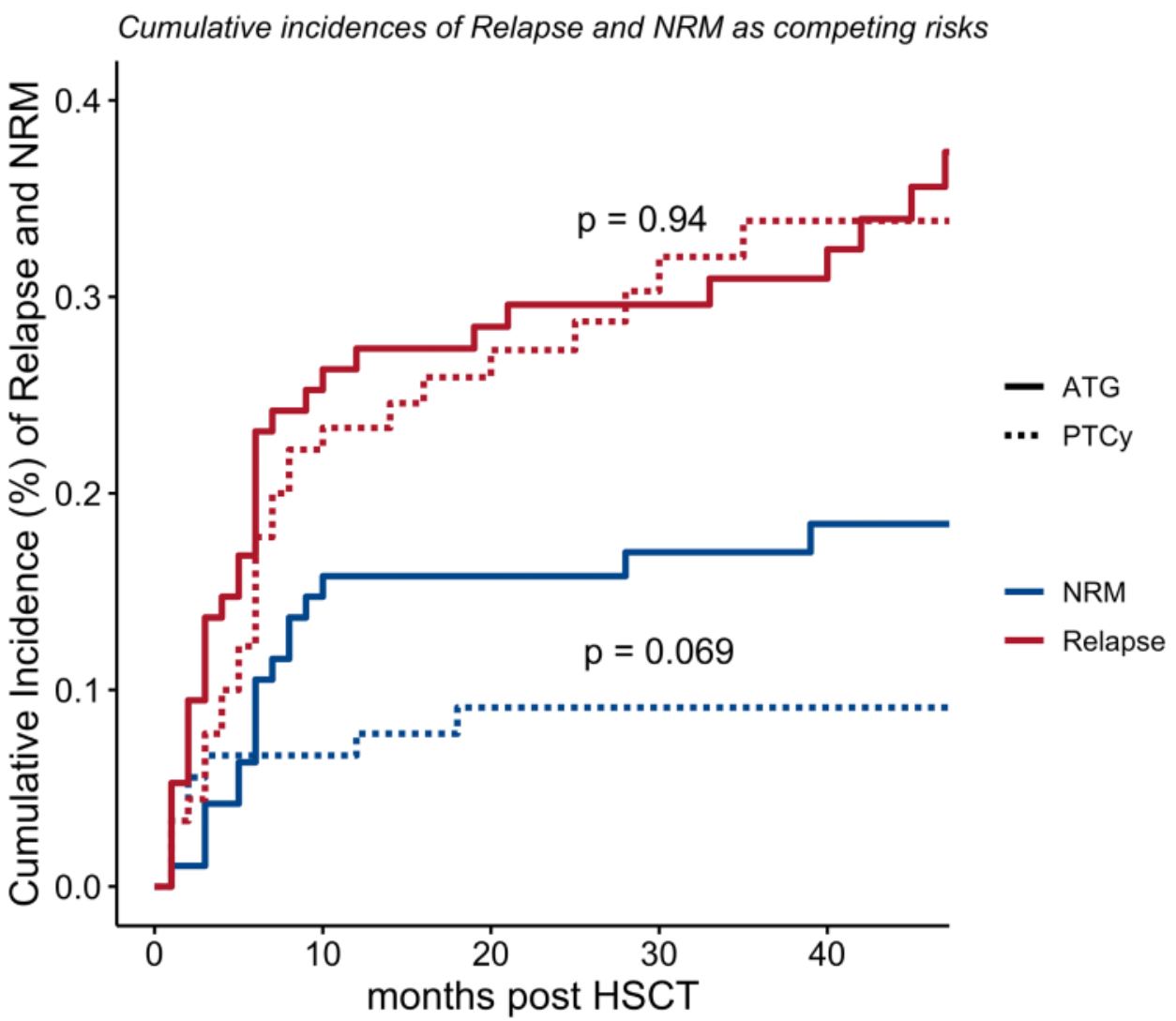


FIGURE 3 Cumulative incidence of relapse and NRM in the competing risk setting.

COMMENT

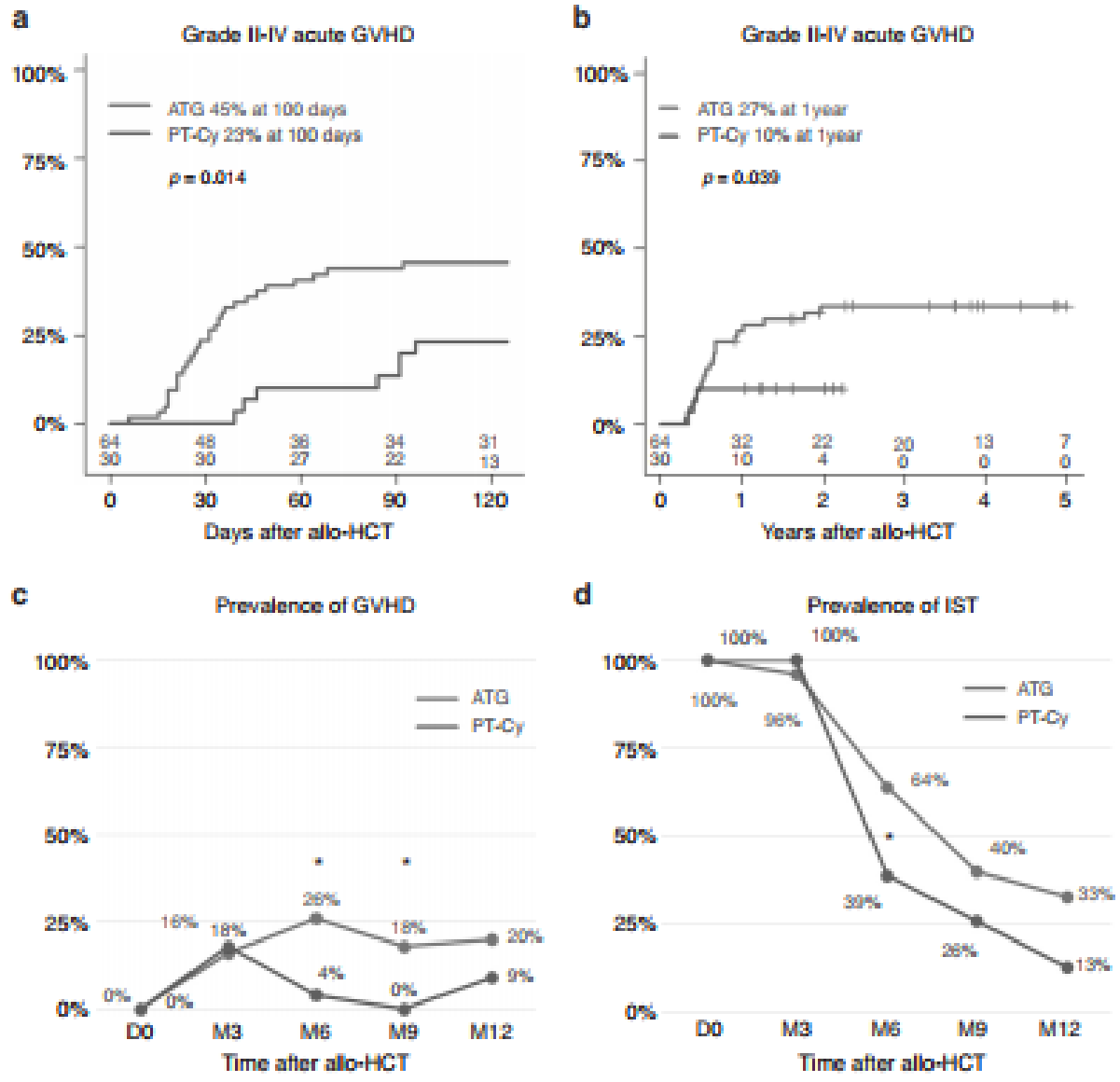
Check for updates

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]✉

We analyzed 30 consecutive patients who received PBSC MUD allo-HCT with PT-Cy as GVHD prophylaxis from April 2020 to July 2021. PT-Cy (50 mg/kg/day) was given on days+3 and 4, reduced at 40 mg/kg/day for patients ≥65 years. Cyclosporine A (CSA) and mycophenolate mofetil (MMF) were given as additional GVHD prophylaxis starting on day+5 and granulocyte-colony stimulating factor (G-CSF) was administered from day+5 to neutrophil recovery. In the absence of GVHD, MMF was discontinued at day+35 and CSA was progressively tapered from day+60 to day+120. We compared these patients to an historical cohort of 64 consecutive patients undergoing PBSC MUD allo-HCT between 2014 and March 2020 using a homogeneous platform of fludarabine, 2-day i.v. busulfan (FB2) and ATG (Thymoglobuline®, 2.5 mg/kg/day on day −3 and day −2) plus CSA without G-CSF, as previously described [4].

	ATG group (n = 64)		PT-Cy group (n = 30)		p
	n	%	n	%	
Age, median (range)	55	(22-70)	59	(18-75)	0.629
Diagnosis					
ALL	7	11%	5	17%	0.830
AML	31	48%	12	40%	
HL	2	3%	2	7%	
MDS	8	13%	4	13%	
NHL	16	25%	7	23%	
HCT-CI					
≥3	36	56%	16	53%	0.966
<3	28	44%	14	47%	
DRI					
Low	6	9%	7	23%	0.156
Intermediate	51	80%	19	63%	
High - very high	7	11%	4	13%	
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%	
Status					
CR	56	88%	29	97%	0.302
Non-CR	8	13%	1	3%	
CMV status (D/R)					
Positive/Negative	11	17%	2	7%	0.264
Negative/Negative	18	28%	6	20%	
Positive/Positive	15	23%	15	50%	
Negative/Positive	20	31%	7	23%	
Follow-up (months)	52		19		


a
Grade II-IV acute GVHD
100%
75%
50%
25%
0%
ATG 45% at 100 days
PT-Cy 23% at 100 days
p = 0.014
64
30
48
30
36
27
34
22
31
13
0
30
60
90
120
Days after allo-HCT
b
Grade II-IV acute GVHD
ATG 27% at 1year
PT-Cy 10% at 1year
p = 0.039
64
30
32
10
22
4
20
0
13
0
7
0
0
1
2
3
4
5
Years after allo-HCT
c
Prevalence of GVHD
ATG
PT-Cy
0%
16%
18%
26%
18%
20%
0%
4%
0%
9%
D0
M3
M6
M9
M12
Time after allo-HCT
d
Prevalence of IST
100%
100%
100%
96%
64%
40%
33%
39%
26%
13%
Time after allo-HCT

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Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

Full Length Article
Allogeneic – Adult

Post-Transplantation Cyclophosphamide Versus Tacrolimus and Methotrexate Graft-Versus-Host Disease Prophylaxis for HLA-Matched Donor Transplantation

Rohtesh S. Mehta*, Rima M. Saliba, Gabriela Rondon, Gheath Al-Atrash, Qaiser Bashir, Chitra M. Hosing, Partow Kebriaei, Issa Khouri, Yago Nieto, Betul Oran, Uday R. Popat, Muzaffar H. Qazilbash, Jeremy Ramdial, Samer A. Srour, Richard E. Champlin, Katayoun Rezvani, Elizabeth J. Shpall, Amin M. Alousi

Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas

METHODS

We included adult patients who underwent first allogeneic HCT using an MSD or a MUD between January 2015 and July 2020 with any conditioning regimen, and intensity and received either PTCy-based or Tac/MTX-based GVHD prophylaxis. We excluded patients who received manipulated or ex vivo TCD grafts. The objectives were to compare the rates of acute and chronic GVHD, neutrophil and platelet engraftment, chimerism, non-relapse mortality (NRM), relapse, progression-free survival (PFS), overall survival (OS), GRFS, infections, organ toxicities, and immune reconstitution.

and 11. All MUD recipients also received rabbit ATG (Thymoglobulin) at a total dose of 4 mg/kg given over 3 days (day −3 to day −1). In the PTCy group, patients received PTCy 50 mg/kg IV on days 3 and 4 and tacrolimus from day 5. In patients who received MMF with PTCy/Tac, it was started from day 5 at a dose of 15 mg/kg IV or orally every 8 hours, with a maximum dose of 1 g/dose, and continued through day 35. The decision to use MMF or not with PTCy was dictated by specific protocols that the patients were enrolled on.

	MUD		
	Tac/MTX/ATG(N = 306)	PTCy(N = 246)	*P* Value
Age (y), median (range)			
Recipient	53 (18-79)	61 (18-77)	<.001
Donor	29 (18-59)	29 (18-60)	.9
Gender (donor/recipient)			
Female/Male	41 (13)	37 (15)	.7
Others	265 (87)	208 (85)	
Missing	0	1	
Race/Ethnicity			<.001
White, non-Hispanic	220 (72)	203 (82)	
Black, non-Hispanic	3 (1)	7 (3)	
Hispanic or Latino	37 (12)	19 (8)	
Other/unknown	46 (15)	17 (7)	
Disease			<.001
Myeloid	180 (59)	221 (90)	
Lymphoid	126 (41)	25 (10)	
Disease			<.001
AML/MDS	158 (52)	184 (75)	
ALL	63 (21)	10 (4)	
Chronic lymphoid malignancies*	63 (21)	15 (6)	
Chronic myeloid malignancies†	22 (7)	37 (15)	
Graft			
Peripheral blood	195 (64)	190 (77)	.001
Bone marrow	111 (36)	56 (23)	
Conditioning intensity			.3
Myeloablative	196 (64)	148 (60)	
Reduced-intensity	110 (36)	98 (40)	
MAC regimens			
Bu/Flu ± other	185 (94)	148 (0)	.002
TBI-MAC	11 (6)	0 (0)	
RIC regimens			<.001
Flu/Mel100	36 (33)	69 (70)	
Flu/Mel140	35 (32)	23 (23)	
Bu/Flu (RIC)	1 (1)	6 (6)	
Other RIC	38 (34)	0 (0)	
GVHD prophylaxis			NA
Tac/MTX	0 (0)	0 (0)	
Tac/MTX/ATG	306 (100)	0 (0)	
PTCy/Tac	0 (0)	138 (56)	
PTCy/Tac/MMF	0 (0)	108 (43)	
DRI			.9
Low/Intermediate	196 (64)	159 (65)	
High/Very high	110 (36)	87 (35)	
Missing		0	
HCT-CI			.1
0-2	123 (40)	116 (47)	
≥3	182 (60)	130 (53)	
Missing	1	0	
Recipient CMV serostatus			<.001
Positive	259 (84)	172 (70)	
Negative	46 (15)	74 (30)	
Missing	1	0	
HCT year			
Median (range)	2016 (2015-2020)	2018 (2015-2020)	
Follow-up in surviving patients (mo), median (range)	53 (16-79)	29 (3-64)	

Table 2
Outcomes

	Cumulative incidence (95% CI)					
	MUD			MSD		
	Tac/MTX/ATG	PTCy	*P* Value	Tac/MTX	PTCy	*P* Value
Acute GVHD, grade II-IV, Day 180	42% (37-48)	52% (46-58)	.03	37% (31-43)	44% (36-53)	.2
Acute GVHD, grade III-IV, Day 180	9% (7-13)	8% (5-12)	.4	8% (5-12)	11% (7-17)	.5
Steroid-refractory/dependent acute GVHD	16% (13-21)	11% (8-16)	.1	10% (7-15)	13% (8-21)	.6
Overall chronic GVHD, 3 years	19% (15-24)	18% (13-24)	.5	37% (32-44)	19% (13-27)	<.001
Therapy-requiring chronic GVHD, 3 years	11% (8-15)	9% (6-14)	.4	29% (24-35)	10% (6-17)	<.001
Nonrelapse mortality, 3 years	23% (19-29)	13% (9-19)	.002	13% (9-18)	11% (6-18)	.4
Relapse, 3 years	28% (24-34)	29% (24-36)	.9	33% (28-39)	32% (25-41)	.6
Progression-free survival, 3 years	48% (42-53)	57% (51-64)	.01	54% (48-60)	57% (48-66)	.3
Overall survival, 3 years	55% (49-61)	61% (54-67)	.05	61% (55-67)	65% (55-73)	.2
GVHD-Free Relapse-Free Survival	37% (32-43)	47% (40-54)	.01	29% (23-34)	47% (38-56)	<.001

RESEARCH LETTER

blood advances

TO THE EDITOR:

Letermovir reduces chronic GVHD risk in calcineurin inhibitor-free GVHD prophylaxis after hematopoietic cell transplantation

Francesca Lorentino,[1,2,*] Elisabetta Xue,[1,*] Sara Mastaglio,[1] Fabio Giglio,[1] Daniela Clerici,[1] Francesca Farina,[1] Simona Piemontese,[1] Alessandro Bruno,[1] Lorenzo Lazzari,[1] Annalisa Ruggeri,[1] Elena Guggiari,[1] Francesca Lunghi,[1] Andrea A. Assanelli,[1] Sarah Marktel,[1] Magda Marcatti,[1] Matteo G. Carrabba,[1] Massimo Bernardi,[1] Consuelo Corti,[1] Jacopo Peccatori,[1] Fabio Ciceri,[1,3] Raffaella Greco,[1,†] and Maria Teresa Lupo-Stanghellini[1,†]

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BRIEF RESEARCH REPORT
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Evidence for a Bidirectional Relati Cytomegalovirus Replication Graft-versus-Host Dise

Nathan Cantoni,[1] Hans H. Hirsch,[2,3] Nina Khanna,[2,3] Sabi Christoph Bucher,[1] Jörg Halter,[1] Dominik Heim,[1] Alois Gratwohl,[1] Martin Stern[1]

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Reviewed by:
Suparno Chakrabarti,
Narayana Health, India

Letermovir Administration to Prevent Cytomegalovirus Reactivation Is the Potential Risk of Chronic Graft-*Versus*-Host Disease in Patients Who Received Haploidentical Stem-Cell Transplantation With Post-Transplant Cyclophosphamide

Toshiki Terao[1], Ken-ichi Matsuoka[2], Kentaro Narita[1], Takafumi Tsushima[1], Satoshi Yuyama[3], Ayumi Kuzume[1], Rikako Tabata[1], Daisuke Miura[1], Masami Takeuchi[1] and Kosei Matsue[1]*

Augmented Reduced-Intensity Regimen Does Not Improve Postallogeneic Transplant Outcomes in Acute Myeloid Leukemia

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Naeem Khan, PhD[3]; Nicholas McCarthy, PhD[3]; and Sylvie D. Freeman, MD[3]

Non sempre i dati dei lavori retrospettivi sono confermati dagli studi prospettici

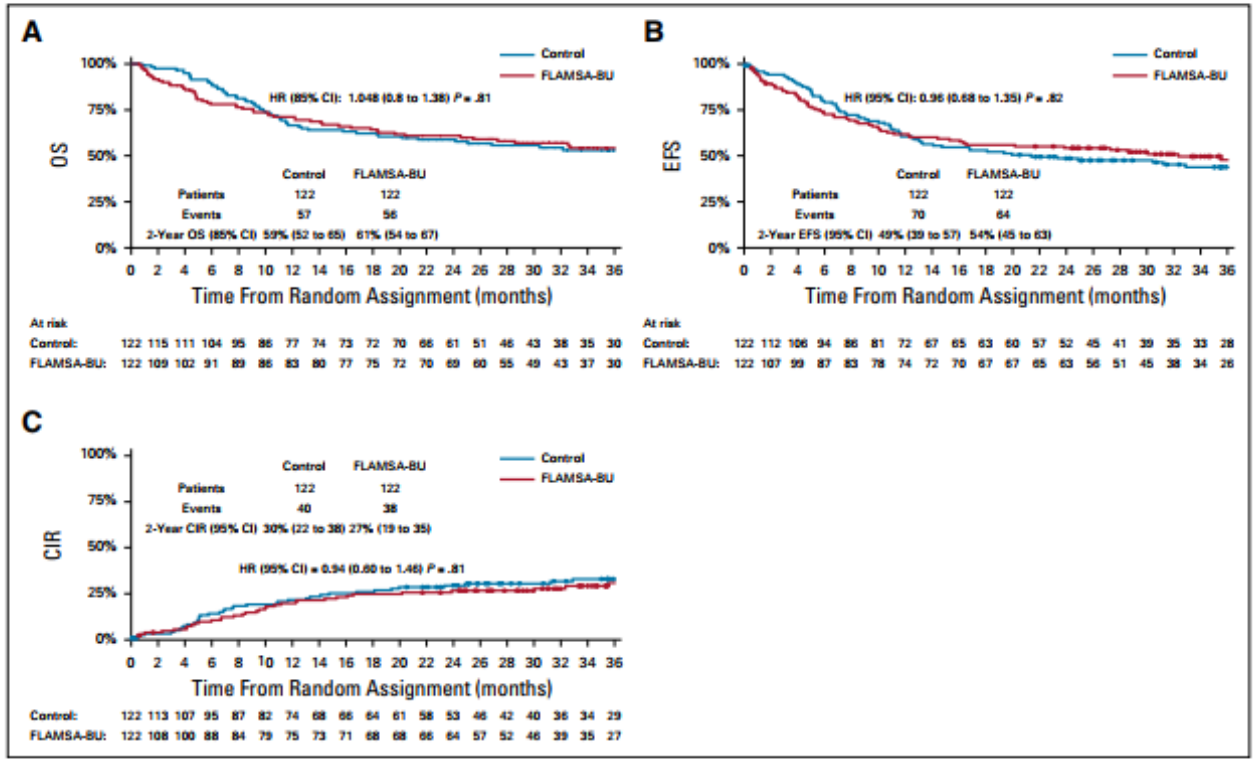

FIG 2. (A) OS, (B) EFS, and (C) CIR by conditioning regimen in the intention-to-treat population. 85% CIs are reported for overall survival to align with the type I error rate applied in the sample size calculation (described in the Data Supplement). CIR, cumulative incidence of relapse; EFS, event-free survival; FLAMSA-Bu, fludarabine/amsacrine/cytarabine-busulphan; HR, hazard ratio; OS, overall survival.

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Fattori confondenti

Dosi e schedule ATG

Immunosoppressione associata con CTX

Stato al trapianto

Patologia di base

Regimi di condizionamento

Ruolo del letermovir

Follow up

Manca uno studio prospettico randomizzato

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