

Impact of ABO incompatibility on patients' outcome after haploidentical hematopoietic stem cell transplantation for acute myeloid leukemia - a report from the Acute Leukemia Working Party of the EBMT

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Received: November 23, 2016.

Accepted: February 20, 2017.

Pre-published: March 2, 2017.

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Supplementary table 1. Cause of death per ABO incompatibility category.

	ABO matched	Minor ABO mismatch	Major ABO mismatch	Bidirectional mismatch
Cardiac toxicity	3 (1.2%)	1 (1.5%)	0	0
Hemorrhage	3 (1.2%)	1 (1.5%)	1 (1.4%)	0
Failure/Rejection	3 (1.2%)	0	1 (1.4%)	0
VOD	3 (1.2%)	4 (5.9%)	3 (4.3%)	1 (9.1%)
Infection	83 (32%)	20 (29.4%)	20 (28.6%)	4 (36.4%)
IP	7 (2.7%)	2 (2.9%)	4 (5.7%)	1 (9.1%)
GVHD	43 (16.6%)	13 (19.1%)	9 (12.9%)	1 (9.1%)
Leukemia	106 (40.9%)	23 (33.8%)	26 (37.1%)	3 (27.3%)
Second malignancy	0	0	1 (1.4%)	0
Other	8 (3.1%)	4 (5.9%)	5 (7.1%)	1 (9.1%)
Unknown	9	2	2	1

IP, Interstitial pneumonitis; VOD, veno-occlusive disease; GVHD, graft versus host disease.

Supplementary Table 2. Univariate analysis of clinical outcome according to ABO mismatch group.

	3 year RI	P	3 year NRM	P	3 year LFS	P	3 year OS	P	3 year GRFS	P	3 year acute GVHD II-IV	P	3 year chronic GVHD	P	3 year extensive chronic GVHD	P
ABO matched	29.1% [25.2-33.1]	0.063	26.2% [22.4-30.1]	0.769	44.7% [40.3-49.1]	0.024	47.7% [43.2-52.2]	0.322	36.9% [32.6-41.1]	0.033	28.9% [25-32.9]	0.124	29.1% [25.2-33.2]	0.391	12.5% [9.7-15.5]	0.895
Minor ABO mismatch	23.9% [17.3-31.1]		26% [19.1-33.4]		50.1% [41.9-58.4]		51.6% [43.3-59.9]		42.8% [34.7-51]		33.6% [26.1-41.3]		36.2% [28.3-44]		13.3% [8.3-19.6]	
Major ABO mismatch	31.1% [23-39.5]		28.8% [21.1-37]		40.1% [31.3-48.9]		45.3% [36.4-54.1]		33.3% [24.8-41.7]		34.2% [25.9-42.6]		30.9% [22.8-39.3]		10.4% [5.8-16.6]	
Bidirectional mismatch	10.6% [3.3-22.9]		22.2% [10.2-37.2]		67.2% [51.8-82.6]		67% [51.6-82.5]		54.2% [38-70.4]		44.9% [28.5-60]		27.4% [14-42.5]		11% [3.4-23.7]	
ABO matched	29.1% [25.2-33.1]	0.213	26.2% [22.4-30.1]	0.976	44.7% [40.3-49.1]	0.266	47.7% [43.2-52.2]	0.533	36.9% [32.6-41.1]	0.371	28.9% [25-32.9]	0.057	29.1% [25.2-33.2]	0.234	12.5% [9.7-15.5]	0.635
ABO mismatch	25.2% [20.4-30.2]		26.7% [21.8-31.7]		48.2% [42.5-53.8]		50.8% [45.1-56.5]		40.4% [34.8-46]		35.2% [29.9-40.6]		33% [27.7-38.3]		11.9% [8.5-15.8]	
ABO matched	29.1% [25.2-33.1]	0.085	26.2% [22.4-30.1]	0.819	44.7% [40.3-49.1]	0.188	47.7% [43.2-52.2]	0.351	36.9% [32.6-41.1]	0.235	28.9% [25-32.9]	0.187	29.1% [25.2-33.2]	0.806	12.5% [9.7-15.5]	0.464
Major O mismatch	32.8% [23.5-42.5]		25.7% [17.5-34.7]		41.5% [31.4-51.5]		44.7% [34.7-54.8]		33.5% [23.8-43.1]		33.5% [24.2-43.1]		30.8% [21.6-40.5]		9.4% [4.6-16.4]	
Major A mismatch	32.6% [10.8-56.9]		32.6% [10.9-56.8]		34.7% [10.5-58.9]		44.6% [23.5-73.7]		35.2% [10.9-59.4]		26.7% [7.7-50.6]		26% [7.2-50.3]		6.2% [0.4-25.7]	
Major B mismatch	15.4% [2.1-40.5]		47.7% [17.6-72.9]		36.9% [9.9-64]		44.9% [17.2-72.6]		30.8% [5.7-55.9]		46.2% [17.7-70.8]		38.5% [12.3-64.7]		23.1% [4.9-49.1]	
Minor A mismatch	25.8% [16.4-36.3]		24.4% [15.3-34.8]		49.7% [38.3-61.2]		50.5% [38.9-62.1]		40.8% [29.6-52]		40.7% [29.3-51.8]		35.3% [24.5-46.3]		16.2% [8.8-25.5]	
Minor B mismatch	9.1% [2.3-22]		31.8% [16.1-48.8]		59.1% [41.6-76.6]		47.2% [31.2-63.3]		48.2% [29.3-67]		33.3% [17.9-49.6]		42.4% [23.1-60.6]		18.5% [5.9-36.6]	
Minor AB mismatch	32.4% [18.3-47.4]		23.8% [12.2-37.6]		43.8% [28.2-59.3]		47.2% [31.2-63.3]		41.3% [25.8-56.7]		21.5% [10.5-35]		33.8% [19.7-48.5]		4.8% [0.8-14.4]	
Bi-directional A mismatch	15.3% [3.6-34.8]		26% [9-47.1]		58.7% [36.6-80.7]		58.2% [36.1-80.4]		54.2% [32-76.3]		45.5% [22.5-65.9]		21.3% [6.3-42.2]		5.3% [0.3-22.4]	
Bi-directional B mismatch	5.6% [0.3-23.1]		19.4% [1-43.2]		75% [53.1-96.9]		75% [53.1-96.9]		53.5% [29.3-77.6]		44.4% [20.7-65.8]		34% [13.1-56.3]		17.1% [3.9-38.3]	

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non relapse mortality; GVHD, graft versus host disease; GRFS, GVHD-free/relapse-free survival.

Supplementary Table 3. Univariate analysis of patient outcome per ABO incompatibility status and T-cell repletion status

	3 year RI	P	3 year NRM	P	3 year LFS	P	3 year OS	P	3 year GRFS	P	3 year acute GVHD II-IV	P	3 year chronic GVHD	P	3 year extensive chronic GVHD	P
T-cell replete grafts																
ABO matched	28.9% [24.7-33.3]	0.055	23.9% [20-28]	0.846	47.2% [42.4-51.9]	0.029	50.9% [46.1-55.8]	0.077	38.9% [34.3-43.5]	0.039	29.9% [25.6-34.2]	0.315	29.6% [25.3-34]	0.06	12.2% [9.3-15.5]	0.682
Minor ABO mismatch	24.3% [17.1-32.3]		22.2% [15.1-30]		53.5% [44.5-62.5]		55.2% [46.1-64.3]		44.8% [35.7-53.8]		34.2% [26-42.5]		42.1% [33.1-50.9]		15.9% [9.8-23.3]	
Major ABO mismatch	32.1% [23.1-41.5]		24.5% [16.6-33.3]		43.4% [33.5-53.2]		48.6% [38.8-58.4]		34.7% [25.3-44.2]		36.2% [26.8-45.7]		32.8% [23.8-42.2]		9.9% [5.1-16.7]	
Bidirectional mismatch	8.8% [2.2-21.4]		21.9% [9.3-37.5]		69.4% [53.5-85.4]		69.3% [53.2-85.3]		54.9% [37.8-71.9]		41.3% [24.5-57.4]		30.7% [15.8-47.1]		12.4% [3.8-26.3]	
ABO matched	28.9% [24.7-33.3]	0.278	23.9% [20-28]	0.65	47.2% [42.4-51.9]	0.172	50.9% [46.1-55.8]	0.399	38.9% [34.3-43.5]	0.374	29.9% [25.6-34.2]	0.079	29.6% [25.3-34]	0.035	12.2% [9.3-15.5]	0.915
ABO mismatch	25.4% [20.2-31]		23% [18-28.4]		51.5% [45.3-57.7]		54.4% [48.2-60.6]		42.1% [36-48.3]		35.9% [30.1-41.8]		37% [31-42.9]		13% [9.2-17.6]	
T-cell depleted grafts																
ABO matched	30.1% [19.7-41.1]	0.551	40.4% [28.7-51.9]	0.584	29.5% [18.6-40.4]	0.851	28.9% [18-39.8]	0.949	24% [13.8-34.3]	0.817	22.3% [13.2-32.9]	0.308	26% [16-37.2]	0.057	13.9% [6.7-23.6]	0.148
ABO mismatch	24% [13-36.7]		45.3% [31-58.5]		30.8% [17.8-43.8]		32.8% [19.7-45.9]		31.5% [18.7-44.4]		32.1% [19.6-45.4]		13% [5.1-24.7]		5.9% [1.5-14.8]	

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non relapse mortality; GVHD, graft versus host disease; GRFS, GVHD-free/relapse-free survival.

Supplementary Table 4. Univariate analysis of patient outcome following transplantation with peripheral blood derived grafts.

	3 year RI	P	3 year NRM	P	3 year LFS	P	3 year OS	P	3 year GRFS	P	3 year acute GVHD II-IV	P	3 year chronic GVHD	P	3 year extensive chronic GVHD	P
ABO matched	34.9% [28.8-41.2]	0.566	32.4% [26.5-38.5]	0.783	32.6% [26.4-38.8]	0.845	35.7% [29.3-42.2]	0.851	25.6% [19.8-31.5]	0.554	28.9% [23.2-34.8]	0.452	29.4% [23.5-35.5]	0.71	13.3% [9.2-18.2]	0.536
Minor ABO mismatch	28.7% [18.3-39.9]		35.6% [23.8-47.6]		35.7% [23.7-47.6]		37.6% [25.3-50]		33.6% [22.1-45]		35% [23.6-46.6]		24.8% [14.9-36]		9.2% [3.7-17.9]	
Major ABO mismatch	37.3% [25.2-49.3]		28.8% [18.3-40.1]		34% [22-45.9]		39.4% [27.4-51.4]		25.7% [14.8-36.7]		36.9% [25.2-48.6]		30.2% [19.5-41.7]		15.1% [7.7-24.9]	
ABO matched	34.9% [28.8-41.2]	0.769	32.4% [26.5-38.5]	0.774	32.6% [26.4-38.8]	0.587	35.7% [29.3-42.2]	0.634	25.6% [19.8-31.5]	0.488	28.9% [23.2-34.8]	0.209	29.4% [23.5-35.5]	0.767	13.3% [9.2-18.2]	0.62
ABO mismatch	32.9% [24.9-41.1]		32.2% [24.2-40.4]		35% [26.5-43.4]		38.6% [30-47.2]		29.7% [21.7-37.6]		36% [27.8-44.3]		27.6% [20.1-35.5]		12.2% [7.3-18.5]	

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non relapse mortality; GVHD, graft versus host disease; GRFS, GVHD-free/relapse-free survival.

Supplementary Table 5. Univariate analysis of patient outcome following transplantation with bone marrow grafts.

	3 year RI	P	3 year NRM	P	3 year LFS	P	3 year OS	P	3 year GRFS	P	3 year acute GVHD II-IV	P	3 year chronic GVHD	P	3 year extensive chronic GVHD	P
ABO matched	24.4%[19.5-29.7]	0.41	21%[16.3-26.1]	0.35	54.6%[48.6-60.5]	0.36	57.8%[51.7-63.8]	0.47	46.2%[40.2-52.1]	0.41	28.9%[23.6-34.3]	0.3	29.1%[23.8-34.6]	0.016	11.8%[8.3-16]	0.21
Minor ABO mismatch	20%[12-29.4]		18.3%[10.8-27.4]		61.7%[51.1-72.4]		62.5%[51.8-73.2]		50.3%[39-61.5]		32.5%[22.7-42.7]		45.5%[34.1-56.3]		16.6%[9.2-26.1]	
Major ABO mismatch	19%[11.8-27.6]		26.2%[17.8-35.4]		54.8%[44.7-64.8]		57.9%[47.9-67.9]		46.8%[36.7-56.8]		36.7%[27-46.3]		29.9%[20.9-39.5]		7.3%[3.2-13.7]	
ABO matched	24.4%[19.5-29.7]	0.18	21%[16.3-26.1]	0.68	54.6%[48.6-60.5]	0.44	57.8%[51.7-63.8]	0.86	46.2%[40.2-52.1]	0.69	28.9%[23.6-34.3]	0.15	29.1%[23.8-34.6]	0.08	11.8%[8.3-16]	0.84
ABO mismatched	19.5%[14-25.7]		22.6%[16.7-29]		58%[50.6-65.3]		59.9%[52.6-67.3]		48.3%[40.8-55.8]		34.7%[27.8-41.8]		37.1%[29.8-44.3]		11.6%[7.3-17.1]	

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non relapse mortality; GVHD, graft versus host disease; GRFS, GVHD-free/relapse-free survival.

Supplementary Table 6. Multivariable analysis of patient outcome following transplantation with bone marrow grafts.

Parameter	LFS HR (95% CI)	OS HR (95% CI)	RI HR (95% CI)	NRM HR (95% CI)	Acute GVHD grade II-IV HR (95% CI)	Chronic GVHD HR (95% CI)
Matched ABO (ref)	1	1	1	1	1	1
Minor ABO mismatch	0.83 (0.48-1.44), P=0.51	0.88 (0.5-1.54), P=0.66	0.67 (0.3-1.52), P=0.34	1 (0.47-2.14), P=0.98	2.01 (0.99-4.07), P=0.0504	2 (0.87-4.62), P=0.1
Major ABO mismatch	1.58 (0.91-2.72), P=0.09	1.82 (1.04-3.18), P=0.03	1.53 (0.65-3.61), P=0.32	1.64 (0.79-3.38), P=0.17	1.47 (0.69-3.12), P=0.3	0.0.94 (0.3-2.88), P=0.91

Abbreviations: LFS, leukemia free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; RI, relapse incidence; NRM, non relapse mortality; GVHD, graft versus host disease.

Supplementary table 7. Clinical impact of ATG versus PTCy in T-cell replete grafts.

Univariate analysis	ABO matched	Minor ABO mismatch	Major ABO mismatch	Bidirectional ABO mismatch	P																
	N	406	118	94	29																
PTCy, n(%)	166 (40.8)	44 (37.2)	36 (38.3)	11 (37.9)	0.887																
ATG, n(%)	240 (59.1)	74 (62.7)	58 (61.7)	18 (62)																	
Multivariate analysis	RELAPSE				NRM	LFS				OS				Acute GVHD II-IV				Chronic GVHD			
	HR	CI	P	HR		CI	P	HR	CI	P	HR	CI	P	HR	CI	P	HR	CI	P		
ATG vs PTCy	0.74	0.41 - 1.32	0.31	1.44	0.84 - 2.47	0.18	1.05	0.7 - 1.57	0.8	1.11	0.74 - 1.66	0.58	1.53	0.95 - 2.45	0.075	0.76	0.34 - 1.69	0.5			

PTCy, post-transplant Cyclophosphamide; ATG, anti-thymocyte globulin; RI, relapse incidence; NRM, nonrelapse mortality; LFS, leukemia-free survival; OS, overall survival; GVHD, graft versus host disease.

Appendix: Participating centers

Patients were reported from the following EBMT transplant centers, whose contribution to this analysis is highly appreciated (numbers indicate EBMT center identification code):

443 Beijing [Univ People], 813 Milano [S Raffaele], 756 Rome [Tor Vergata], 513 Munich [KI Grosshadern], 919 Antalya [Medical Park H], 231 Torino [S. Giovanni (CTO)], 440 Kocaeli [Anadolu], 230 Marseille [Paoli Calmettes], 209 Leuven [Univ H], 808 Dresden [Universitaets KI], 725 St._Petersburg [Pavlov Med Univ], 245 Parma [Centro Trapianti], 705 Udine [Univ H], 587 Reggio_Calabria [Centro Trapianti], 775 Paris [St Antoine], 215 Brussels [Jules Bordet], 354 Milano [Trap Mid Osseo], 931 Suzhou [First Soochow], 401 Hangzhou [Univ H], 763 London [Kings College H], 862 Ankara [Medicana], 544 Monza [Osp S Gerardo], 565 Maastricht [Univ H], 692 Palermo [La Maddalena], 233 Besancon [H Jean Minjoz], 242 Santander [Valdecilla], 259 Essen [Univ H], 286 Pavia [S Matteo], 295 Hannover [Medical Univ], 307 Rome [Univ S Cuore], 561 Thessaloniki [G Papanicolaou G H], 788 Ancona [Umberto I], 789 Avellino [S G Moscati], 160 Paris [H Necker], 163 Piacenza [Osp Civile], 524 Heidelberg [Medizinische KI], 623 Verona [Policlinico], 658 Bergamo [Ospedale, ematol], 717 Nottingham [City H], 727 Salamanca [H Clinico], 141 Brescia [Civili, Adulti], 207 Paris [St Louis], 232 Rome [Emat, La Sapienza], 250 Saint_Etienne [St Etienne], 253 Nantes [Hotel Dieu], 277 Lille [H Claude Huriez], 323 Murcia [V Arrixaca], 397 Riyadh [King Faisal], 556 Budapest [National Med Ctr], 606 Cuneo [S Croce e Carle], 649 Bari [Univ Studi], 718 Pilsen [Charles Univ H], 119 Ascoli_Piceno [Osp Mazzoni], 161 Tel_Aviv [Sourasky], 169 Ankara [Gazi Univ], 202 Basel [202], 205 London [Hammersmith], 211 Sao_Paulo [H Sirio-Libanes], 212 Stockholm [Univ H], 614 Hamburg [Univ H], 616 Milano [INT], 624 Toulouse [H Purpan], 645 Marburg [Philipps Univ], 646 Roeselare [AZ Delta], 703 Alger [P et M Curie], 722 Palma_De_Mallorca [Son Dureta], 955 Amiens [H Sud], 138 Frankfurt_am_Main [KI Goethe U], 214 Barcelona [H Clinic], 260 Barcelona [SCreu i S Pau], 267 Pessac [H Haut-Leveque], 270 Grenoble [H A Michallon], 273 Clermont-Ferrand [Jean Perrin], 281 Patras [Univ H], 283 Lund [Univ H], 304 Firenze [Careggi-Meyer], 346 Sofia [Queen Johanna], 387 Birmingham [Queen Elizabeth], 506 Brugge [AZ Sint-Jan], 625 Nürnberg [Klinikum], 650 Angers [CHRU], 665 Clamart [H Percy], 680 Münster [University], 693 Warsaw [Inst Haematology], 726 Liege [University], 731 Umeå [Univ H], 744 Gent [Univ H], 754 Tel-Hashomer [Univ Adults], 810 Freiburg [University], 819 Madrid [H G Marañón], 996 Antwerp_Edegem [UZA]