Allogeneic peripheral blood stem cell transplantation with anti-thymocyte globulin *versus* allogeneic bone marrow transplantation without anti-thymocyte globulin

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Supplemental method

Data collection and definitions

This survey is a retrospective study performed by the Acute Leukemia Working Party (ALWP) of the EBMT society. The EBMT society is a voluntary working group of more than 600 transplant centers, participants of which are required to report annually, all consecutive stem cell transplantations and follow-up. Audits are routinely performed to determine data accuracy. Since 1990, patients have provided informed consent authorizing the use of their personal information for research purposes.

For unrelated donor transplantation, human leukocyte antigen (HLA)-compatibility was determined at the allele level, typing for HLA-A, -B, -C, -DRB1 and HLA-DQB1.

Supplemental statistical analyses

Data from all patients meeting the inclusion/exclusion criteria were included in the analyses. Baseline characteristics were described by the median and first and third quartile for continuous variables and by number and percentage for categorical variables. Baseline characteristics were compared between the 2 groups (PB+ATG, or BM) using the chi-square test for categorical variables and the Mann-Whitney test for continuous variables.

The cytogenetic AML risk was determined as followed (adapted from the MRC classification). Good cytogenetic risk was defined as abnormalities t(8;21), t(15;17), inv or del16, only, or these combined with others. Intermediate cytogenetic risk was defined as all cytogenetics not belonging to the good or high-risk categories. Finally, poor cytogenetic risk was defined as 11q23 abnormalities other than t(9;11), complex karyotype defined as 3 or more abnormalities, deletion or monosomies 5 and 7, as well as 3q26 and 17p/-17 abnormalities. Missing data on cytogenetics were processed by creating a missing category to correctly adjust the multivariate analysis. This meant however, that the coefficient of cytogenetic risk should not be interpreted.

Start time was date of transplant for all endpoints. Patients were censored at the time of last follow-up.

All tests were two sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with SPSS 19 (SPSS Inc, Chicago, IL), and R 3.4.3 (R Development Core Team, Vienna, Austria) software packages.

Supplemental table 1: Multivariate Cox models in the MSD group

		Relapse incidence		Nonrelapse mortality		Acute GVHD II-IV		Chronic GVH	
variable	level	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
CELLSOURCE	PBSC vs BM	0.955 (0.79-1.16)	0.64	1.07 (0.788-1.44)	0.68	0.818 (0.635-1.05)	0.12	0.744 (0.594-0.931)	0.01
ETAT2	CR2 vs CR1	1.25 (0.995-1.56)	0.06	1.13 (0.787-1.61)	0.52	1.02 (0.781-1.34)	0.88	0.975 (0.77-1.23)	0.83
FM	F->M	1.01 (0.845-1.21)	0.89	1.03 (0.792-1.35)	0.81	0.834 (0.677-1.03)	0.09	1.47 (1.25-1.73)	<0.0001
CMVDP	"+/-" vs " -/-"	1.1 (0.815-1.48)	0.54	0.838 (0.526-1.34)	0.46	1.03 (0.752-1.4)	0.87	1.12 (0.837-1.5)	0.45
	"-/+" vs " -/-"	1.04 (0.806-1.35)	0.75	0.928 (0.63-1.37)	0.71	0.91 (0.69-1.2)	0.50	1.05 (0.822-1.35)	0.68
	"+/+" vs " -/-"	1.06 (0.866-1.31)	0.56	1.02 (0.752-1.39)	0.89	0.929 (0.736-1.17)	0.54	1.05 (0.858-1.3)	0.62
TBI	TBI vs no TBI	0.911 (0.74-1.12)	0.38	1.09 (0.811-1.47)	0.56	1.42 (1.12-1.79)	0.0035	0.917 (0.741-1.13)	0.43
YEARTX by 5 y		1.12 (1.02-1.24)	0.02	0.717 (0.619-0.831)	<0.0001	0.825 (0.743-0.917)	0.0004	0.959 (0.869-1.06)	0.41
AGETX by 10 y		1.04 (0.971-1.11)	0.27	1.5 (1.35-1.68)	<0.0001	1.08 (0.999-1.17)	0.052	1.07 (1-1.14)	0.049
SECAML	secAML vs de novo	0.994 (0.751-1.32)	0.97	1.47 (1.03-2.09)	0.03	1.07 (0.776-1.47)	0.68	1.26 (0.968-1.64)	0.09
CYTOAML2	interm vs good	0.92 (0.683-1.24)	0.59	1.03 (0.658-1.62)	0.89	1.11 (0.81-1.53)	0.51	1.32 (0.992-1.76)	0.06
	poor vs good	2.14 (1.53-2.99)	<0.0001	1.16 (0.665-2.02)	0.60	0.97 (0.651-1.45)	0.88	1.59 (1.12-2.26)	0.01
	NA/failed vs good	1.25 (0.924-1.69)	0.15	1.19 (0.744-1.9)	0.47	0.947 (0.674-1.33)	0.75	1.3 (0.96-1.76)	0.09

	MSD	OS		PFS		GRFS	
variable	level	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
CELLSOURCE	PBSC vs BM	0.971 (0.812-1.16)	0.75	0.988 (0.841-1.16)	0.89	0.944 (0.813-1.1)	0.45
ETAT2	CR2 vs CR1	1.26 (1.02-1.54)	0.03	1.22 (1.01-1.48)	0.04	1.14 (0.964-1.36)	0.12
FM	F->M	1.06 (0.904-1.25)	0.47	1.01 (0.873-1.18)	0.85	1.18 (1.04-1.34)	0.01
CMVDP	"+/-" vs " -/-"	1.06 (0.813-1.39)	0.65	1.01 (0.789-1.3)	0.91	0.946 (0.756-1.18)	0.63
	"-/+" vs " -/-"	1.07 (0.85-1.34)	0.57	1.01 (0.815-1.25)	0.93	0.995 (0.825-1.2)	0.96
	"+/+" vs " -/-"	1.04 (0.861-1.25)	0.70	1.05 (0.884-1.24)	0.59	1.05 (0.901-1.22)	0.54
TBI	TBI vs no TBI	0.957 (0.796-1.15)	0.64	0.961 (0.811-1.14)	0.64	1.04 (0.895-1.21)	0.59
YEARTX by 5 y		0.935 (0.853-1.02)	0.14	0.979 (0.902-1.06)	0.62	0.942 (0.875-1.01)	0.11
AGETX by 10 y		1.21 (1.14-1.29)	<0.0001	1.15 (1.09-1.22)	<0.0001	1.14 (1.08-1.2)	<0.0001
SECAML	secAML vs de novo	1.19 (0.941-1.5)	0.15	1.15 (0.925-1.43)	0.21	1.13 (0.931-1.38)	0.21
CYTOAML2	interm vs good	1.05 (0.791-1.38)	0.75	0.951 (0.741-1.22)	0.69	1.07 (0.858-1.33)	0.55
	poor vs good	2.14 (1.56-2.92)	<0.0001	1.8 (1.36-2.39)	<0.0001	1.64 (1.27-2.11)	0.0002
	NA/failed vs good	1.36 (1.02-1.8)	0.04	1.22 (0.943-1.57)	0.13	1.19 (0.952-1.5)	0.13

Supplemental table 2. Unadjusted comparison of relapse and nonrelapse mortality incidences in PBSC+ATG versus BM patients per 6-year periods.

		BM without ATG				PBSCT+ATG			
	Years of Tx	N	RI at 2 years	Lower 95 CI	Lower 95 CI	N	RI at 2 years	Lower 95 CI	Lower 95 CI
MSD	[2000-2005]	567	19.1	16	22.5	47	25.5	14	38.7
	(2005-2011]	620	26.9	23.4	30.6	225	28.6	22.7	34.7
	(2011-2017]	446	28.5	23.8	33.2	749	27.2	23.6	31

		BM without ATG				PBSCT+ATG			
	Years of Tx	N	NRM at 2 years	Lower 95 CI	Lower 95 CI	N	NRM at 2 years	Lower 95 CI	Lower 95 CI
MSD	[2000-2005]	567	15.3	12.5	18.4	47	19.1	9.4	31.6
	(2005-2011]	620	10.7	8.4	13.4	225	15	10.7	20.1
	(2011-2017]	446	7.4	5	10.4	749	9.7	7.5	12.3

		BM without ATG				PBSCT+ATG			
	Years of Tx	N	RI at 2 years	Lower 95 CI	Lower 95 CI	N	RI at 2 years	Lower 95 CI	Lower 95 CI
MUD	[2000-2005]	24	20.8	7.3	39.1	26	23.1	9.1	40.8
	(2005-2011]	127	20.9	14.2	28.4	738	20.7	17.7	23.8
	(2011-2017]	152	25.7	18.5	33.6	1554	26.9	24.3	29.5

		BM without ATG				PBSCT+ATG			
	Years of Tx	N	NRM at 2 years	Lower 95 CI	Lower 95 CI	N	NRM at 2 years	Lower 95 CI	Lower 95 CI
MUD	[2000-2005]	24	20.8	7.4	38.9	26	19.2	6.8	36.4
	(2005-2011]	127	21.6	14.8	29.2	738	17.9	15.2	20.9
	(2011-2017]	152	15	9.5	21.7	1554	14.4	12.5	16.5

Supplemental table 3 : Causes of death

		MSD group		UD group	
		BM w/o ATG (N=590)	**PB+ATG (N=308)**	**BM w/o ATG (N=123)**	**PB+ATG (N=756)**
Cause of death	Original disease	328 (58.26%)	153 (52.22%)	52 (44.07%)	304 (43.06%)
	Infection	61 (10.83%)	67 (22.87%)	20 (16.95%)	168 (23.8%)
	GVHD	82 (14.56%)	43 (14.68%)	27 (22.88%)	123 (17.42%)
	second malignancy	10 (1.78%)	2 (0.68%)	2 (1.69%)	12 (1.7%)
	VOD	16 (2.84%)	9 (3.07%)	4 (3.39%)	19 (2.69%)
	Cardiac toxicity	2 (0.36%)	0 (0%)	1 (0.85%)	7 (0.99%)
	Failure/Rejection	2 (0.36%)	0 (0%)	0 (0%)	4 (0.57%)
	haemorhage	8 (1.42%)	1 (0.34%)	2 (1.69%)	10 (1.42%)
	IP	14 (2.49%)	4 (1.37%)	1 (0.85%)	24 (3.4%)
	other transp related	40 (7.1%)	14 (4.78%)	9 (7.63%)	35 (4.96%)
	missing cause of death	27	15	5	50

VOD, veno-occlusive disease of the liver ; IP, interstitial pneumonia.

Supplemental table 4: Multivariate Cox models in the MUD group

MUD		Relapse incidence		Nonrelapse mortality		Acute GVHD II-IV		Chronic GVH	
variable	Level	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
CELLSOURCE	PBSC vs BM	0.988 (0.766-1.27)	0.93	0.718 (0.503-1.02)	0.07	0.538 (0.406-0.713)	<0.0001	0.619 (0.47-0.814)	0.0006
ETAT2	CR2 vs CR1	1.14 (0.929-1.4)	0.21	1.1 (0.854-1.42)	0.45	1.17 (0.962-1.43)	0.12	0.986 (0.807-1.21)	0.89
FM	F->M	0.902 (0.698-1.17)	0.43	1.25 (0.93-1.69)	0.14	1.19 (0.94-1.5)	0.15	1.11 (0.885-1.4)	0.36
CMVDP	"+/-" vs " -/-"	1.05 (0.764-1.44)	0.77	1.11 (0.75-1.64)	0.60	1.05 (0.765-1.43)	0.77	1.1 (0.813-1.47)	0.55
	"-/+" vs " -/-"	1.17 (0.946-1.44)	0.15	0.978 (0.746-1.28)	0.87	1.09 (0.876-1.35)	0.44	0.974 (0.793-1.2)	0.80
	"+/+" vs " -/-"	0.904 (0.729-1.12)	0.36	0.866 (0.659-1.14)	0.30	1.13 (0.916-1.4)	0.25	0.947 (0.774-1.16)	0.60
TBI	TBI vs no TBI	0.852 (0.688-1.06)	0.15	1.13 (0.854-1.49)	0.39	1.05 (0.827-1.33)	0.70	0.967 (0.775-1.21)	0.77
YEARTX by 5 y		1.17 (1.01-1.36)	0.03	0.81 (0.674-0.975)	0.03	0.943 (0.822-1.08)	0.41	0.903 (0.785-1.04)	0.15
AGETX by 10 y		1.01 (0.941-1.07)	0.88	1.4 (1.27-1.54)	<0.0001	0.947 (0.887-1.01)	0.11	1.06 (0.998-1.14)	0.06
SECAML	secAML vs de novo	0.896 (0.697-1.15)	0.39	1.42 (1.09-1.85)	0.01	0.952 (0.738-1.23)	0.71	1.2 (0.962-1.51)	0.10
CYTOAML2	interm vs good	1.93 (1.28-2.92)	0.002	1.07 (0.677-1.69)	0.77	0.947 (0.699-1.28)	0.72	0.992 (0.731-1.35)	0.96
	poor vs good	3.72 (2.4-5.77)	<0.0001	1.2 (0.706-2.04)	0.50	1.06 (0.743-1.51)	0.75	1.16 (0.807-1.67)	0.42
	NA/failed vs good	1.97 (1.31-2.97)	0.001	1.2 (0.766-1.89)	0.42	0.964 (0.708-1.31)	0.81	0.978 (0.718-1.33)	0.89

MUD		OS		PFS		GRFS	
variable	level	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
CELLSOURCE	PBSC vs BM	0.803 (0.648-0.995)	0.04	0.872 (0.717-1.06)	0.17	0.757 (0.639-0.898)	0.001
ETAT2	CR2 vs CR1	1.09 (0.918-1.3)	0.33	1.13 (0.96-1.32)	0.15	1.06 (0.92-1.22)	0.42
FM	F->M	1.06 (0.86-1.3)	0.59	1.02 (0.843-1.24)	0.82	1.11 (0.937-1.31)	0.23
CMVDP	"+/-" vs " -/-"	1.1 (0.842-1.44)	0.48	1.08 (0.844-1.38)	0.54	0.997 (0.798-1.25)	0.98
	"-/+" vs " -/-"	1.13 (0.944-1.35)	0.18	1.09 (0.929-1.29)	0.28	1.13 (0.973-1.3)	0.11
	"+/+" vs " -/-"	0.947 (0.79-1.14)	0.56	0.892 (0.755-1.06)	0.18	0.929 (0.801-1.08)	0.34
TBI	TBI vs no TBI	1.05 (0.874-1.25)	0.63	0.964 (0.817-1.14)	0.66	1.02 (0.883-1.18)	0.77
YEARTX by 5 y		0.999 (0.883-1.13)	0.99	1.02 (0.915-1.15)	0.67	1.03 (0.932-1.14)	0.57
AGETX by 10 y		1.21 (1.14-1.28)	<0.0001	1.13 (1.07-1.19)	<0.0001	1.07 (1.02-1.12)	0.004
SECAML	secAML vs de novo	1.14 (0.938-1.38)	0.19	1.11 (0.928-1.33)	0.25	1.1 (0.937-1.3)	0.24
CYTOAML2	interm vs good	1.56 (1.11-2.19)	0.01	1.54 (1.14-2.09)	0.01	1.25 (0.971-1.6)	0.08
	poor vs good	2.58 (1.79-3.72)	<0.0001	2.47 (1.77-3.44)	<0.0001	1.98 (1.5-2.62)	<0.0001
	NA/failed vs good	1.67 (1.19-2.33)	0.003	1.64 (1.22-2.22)	0.001	1.31 (1.02-1.68)	0.03

Supplemental table 5: Outcomes (multivariate Cox models) among patients given cyclosporine (or) tacrolimus + MTX as postgrafting immunosuppression.

Outcomes	HR (95% CI) PBSC with ATG vs BMT without ATG	P value[1]
MSD (n=1995)		
Grade II-IV acute GVHD	*0.89 (0.64-1.22)*	0.46
Chronic GVHD	*0.82 (0.61-1.09)*	0.16
Relapse incidence	*1.01 (0.81-1.25)*	0.96
Non relapse mortality	*1.16 (0.80-1.66)*	0.44
Leukemia-free survival	*1.05 (0.87-1.27)*	0.61
Overall survival	*1.04 (0.84-1.28)*	0.75
GVHD-free and relapse-free survival	*1.01 (0.84-1.21)*	0.93
MUD (n=1730)		
Grade II-IV acute GVHD	*0.47 (0.33-0.65)*	<0.001
Chronic GVHD	*0.54 (0.39-0.75)*	<0.001
Relapse incidence	*1.03 (0.79-1.35)*	0.81
Non relapse mortality	*0.75 (0.50-1.14)*	0.18
Leukemia-free survival	*0.91 (0.74-1.13)*	0.41
Overall survival	*0.85 (0.68-1.08)*	0.18
GVHD-free and relapse-free survival[2]	*0.76 (0.64-0.94)*	0.01

MSD, HLA-identical sibling donor; MUD, 10/10 HLA-matched unrelated donors; BM, bone marrow; PBSC, peripheral blood stem cells; ATG, anti-thymocyte globulin; GVHD, graft-versus-host-disease

[1] *Factors included in the models are: disease status at transplantation, female donor to male recipient or not, CMV serostatus, use or not of TBI, year of transplantation, age at transplantation, primary versus secondary AML, cytogenetic risk and frailty center effect;* [2] *defined as no death, no relapse, no grade III-IV acute GVHD and no extensive chronic GVHD.*