Allogeneic stem cell transplantation in second complete remission for core binding factor acute myeloid leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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Supplemental Table 1. Comparison of patient and transplant characteristics of inv(16) and t(8;21) AML groups.

		inv(16)	t(8;21)	p-value
N		366	265	
Age at transplantation (years)	median (range)[IQR]	41.9 (18.1-73.9)[30.9-50.9]	41.5 (18-73.3)[31.6-51.2]	0.92
Year of transplantation	median (range)[IQR]	2010 (2000-2014)[2007-2012]	2009 (2000-2014)[2006-2012]	0.49
Time from diagnosis to CR1 (days)	median (range)[IQR] missing	38 (10-275) [30-49.8] 100	43 (10-162) [31-59.2] 97	0.043
CR1 duration (days)	median (range)[IQR] missing	311 (14-2380) [244-434] 109	341 (14-2068) [249-533] 108	0.08
Time form CR2 to transplantation (days)	median (range)[IQR] missing	56 (7-252) [28.5-100.5] 260	55 (6-234) [23-88] 212	0.38
Time diagnosis to transplantation (months)	median (range)[IQR] missing	16.5 (3.5-87.3) [13.9-21.6] 0	18.2 (3.9-222.9) [14.3-24.8] 0	0.005
FLT3-ITD	negative positive missing	82 (85.42%) 14 (14.58%) 270	49 (80.33%) 12 (19.67%) 204	0.40
NPM1 mutation	absent present missing	24 (85.71%) 4 (14.29%) 338	17 (94.44%) 1 (5.56%) 247	0.63

≥3 chromosomal abnormalities at diagnosis	no	347 (94.81%)	252 (95.09%)	0.87
	yes	19 (5.19%)	13 (4.91%)	
Associated chromosomal abnormalities	no associated abnormalities	294 (80.33%)	203 (76.6%)	
	t(11;23)	2 (0.55%)	1 (0.38%)	
	abn5	0 (0%)	2 (0.75%)	
	abn7	8 (2.19%)	2 (0.75%)	
	del9	0 (0%)	5 (1.89%)	
	del X or del Y	0 (0%)	18 (6.79%)	
	trisomy22	9 (2.46%)	0 (0%)	
	trisomy 8	9 (2.46%)	1 (0.38%)	
	hyperiploidy	3 (0.82%)	1 (0.38%)	
	hypodiplidy	0 (0%)	7 (2.64%)	
	other abnormalities	22 (6.01%)	12 (4.53%)	
Extramedullary disease at diagnosis	no	131 (88.51%)	68 (89.47%)	0.83
	yes	17 (11.49%)	8 (10.53%)	
	missing	218	189	
Patient sex	male	189 (51.64%)	172 (64.91%)	0.0009
	female	177 (48.36%)	93 (35.09%)	
Donor sex	male	216 (59.83%)	153 (58.85%)	0.80
	female	145 (40.17%)	107 (41.15%)	
	missing	5	5	

Sex matching	female to male transplant other missing	69 (18.9%) 296 (81.1%) 1	64 (24.43%) 198 (75.57%) 3	0.09
Karnofsky performance score at transplantation	<80% ≥80% missing	12 (3.54%) 327 (96.46%) 27	4 (1.69%) 232 (98.31%) 29	0.18
Donor	matched sibling unrelated	154 (42.08%) 212 (57.92%)	110 (41.51%) 155 (58.49%)	0.89
Graft source	bone marrow peripheral blood missing	73 (19.95%) 293 (80.05%) 0	44 (16.6%) 221 (83.4%) 0	0.29
Molecular MRD at transplantation	negative positive missing	206 (76.58%) 63 (23.42%) 97	137 (68.84%) 62 (31.16%) 66	0.06
Patient anti-CMV IgG at transplantation	negative positive missing	132 (36.87%) 226 (63.13%) 8	95 (37.11%) 161 (62.89%) 9	0.95
Donor anti-CMV IgG at transplantation	negative positive missing	179 (50.85%) 173 (49.15%) 14	127 (49.03%) 132 (50.97%) 6	0.66
In vivo T-cell depletion	no	170 (46.45%)	132 (50.57%)	0.31

	yes	196 (53.55%)	129 (49.43%)	
	missing	0	4	
Conditioning	myeloablative	238 (65.21%)	186 (70.72%)	0.14
	reduced intensity	127 (34.79%)	77 (29.28%)	
	missing	1	2	

AML, acute myeloid leukemia; IQR, interquartile range, CR1, first complete remission; CR2, second complete remission; FLT3-ITD, fms like tyrosine kinase 3 internal tandem duplication; NPM1, nucleophosmin; MRD, minimal residual disease; anti-CMV IgG, anti cytomegaloviorus antibody class IgG.

Supplemental Table 2. Endpoints stratified by minimal residual disease status before transplantation – univariate analysis.

		2 year results				
		relapse	NRM	LFS	OS	GRFS
MRDneg	inv(16)	11.6%[7.6-16.5]	21%[15.6-26.9]	67.4%[60.8-73.9]	71.8%[65.5-78.1]	46.2%[39-53.3]
	t(8;21)	22.5%[15.7-30]	23.2%[16.3-30.9]	54.3%[45.6-63]	57.4%[48.7-66.1]	38.7%[30.1-47.3]
	P value	0.037	0.56	0.031	0.022	0.22
MRDpos	inv(16)	23.3%[13.5-34.7]	22.9%[13.3-34.2]	53.8%[41.2-66.4]	67.1%[55.3-79]	30%[18.2-41.9]
	t(8;21)	36%[23.5-48.7]	19.9%[10.5-31.4]	43.4%[30.2-56.7]	51.6%[38.2-65.1]	28.2%[16.4-40]
	P value	0.12	0.66	0.30	0.08	0.92

MRDneg, minimal residual disease negative; MRDpos, minimal residual disease positive; inv(16), acute myeloid leukemia with inv(16); t(8;21), acute myeloid leukemia with t(8;21); NRM, non-relapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, graft-versus-host disease-free, relapse-free survival.

Supplemental Table 3. Univariate analysis of factors influencing outcomes in core-binding factor acute myeloid leukemia patients transplanted in second complete remission. Values in parentheses represent 95% confidence interval.

		2-year Probability						100-day Risk
		RI	NRM	LFS	OS	GRFS	cGVHD	aGVHD II-IV
Data reporting	No MEDC	19.7% [16.1-23.6]	21.5% [17.8-25.6]	58.6% [53.9-63.3]	63.8% [59.1-68.4]	41.5% [36.8-46.3]	45.7% [40.6-50.5]	28.5% [24.4-32.8]
	MEDC	19.8% [14.2-26.1]	19.7% [14.2-26]	60.4% [53.1-67.7]	68% [61-75]	36.9% [29.5-44.2]	49.2% [41.3-56.6]	26.4% [19.9-33.3]
	P value	0.83467	0.99805	0.83073	0.74124	0.4379	0.6251	0.63976
Type of CBF AML	inv(16)	15.6% [12-19.6]	20.5% [16.5-24.9]	63.8% [58.8-68.8]	70.5% [65.8-75.3]	44.1% [38.8-49.4]	48.6% [43-53.9]	26.4% [21.9-31]
	t(8;21)	25.8% [20.5-31.4]	21.6% [16.7-27]	52.5% [46.2-58.8]	57% [50.7-63.2]	34.7% [28.6-40.7]	44.2% [37.7-50.6]	30.2% [24.7-35.9]
	P value	0.0089579	0.37316	0.0031748	0.0003229	0.048775	0.16845	0.29303
Extramedullary disease	No	21.4% [16-27.4]	20.3% [15-26.2]	58.2% [51.3-65.1]	65.3% [58.6-72]	37.8% [30.9-44.8]	45.1% [37.9-52.1]	26.3% [20.3-32.7]
at diagnosis	Yes	25% [9.8-43.6]	20.6% [7.2-38.6]	54.5% [34.6-74.4]	62.7% [43.4-82]	26.5% [8.4-44.6]	52.2% [29.1-71]	40% [20.8-58.6]
	P value	0.6251	0.95048	0.65326	0.4521	0.53929	0.70145	0.21097
Additional cytogenetic	no abnormality	17.7% [14.4-21.3]	20.7% [17.2-24.5]	61.5% [57-65.9]	66.5% [62.2-70.8]	42.5% [38-47.1]	46.3% [41.5-50.9]	28.8% [24.8-32.9]
abnormalities	abn7 (n=10)	10% [0.4-38.2]	30% [6.2-59.3]	60% [29.6-90.4]	70% [41.6-98.4]	22.2% [0-49.4]	55.6% [16.2-82.7]	60% [21.7-84.3]
	≥ 3 (n=32)	34.4% [18.4-51]	28.1% [13.8-44.4]	37.5% [20.7-54.3]	49.6% [32.2-67.1]	20% [5.7-34.3]	44.8% [25.6-62.4]	19.4% [7.7-34.9]
	del X or Y (n=18)	30.4% [10.4-53.6]	17.6% [4-39.2]	51.9% [27.6-76.3]	64.6% [41.7-87.6]	31.2% [9.1-53.4]	38.9% [16.6-60.9]	44.4% [20.8-65.8]
	trisomy 22 (n=9)	0%	11.1% [0.5-40.6]	88.9% [68.4-100]	88.9% [68.4-100]	71.4% [38-100]	71.4% [15.5-94.1]	11.1% [0.5-40.9]
	trisomy 8 (n=10)	20%	40%	40%	40%	20%	50%	30%

		[2.5-49.6]	[10.5-68.9]	[9.6-70.4]	[9.6-70.4]	[0-44.8]	[15.5-77.3]	[6.2-59.3]
	other (n=34)	30.2% [15.5-46.3]	11.9% [3.7-25.3]	58% [41.1-74.8]	67% [51-83]	42.8% [25.9-59.7]	45.2% [26.8-62]	11.8% [3.6-25.1]
≥ 3 cytogenetic abnormalities	No	19% [15.9-22.3]	20.6% [17.4-24]	60.4% [56.3-64.4]	65.9% [62-69.8]	41.3% [37.2-45.4]	46.8% [42.5-51]	28.4% [24.8-32.1]
	Yes	34.4% [18.4-51]	28.1% [13.8-44.4]	37.5% [20.7-54.3]	49.6% [32.2-67.1]	20% [5.7-34.3]	44.8% [25.6-62.4]	19.4% [7.7-34.9]
	P value	0.032235	0.2903	0.0022938	0.013	0.013759	0.80179	0.3306
Molecular CR at transplantation	No	29.3% [21.2-37.8]	21.5% [14.5-29.4]	49% [39.8-58.2]	59.9% [50.8-68.9]	29.2% [20.8-37.5]	48.9% [39.3-57.9]	27.2% [19.6-35.4]
	Yes	16.2% [12.4-20.4]	22.2% [17.8-26.8]	61.6% [56.3-66.9]	65.8% [60.7-71]	42.9% [37.4-48.4]	45.9% [40.1-51.5]	29.5% [24.7-34.4]
	P value	0.0028876	0.49498	0.046352	0.4667	0.014591	0.61705	0.71792
WBC at diagnosis, median 28.9 G/l	≤ median	21.9% [15.9-28.5]	16.9% [11.6-23]	61% [53.5-68.5]	67.1% [59.8-74.3]	35.9% [28.4-43.4]	48.3% [40.2-55.9]	29.4% [22.6-36.4]
	> median	16.5% [11.4-22.5]	22.4% [16.4-28.9]	61.1% [53.7-68.4]	66.4% [59.3-73.5]	45.2% [37.6-52.7]	47.7% [39.8-55.1]	30% [23.3-37]
	P value	0.41534	0.16296	0.64058	0.97605	0.24469	0.89203	0.84125
Patient age, median 41.7 years	≤ median	17.9% [13.8-22.5]	21.2% [16.8-26.1]	60.7% [55.1-66.3]	66.5% [61.1-71.9]	39.9% [34.2-45.7]	48.5% [42.4-54.4]	30% [24.9-35.2]
	> median	21.7% [17.2-26.5]	20.7% [16.3-25.4]	57.6% [52-63.2]	63.6% [58.1-69]	40.4% [34.8-46]	45% [39.2-50.7]	25.9% [21.1-31]
	P value	0.14708	0.9807	0.29435	0.39368	0.95855	0.34313	0.27792
Patient sex	Male	21.4% [17.2-25.9]	20.3% [16.2-24.7]	58.3% [53-63.5]	65% [59.9-70.1]	40% [34.6-45.3]	46.5% [40.9-52]	28.7% [24.1-33.5]
	Female	17.8% [13.4-22.7]	21.9% [17.1-27.1]	60.3% [54.3-66.2]	65% [59.1-70.8]	40.4% [34.3-46.5]	47% [40.5-53.2]	27% [21.7-32.5]
	P value	0.16887	0.63076	0.52692	0.72766	0.70516	0.92355	0.66892

Donor sex	Male	20.3% [16.3-24.6]	23.5% [19.2-28]	56.2% [51-61.3]	62.9% [57.8-67.9]	39% [33.7-44.2]	43.4% [37.9-48.7]	29% [24.4-33.8]
	Female	19.9% [15-25.2]	17.1% [12.6-22.2]	62.9% [56.7-69.1]	67.8% [61.8-73.8]	41.3% [35-47.7]	52.1% [45.4-58.4]	27.1% [21.7-32.7]
	P value	0.94983	0.2524	0.24726	0.49223	0.76808	0.010383	0.62344
Donor and recipient	Female to male	21.9% [15-29.6]	15.9% [10.1-22.9]	62.1% [53.5-70.7]	68.1% [59.8-76.4]	39.1% [30.5-47.7]	55.2% [45.8-63.7]	26.8% [19.5-34.6]
sex matching	Other	19.4% [16-23.1]	22.5% [18.8-26.3]	58.1% [53.6-62.5]	63.9% [59.6-68.3]	40.2% [35.6-44.7]	44.5% [39.8-49.1]	28.3% [24.3-32.4]
	P value	0.5376	0.22135	0.51464	0.66644	0.67045	0.026565	0.6827
Patient anti-CMV IgG	Negative	23.1% [17.7-28.9]	20.6% [15.5-26.3]	56.2% [49.6-62.9]	64.9% [58.5-71.3]	39.9% [33.2-46.6]	45.7% [38.6-52.5]	28% [22.1-34.1]
	Positive	18% [14.2-22.1]	21.1% [17.1-25.4]	60.9% [55.9-65.9]	65.1% [60.2-70]	40.6% [35.4-45.7]	47% [41.6-52.2]	28.7% [24.2-33.3]
	P value	0.071864	0.89372	0.22939	0.50705	0.82786	0.85399	0.9521
Donor anti-CMV IgG	Negative	22.5% [17.9-27.5]	20% [15.7-24.8]	57.4% [51.7-63.2]	65.3% [59.8-70.8]	41.8% [36-47.5]	40.5% [34.6-46.3]	30.5% [25.3-35.8]
	Positive	17.7% [13.6-22.3]	21.2% [16.7-26.1]	60.9% [55.3-66.6]	65.3% [59.7-70.8]	38.4% [32.7-44.2]	53.2% [47-59]	26% [21.1-31]
	P value	0.38964	0.49007	0.95438	0.9656	0.064535	0.0020307	0.19717
Karnofsky performance score	KPS<80	12.5% [1.8-34.2]	50% [23.3-71.9]	37.5% [13.8-61.2]	37.5% [13.8-61.2]	37.5% [13.8-61.2]	21.4% [4.4-46.9]	25% [7.3-48]
at transplantation	KPS≥80	20.3% [17-23.8]	19.8% [16.5-23.3]	59.9% [55.7-64.1]	66.1% [62.1-70.2]	40.8% [36.5-45.1]	48% [43.5-52.3]	28% [24.3-31.9]
	P value	0.7175	0.0018721	0.0026102	0.0026872	0.23993	0.098761	0.82352
Year of transplantation,	≤ median	19.8% [15.8-24.2]	20.9% [16.7-25.3]	59.3% [54.1-64.5]	65% [60-70.1]	42.3% [36.9-47.6]	48.3% [42.7-53.7]	28.7% [24-33.6]
median 2010	> median	19.8% [15.2-24.9]	21.3% [16.5-26.5]	58.8% [52.7-64.9]	64.9% [59-70.8]	37.2% [31.2-43.3]	44.7% [38.2-50.9]	27% [21.8-32.5]

	P value	0.86894	0.51948	0.7491	0.75484	0.28024	0.33187	0.45657
Time from diagnosis to CR1,	≤ median	19.1% [14.1-24.6]	22.3% [17-28.1]	58.5% [51.9-65.1]	63.6% [57.1-70]	37.5% [30.9-44.1]	50% [42.9-56.7]	28.7% [22.7-34.9]
median 39 days	> median	20.9% [15.7-26.7]	20.4% [15.2-26.1]	58.6% [51.9-65.3]	64.8% [58.3-71.2]	42.1% [35.3-48.9]	45.5% [38.4-52.3]	27% [21.2-33.2]
	P value	0.29401	0.7577	0.56825	0.88722	0.50595	0.60636	0.74324
CR1 duration,	≤ median	26.4% [20.5-32.6]	17.1% [12.3-22.5]	56.6% [49.8-63.4]	62.4% [55.8-69.1]	37.8% [31-44.6]	49.8% [42.5-56.6]	26.2% [20.3-32.4]
median 318 days	> median	13% [8.8-18.1]	25.8% [19.9-32]	61.2% [54.4-67.9]	66.7% [60.1-73.2]	42.3% [35.3-49.2]	47.1% [39.8-54]	30.2% [24-36.6]
	P value	5.8795e-05	0.0067452	0.3257	0.453	0.21993	0.54701	0.37179
Time from CR2 to transplantation,	≤ median	16% [9-24.8]	18.4% [10.8-27.5]	65.7% [55.4-76]	70.6% [60.7-80.5]	45.2% [34-56.4]	47.8% [36.2-58.5]	25.7% [16.6-35.8]
median 56 days	> median	26.3% [17-36.6]	19.6% [11.6-29.2]	54.1% [42.9-65.3]	65.9% [55.2-76.5]	28.5% [18.2-38.8]	50.7% [38.6-61.6]	27.7% [18.1-38.1]
	P value	0.36312	0.97782	0.41071	0.32318	0.26791	0.49986	0.79544
Time from diagnosis to transplantation,	≤ median	26.4% [21.6-31.5]	18% [13.9-22.5]	55.5% [49.9-61.2]	62.9% [57.4-68.4]	38.3% [32.7-43.9]	45.1% [39.2-50.9]	27.9% [23-33]
median 17 months	> median	13.1% [9.5-17.2]	24% [19.3-29]	62.8% [57.3-68.4]	67.2% [61.9-72.6]	42.1% [36.4-47.8]	48.4% [42.3-54.2]	28% [23.1-33.2]
	P value	3.2283e-05	0.013632	0.21426	0.48203	0.28012	0.34122	0.9553
Donor	Matched sibling	20.8% [16-26]	20.4% [15.7-25.6]	58.7% [52.6-64.8]	65.5% [59.6-71.5]	37% [30.9-43.1]	50.9% [44.3-57.2]	24.1% [19.1-29.5]
	Unrelated	19.1% [15.2-23.4]	21.3% [17.2-25.7]	59.5% [54.3-64.7]	64.7% [59.6-69.7]	42.5% [37.2-47.7]	43.7% [38.2-49.1]	30.8% [26-35.6]
	P value	0.6424	0.4439	0.89774	0.8574	0.4399	0.082295	0.048713
Conditioning intensity	MAC	17% [13.5-20.9]	22% [18.1-26.2]	60.9% [56.2-65.7]	66.9% [62.3-71.5]	39.9% [35-44.8]	46.5% [41.4-51.6]	30.8% [26.4-35.2]

	RIC	25.9% [19.9-32.2]	18.4% [13.3-24.2]	55.6% [48.6-62.6]	61.5% [54.7-68.4]	40.9% [34-47.9]	47.4% [40-54.4]	21.6% [16.1-27.7]
	P value	0.0023561	0.28638	0.17549	0.21936	0.6978	0.8531	0.012579
Graft source	Bone marrow	18.9% [12.2-26.8]	21.9% [14.8-29.9]	59% [49.9-68.2]	65.3% [56.4-74.1]	44.3% [34.9-53.6]	37.1% [28-46.2]	36% [27.3-44.8]
	Peripheral blood	20% [16.6-23.7]	20.8% [17.3-24.5]	59.2% [54.8-63.6]	65% [60.7-69.2]	39.2% [34.8-43.7]	49.1% [44.3-53.6]	26.1% [22.3-30]
	P value	0.34853	0.90128	0.62518	0.91932	0.22462	0.039322	0.037095
in vivo T-cell depletion	No	16.7% [12.7-21.3]	22% [17.4-27]	61.2% [55.5-66.8]	66.6% [61.1-72]	33.9% [28.3-39.5]	55.9% [49.7-61.6]	32.7% [27.4-38.1]
	Yes	22.6% [18.1-27.4]	20.2% [15.9-24.9]	57.1% [51.5-62.6]	63.5% [58.1-68.9]	46.1% [40.5-51.8]	37.7% [32.1-43.3]	23.6% [19-28.4]
	P value	0.024458	0.45092	0.24087	0.84598	0.0036315	3.7709e-05	0.014416

MEDC, EBMT detailed reporting form with additional patient and treatment information; RI, relapse incidence; NRM, non-relapse mortality; LFS, leukemia-free survival; OS, overall survival; GRFS, graft-versus-host disease-free, relapse-free survival ; cGVHD, chronic graft-versus-host disease; aGvHD II-IV acute graft-versus-host disease, grades II to IV; CBF AML, core-binding factor acute myeloid leukemia; abn 7, chromosome 7 abnormalities including monosomy or partial deletion; ≥3, three or more accompanying chromosomal abnormalities; del X or Y, deletion of chromosome X or Y; trisomy 22, trisomy of chromosome 22; trisomy 8, trisomy of chromosome 8; CR complete remission; WBC, white blood cell count; anti-CMV IgG, anti cytomegaloviorus antibody class IgG; CR1, first complete remission; CR2, second complete remission.