Incidence and outcome of central nervous system relapse after hematopoietic stem cell transplantation in patients suffering from acute myeloid leukemia and acute lymphoblastic leukemia: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Authors

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Supplementary Table 1

Patient characteristics of the entire population

		no CNS relapse (n=7900)	CNS relapse (n=91)
Follow-up (reverse KM) months after HSCT	median (IQR)	72.3 (38.-121.7)	138.1 (97.2-163.1)
Diagnosis	AML	5672 (71.8%)	52 (57.1%)
	ALL	2228 (28.2%)	39 (42.9%)
Patient age (years)	median (min-max) [IQR]	44 (18-83.8) [31.6-55.4]	41 (18.5-75.2) [30.8-50.4]
Year transplant	median (min-max)	2010 (1996-2016)	2012 (1996-2016)
Status at HSCT	CR1	5953 (75.4%)	61 (67.0%)
	CR2	1773 (22.4%)	27 (29.7%)
	CR3	174 (2.2%)	3 (3.3%)
Donor	MSD	3656 (46.3%)	48 (52.7%)
	UD	3790 (48%)	38 (41.8%)
	other relative	454 (5.7%)	5 (5.5%)
MRC in AML	good	373 (12.3%)	13 (26.5%)**
	interm	2107 (69.3%)	26 (53.1%)
	poor	562 (18.5%)	10 (20.4%)
	missing	2630	3
Type ALL	Ph neg B ALL	475 (31.6%)	12 (33.3%)
	Ph pos B ALL	540 (36%)	14 (38.9%)
	T ALL	487 (32.4%)	10 (27.8%)
	missing	726	3
Patient sex	Male	4367 (55.3%)	59 (64.8%)
	Female	3530 (44.7%)	32 (35.2%)
	missing	3	0
Donor sex	donor male	4836 (61.7%)	56 (61.5%)
	donor female	3005 (38.3%)	35 (38.5%)
	missing	59	0
Female to male combination	no F->M	6418 (81.6%)	69 (75.8%)
	F->M	1451 (18.4%)	22 (24.2%)
	missing	31	0
Conditionning	MAC	5059 (67%)	62 (68.1%)
	RIC	2490 (33%)	29 (31.9%)
	missing	351	0

Time diagnosis to HSCT (mo)	median (min-max) [IQR]	5.8 (0.1-324.2) [4.2-11.3]	5.8 (1.6-79.2) [3.8-13.9]
	missing	17	0
Karnofsky score	<80	285 (4%)	1 (1.2%)
	>=80	6816 (96%)	84 (98.8%)
	missing	799	6
Source of SC	BM	1611 (20.4%)	13 (14.3%)
	PB	6289 (79.6%)	78 (85.7%)
Patient CMV	Pat. CMV neg.	2127 (31.8%)	28 (31.5%)
	Pat. CMV pos	4569 (68.2%)	61 (68.5%)
	missing	1204	2
Donor CMV	Don. CMV neg.	3125 (45.7%)	37 (42.5%)
	Don. CMV pos	3716 (54.3%)	50 (57.5%)
	missing	1059	4
Donor/patient CMV	neg to neg	1462 (22.3%)	22 (25.6%)
	pos to neg	618 (9.4%)	5 (5.8%)
	neg to pos	1454 (22.1%)	14 (16.3%)
	pos to pos	3033 (46.2%)	45 (52.3%)
	missing	1333	5
	Pat. CMV neg.	2127 (31.8%)	28 (31.5%)
	Pat. CMV pos	4569 (68.2%)	61 (68.5%)

Supplmentary Table 2

Risk factors for CNS relapse : cumulative incidence at 5 years post HSCT [95% CI]

Diagnosis	AML	0.9%[0.7-1.2]
	ALL	1.9%[1.4-2.6]
	P value	0.002
Median age (44y)	age<median	1.5%[1.1-1.9]
	age>median	1%[0.7-1.3]
	P value	0.08
median year of Tx (2010)	Year<median	0.9%[0.6-1.2]
	Year>median	1.6%[1.2-2]
	P value	0.013
Type of donor	MSD	1.4%[1-1.8]
	UD	1.1%[0.8-1.4]
	other relative	1.6%[0.6-3.7]
	P value	0.49
Cell source	BM	0.8%[0.4-1.4]
	PB	1.3%[1-1.7]
	P value	0.1

Karnofsky score	<90	1%[0.6-1.7]
	>=90	1.6%[1.2-2]
	P value	0.2
Patient sex	Male	1.5%[1.1-1.9]
	Female	0.9%[0.6-1.3]
	P value	0.07
Donor sex	donor male	1.2%[0.9-1.6]
	donor female	1.2%[0.9-1.7]
	P value	0.99
Female to male combination	no F->M	1.1%[0.9-1.4]
	F->M	1.7%[1.1-2.6]
	P value	0.15
Patient CMV	Pat. CMV neg.	1.4%[1-2.1]
	Pat. CMV pos	1.4%[1.1-1.8]
	P value	0.82
Donor CMV	Don. CMV neg.	1.3%[0.9-1.8]
	Don. CMV pos	1.4%[1.1-1.9]
	P value	0.53
Intensity of conditioning	MAC	1.3%[1-1.7]
	RIC	1.2%[0.8-1.7]
	P value	0.7

Abbreviations: Tx: treatment, MSD: matched sibling donor, UD: unrelated donor, BM: bone marrow, PB: peripheral blood, F: female, M: male, CMV: cytomegaly virus, MAC: myeloablative conditioning, RIC: reduced intensity conditioning

Supplementary Table 3

CNS relapse, AML versus ALL

		AML (n=52)	ALL (n=39)	P
Follow-up after CNS relapse	median (IQR) months	83.9 (15.3-163)	119.9 (115.4-151.8)	0.37
Patient age (years)	median (min-max) [IQR]	46.1 (24.1-75.2) [35.3-51.5]	33.3 (18.5-66.9) [23.5-42.9]	0.0006
Year transplant	median (min-max)	2012 (1999-2016) [	2010 (1996-2016)	0.31
Time from HSCT to CNS relapse	median (IQR) days	401 [247.8-834.2]	343 [128.5-665.5]	0.092

Patient sex	Male	31 (59.6%)	28 (71.8%)	0.23
	Female	21 (40.4%)	11 (28.2%)	
Status at HSCT	CR1	35 (67.3%)	26 (66.7%)	0.69
	CR2	16 (30.8%)	11 (28.2%)	
	CR3	1 (1.9%)	2 (5.1%)	
Donor	MSD	26 (50%)	22 (56.4%)	MSD vs other : p=0.54
	UD	23 (44.2%)	15 (38.5%)	
	other relative	3 (5.8%)	2 (5.1%)	
Donor sex	donor male	36 (69.2%)	20 (51.3%)	0.082
	donor female	16 (30.8%)	19 (48.7%)	
Female to male combination	no F->M	42 (80.8%)	27 (69.2%)	0.2
	F->M	10 (19.2%)	12 (30.8%)	
Intensity of conditioning	MAC	32 (61.5%)	30 (76.9%)	0.12
	RIC	20 (38.5%)	9 (23.1%)	
details conditioning	BuCy	21 (40.4%)	10 (25.6%)	
	BuFlu	8 (15.4%)	1 (2.6%)	
	FluMel	4 (7.7%)	6 (15.4%)	
	FluMelBCNU	1 (1.9%)	0 (0%)	
	Treo+Cy	0 (0%)	1 (2.6%)	
	Treo+Flu	3 (5.8%)	0 (0%)	
	Flamsa TBI	1 (1.9%)	0 (0%)	
	Flamsa chemo	2 (3.8%)	0 (0%)	
	Cy TBI	5 (9.6%)	12 (30.8%)	
	Fluda-TBI	4 (7.7%)	2 (5.1%)	
	Fluda-Cy-TBI	2 (3.8%)	0 (0%)	
	TBI VP16	0 (0%)	6 (15.4%)	
	Flu+BCNU	0 (0%)	1 (2.6%)	
	FluMel+ARAC	1 (1.9%)	0 (0%)	
Karnofsky score	<90	11 (25.6%)	5 (16.7%)	0.37
	>=90	32 (74.4%)	25 (83.3%)	
	missing	9	9	
Source of SC	BM	6 (11.5%)	7 (17.9%)	0.39
	PB	46 (88.5%)	32 (82.1%)	
Patient CMV	Pat. CMV neg.	15 (29.4%)	13 (34.2%)	0.63
	Pat. CMV pos	36 (70.6%)	25 (65.8%)	
	missing	1	1	
Donor CMV	Don. CMV neg.	23 (45.1%)	14 (38.9%)	0.56
	Don. CMV pos	28 (54.9%)	22 (61.1%)	
	missing	1	3	

Acute GVHD before CNS relapse	no	38 (73.1%)	28 (71.8%)	0.89
	Yes	14 (26.9%)	11 (28.2%)	
Type of CNS relapse	First relapse	36 (69.2%)	30 (76.9%)	
	2nd relapse after hematological relapse	15 (28.8%)	8 (20.5%)	
	2nd relapse after molecular relapse	1 (1.9%)	1 (2.6%)	
Type of CNS relapse (sites)	CNS isolated	17 (32.7%)	19 (48.7%)	
	CNS+BM	19 (36.5%)	11 (28.2%)	
	2nd relapse after hematological relapse	1 (1.9%)	1 (2.6%)	
	2nd relapse after molecular relapse	15 (28.8%)	8 (20.5%)	
AGVH after CNS relapse	No agvh post CNS relapse	38 (77.6%)	31 (91.2%)	0.14
	agvh post CNS relapse	11 (22.4%)	3 (8.8%)	
	missing	3	5	
grade	Grade I	0 (0%)	1 (2.9%)	
	Grade II	6 (12.2%)	2 (5.9%)	
	Grade III	2 (4.1%)	0 (0%)	
	Grade IV	1 (2%)	0 (0%)	
	Present, grade unknown	2 (4.1%)	0 (0%)	
	No aGvHD present (Grade 0)	38 (77.6%)	31 (91.2%)	
	missing	3	5	
cGVH after CNS relapse	No cgvh post CNS relapse	31 (73.8%)	60 (76.9%)	0.48
	cgvh post CNS relapse	11 (26.2%)	18 (23.1%)	
	missing	10	13	
grade Cgvhd	limited	9 (81.8%)	11 (61.1%)	not done *
	extensive	2 (18.2%)	7 (38.9%)	
Treatment CNS relapse	No treatment	3 (5.8%)	2 (5.1%)	not done **
	Only Intrathecal Chemotherapy	12 (23.1%)	10 (25.6%)	
	Only Systemic therapy	4 (7.7%)	2 (5.1%)	
	Both (IT & Systemic)	29 (55.8%)	21 (53.8%)	
	radiation	3 (5.8%)	0 (0%)	
	IT+radiation	1 (1.9%)	4 (10.3%)	

Abbreviations : IQR : interquartal range, BM bone: marrow, CR: complete remission, MSD: matched sibling donor, UD: unrelated donor, F: female, M: male, MAC: myeloablative conditioning, RIC: reduced intensity conditioning, Bu: Busulfan, Cy: Cyclophosphamide, Flu : fludarabine, Mel: Melphalan, treo: treosulfan, BCNU : carmustine, Flamsa : Fludarabine, Cytarabine and Amsacrine, TBI : total body irradiation, SC : stem cell, PB : peripheral blood, CMV : cytomegaly virus, Don. : donor, GVHD : graft versus host disease, AGVH : acute graft versus host disease, cGVH : chronic graft versus host disease, IT : intrathecal

* Variable on a subpopulation

** more than 5 modalities