SUPPLEMENTARY APPENDIX

Outcome after relapse of myelodysplastic syndrome and secondary acute myeloid leukemia following allogeneic stem cell transplantation: a retrospective registry analysis on 698 patients by the Chronic Malignancies Working Party of the European Society of Blood and Marrow Transplantation

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Online Supplement

I: Details on data collection, definitions and statistical methods and list of contributing centers

Data collection

The registry of the European Society for Blood and Marrow Transplantation (EBMT) was screened for patients fulfilling the inclusion criteria. Reporting centers received a specifically designed questionnaire to collect further details. Centers were asked to report on all sequentially treated patients. Physician review of submitted data ensured data quality. Collected data included age, sex, relationship and HLA compatibility of patients and donors, disease characteristics at HSCT, conditioning, stem cells source (bone marrow, BM, or peripheral blood stem cells, PBSC), disease response and GvHD after transplantation. Relapse-related information included duration of post-transplant remission, basic treatment strategy, and outcome (response, further relapse, survival status, and causes of death). In recipients of HSCT2, additional details on the second transplant (donor, conditioning, stage at transplant) and GvHD were collected. In patients undergoing DLI, additional information on cell doses and transfusion schedule was requested.

Definitions

In addition to the definitions described in the manuscript, the following definitions were used:
Haematological relapse was defined by either detection of blasts in PB, re-appearance of signs of dysplasia in the BM or infiltration of BM with >5% blasts. Duration of remission was calculated from date of HSCT to date of relapse.
For evaluation of response to treatment of post-transplant relapse, remission was defined by the absence of signs of leukemia or myelodysplasia without ongoing specific therapy. Complete reconstitution of hematopoiesis was not required, since factors other than leukemia and radio-chemotherapy might contribute to leukopenia and thrombocytopenia, such as GvHD, or virus reactivation.

Statistics

Overall survival from relapse was defined as the interval from date of relapse to date of death or date of last follow up. OS was estimated by the Kaplan–Meier method. Variables considered included recipient age at time of relapse, sex of the patient, disease characteristics, disease status at transplant, donor characteristics (type, age, sex, HLA compatibility), transplant characteristics (year of transplant, conditioning, source of stem cells, acute and/or chronic GVHD after HSCT), and relapse characteristics (interval from transplant to relapse).

In patients receiving DLI or second HSCT, OS after the intervention was defined as the interval between day of first DLI or HSCT, respectively, and day of death or last follow-up. For patients who received a second HSCT, relapse/progression was defined as the first recurrence of the underlying disease after HSCT2. In contrast, non-relapse mortality was defined by death of any cause in remission of MDS/sAML.

II: Results of univariate risk factor analysis

Table S1: Univariate analysis of risk factors for overall survival from relapse in 698 patients

Variable		Estimated median OS from relapse (months) +/- standard error	p
Patient age	as continuous variable	-	0,011, (HR:1,009, 95%CI: 1,002-1,016)
	< median	5,1±0,6	
	≥ median	4,6±0,3	0,082
Patient sex	female	4,3±0,3	0,077
	male	4,9±0,5	
Year of HSCT	< median.	5,7±0,6	<0,001
	≥ median	3,9±0,3	
Diagnose at time of HSCT	RA/RARS	16,2±8,1	<0,001
	RAEB	7,0±1,4	
	sAML*	3,7±0,3	
Stage at Time of HSCT	Untreated	6,7 ±1,1	0,017
	CR	4,3±0,4	
	Refractory/progressive	4,1±0,4	
Donor	Matched family	5,3±0,4	<0,001
	Mismatched fam/unr	3,6±0,3	
Sex match donor/recipient	Female in male	4,8±0,9	0,688
	other	4,6±0,3	
Conditioning for HSCT	Standard	4,7±0,5	0,573
	reduced	4,6±0,5	
Source of stem cells for HSCT	BM	6,3±1,2	0,020
	PB	4,4±0,3	
T-cell depletion for HSCT	No	4,6±0,4	0,288
	yes	4,7±0,5	
aGVHD after HSCT	Yes	3,7±0,7	0,037
	no	4,8±0,3	
cGVHD after HSCT	Yes	5,6±1,0	0.179
	no	4,8±0,5	
Duration of remission after HSCT	<6 months	3,2±0,2	<0.001
	6-12 months	6,7±1,1	
	<12 months	12,3±2,2	

Table S2: Univariate analysis of risk factors for overall survival from second transplant in 110 patients

Variable		Estimated median OS from HSCT2 (months) +/- standard error	p
Patient age	as continuous variable	-	0,163 (HR:1,012, 95%CI: 0,995-1,030)
	< median	5,3±1,6	
	≥ median	3,0±0,5	0,187
Patient sex	female	2,5±0,4	0,336
	male	4,7±0,7	
Year of HSCT	< median.	3,3±1,4	0,120
	≥ median	4,2±1,3	
Diagnose at time of HSCT	RA/RARS	Not reached	0,184
	RAEB	7,2±2,4	
	sAML*	3,0±0	
Stage at Time of HSCT	Untreated	3,0 ±2,2	0,565
	CR	5,4±1,4	
	Refractory/progressive	2,6±0,8	
Donor	Matched family	4,5±1,6	0,087
	Mismatched fam/unr	3,2±1,5	
Sex match donor/recipient	Female in male	5,0±1,9	0,892
	other	3,2±0,9	
Conditioning for HSCT	Standard	4,6±1,7	0,179
	reduced	3,3±0,9	
Source of stem cells for HSCT	BM	7,1±2,9	0,083
	PB	3,2±1,0	
T-cell depletion for HSCT	No	3,0±1,1	0,344
	yes	5,0±2,3	
aGVHD after HSCT	Yes	4,6±0,7	0,846
	no	2,9±1,0	
cGVHD after HSCT	Yes	1,1±0,9	0.007
	no	6,3±1,2	
Duration of remission after HSCT1	<6 months	2,1±0,5	0.002
	6-12 months	7,2±2,6	
	<12 months	8,9±4,1	
DLI before second HSCT	No	4,6±1,2	0,978
	Yes	2,9±0,3	
Stage at second HSCT	CR	37,8±27,4	0,022
	Active disease	2,9±0,3	
Donor change for second HSCT2	Same donor	3,0±0,8	0,272
	Donor change	9,7±3,6	

Table S3: Univariate analysis of risk factors for overall survival after first therapeutic DLI in 213 patients

Variable		Estimeted median OS from first DLI (months) +/- standard error	p
Patient age	as continuous variable	-	0,011, (HR:1,016, 95%CI: 1,003-1,028)
	< median	6,5±1,56	
	≥ median	4,6±1,4	0,145
Patient sex	female	45,5±0,8	0,038
	male	7,4±2,4	
Year of HSCT	< median.	7,4±1,8	<0,189
	≥ median	4,8±1,1	
Diagnose at time of HSCT	RA/RARS	25,0±15,2	0,546
	RAEB	11,7±3,2	
	sAML*	4,8±0,9	
Stage at Time of HSCT	Untreated	8,3 ±1,9	0,276
	CR	6,1±1,7	
	Refractory/progressive	4,6±1,2	
Donor	Matched family	7,4±1,6	0,054
	Mismatched fam/unr	4,3±1,0	
Sex match donor/recipient	Female in male	13,6±6,0	0,109
	other	5,5±0,9	
Conditioning for HSCT	Standard	6,5±1,4	0,889
	reduced	4,7±1,0	
Source of stem cells for HSCT	BM	8,8±2,7	0,449
	PB	5,2±0,7	
T-cell depletion for HSCT	No	6,4±1,8	0,697
	yes	5,3±0,9	
aGVHD after HSCT	Yes	6,1±4,8	0,532
	no	5,9±1,2	
cGVHD after HSCT	Yes	11,9±1,0	0,06
	no	5,8±1,5	
Duration of remission after HSCT	<6 months	3,1±0,3	<0.001
	6-12 months	8,6±1,3	
	<12 months	25,1±8,5	

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