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The outcome of allogeneic HSCT in older AML patients is determined by disease biology and not by the donor type: An analysis of 96 allografted AML patients ≥50 years from the Czech acute leukaemia clinical register (alert)

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Older patients with AML have poor prognosis after chemotherapy and allo-SCT was historically limited to the young patients. In the multicentre retrospective study we analyzed 96 consecutive AML patients ≥ 50 years allografted with related (n=59) or unrelated (n=37) donor. The 2- year OS and DFS rates were 45 % and 42 % for the whole group. The corresponding figures for related patients were 48% and 42% whereas for unrelated 42% and 42%, respectively (OS p=0,721, DFS p = 0,896). The cumulative incidences of relapse (28% of all patients) and NRM mortality (26%) were low with no significant differences among related and unrelated cohorts. Multivariate analysis revealed the only major independent variables associated with an inferior OS were unfavourable cytogenetics (RR 3.36; CI 1.66-6.83; p=0.001) and advanced disease status (RR 2.30; CI 1.21-4.37; p=0.011). Unfavourable cytogenetics (RR 3.00; CI 1.50-5.99; p=0.002) and advanced disease at SCT (RR 2.27; CI 1.22-4.22; p=0.009) were also the only independent variables associated with inferior DFS. In conclusion, our analysis indicates that outcomes of allografted AML patients aged ≥ 50 years are determined by cytogenetic risk category and disease status at transplantation and not by the type of donor.

Key words: AML, allogeneic HSCT, age, donor

Acute myeloid leukaemia is disease prevalent of elderly patients with the median age at presentation approaching 70 years [1]. In this age group the disease is almost incurable by standard treatments used for younger patients [2,3]. Allogeneic haematopoietic stem cell transplantation (SCT) is currently considered best curative approach for younger patients with acute myeloid leukaemia [4-6]. Because of the high toxicity the procedure was historically limited to the young patients. Advances in supportive care and the advent of reduced-intensity conditioning (RIC) regimens allowed to profit from this procedure to older age groups and promising results using related siblings were published [7]. However there has been reluctance for using matched unrelated donors (MUD) as unrelated HCT for older patients has been considered to be compromised with unacceptable high transplant related-mortality and worse immediate availability of the donor [8]. The more sophisticated HLA typing and expanded pool of unrelated donors worldwide allowed refinements in the donor selection and recently similar outcomes using related and unrelated donors were reported [9-13]. Although genoidentical sibling is still donor of choice, few important drawbacks are obvious. Such a donor is available only in 25-30% and the siblings of elderly pts are naturally older and often ineligible for stem cell collection. Also, it is not possible to take into account donor characteristics that may impact HCT outcome such as donor age, CMV status, sex, cell dose [14-16]. On the other hand, even with high-resolution HLA typing, perfectly matched unrelated donor remains disparate for numerous

minor histocompatibility antigens and/or antigens associated with HLA haplotype matching [17] which may contribute to the higher rates of GVHD and consequently TRM compared to related donors.

As especially older donor age has been reported to be associated with worse outcome of SCT [14] the question is whether younger age of unrelated donors could compensate for the higher immune incompatibility.

We have retrospectively investigated the outcomes of 96 consecutive patients with AML older than 50 years who underwent allogeneic SCT in the 5 Czech and Slovak centres and were reported to the Czech Acute Leukaemia Register (ALERT). The aim was (1) to evaluate the impact of donor type on survival after SCT and (2) to assess which other factors seemed to be the most significant determinants of SCT outcome in this specific patient group.

Patients and methods

Study population. The study was retrospective historical design based on the anonymized data included in the Czech Acute Leukaemia Registry (ALERT) database. Inclusion criteria were AML diagnosed according the WHO criteria, age older than 50 years at the time of SCT, allogeneic SCT performed between January 2000 and December 2007 either with HLA identical sibling or 9-10/10 HLA identical MUD. Included were all consecutive patients fulfilling inclusion criteria. Patients transplanted with haploidentical donors were excluded. Preparative regimens were classified as either RIC or standard myeloablative (MA). All patients signed local informed consent for the anonymized analyses of clinical data.

Study endpoints and definitions. Favourable, intermediate and unfavourable risk cytogenetics was assigned according to SWOG/ECOG criteria [18]. For analysis the AML status at the time of SCT was classified as either early (CR 1, 2) or advanced (CR3, PR, primary induction failure - PIF, refractory relaps). Primary outcomes were overall survival (OS), disease-free survival (DFS, defined as survival without death or relapse), non-relapse mortality (NRM, defined as any death in continuous remission) and hematologic relapse. Secondary endpoints were incidence of acute graft-versus-host disease (GVHD) and presence or absence of chronic GVHD [19,20]

Patient characteristics. Table 1 lists all patients, diseases, and transplantation related variables for the whole group and for sibling and MUD cohorts, respectively.

The median patient age was 56 years (range, 50 to 68 years) with 73 patients (76%) age 50 to 60 years and 23 (24%) age older than 60 years. There was no difference in age between related and unrelated cohort. Majority of patients were transplanted in early disease and there was no difference in proportion of more advanced disease stage at transplantation between recipients of related donors or MUD (32% vs. 24%, $p = 0.668$). The proportion of cytogenetic risk categories were well balanced in the different donor groups ($p = 0.831$).

Donors & HLA matching&stem cell source. Donors were 59 HLA identical siblings and 37 unrelated HLA-A,-B,-C,-DR,-DQ completely matched donors (10/10, n = 22) or partially mismatched (9/10, n = 14 or 8/10, n = 1). All unrelated donor/recipients pairs were DNA typed at the allelic level (high-resolution typing) for all loci. Peripheral blood stem cells (PBSC) were the stem cell source in all but 5 patients (5%). Unrelated donors were significantly younger than siblings (median 32 v 55 years, $p< 0.001$). Patients in the MUD cohorts received more CD 34+ cells (median $6.5x10^6$/kg, range 2.0-18 vs. $4.7x10^6$/kg, range 1.0-9.6, $p = 0.004$). There was no difference in the representation of CMV negative donor-recipient pairs between the MUD and sibling cohort.

Conditioning. A majority (n = 60, 63%) of the patients received reduced-intensity conditioning which consisted of fludarabine in various combination with melphalan or busulfan or TBI. Conventional myeloablative conditioning regimens were used in 36 patients (37%) and the most frequent were busulfan in combination with cyclophosphamide (75%) or TBI (10-12Gy) combined with cyclophosphamide or fludarabine (25%). There was no difference in donor type between RIC and conventional conditioned patients.

GVHD prophylaxis & treatment. GVHD prophylaxis was based on calcineurin inhibitors (cyclosporine or tacrolimus) in all patients. The treatment of GVHD varied among centres with standard initiation of steroids in all patients. Incidences of grades I-IV acute GVHD and chronic GVHD were determined according the established criteria [19, 20]. Chronic GVHD was evaluated in patients who survived at least 100 days with sustained engraftment.

Statistical analysis. Patient characteristics were summarized using frequency tables and standard descriptive statistics. Probabilities of overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method. Univariate analyses to evaluate differences in survival between groups of patients were performed using the log-rank test and Wald's test. The Cox proportional hazards model was considered for the survival modelling, multivariate survival analysis was used to specify the role of individual prognostic factors in assessing the OS and DFS. A multiple logistic regression model was used for identification of the significant prognostic factors on nonrelapse mortality and relapse. The point estimates were accompanied by 95% confidence intervals (CI). Level of statistical significance $\alpha = 0.05$ was used in all analyses. All computations were performed using the SPSS software (version 12.0.2) and STATISTICA software (version 9.0).

Results

Survival. For the entire cohorts of patients, the 2-year Kaplan-Meier estimate for OS was 45%. DFS of the whole cohort was 42%. There were 49 deaths in total with 29 deaths out of 59 patients in the sibling cohort and 20 deaths out of the 37 patients in the MUD cohort ($p = 0.679$) . The main identifiable

Table 1. Characteristics of the patients

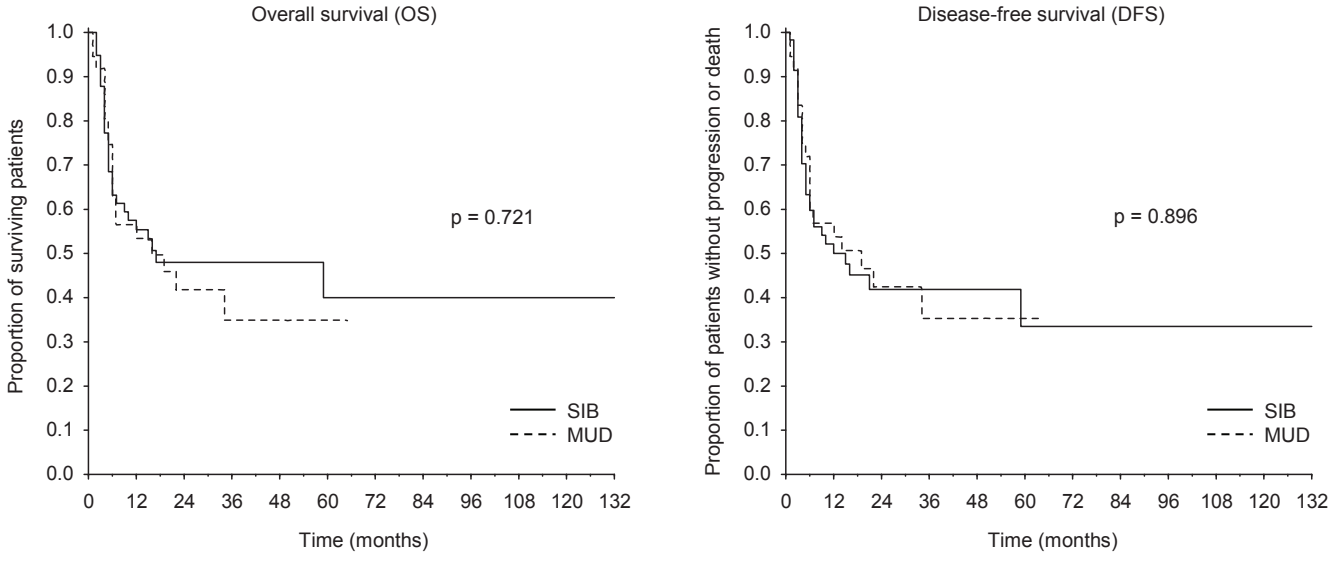
	All patients N = 96		Matched siblings N = 59		Matched unrelated N = 37		P
Characteristic	No	%	No	%	No	%	
Median age at HCT							0,34
years	56		55		57		
Range	50-68		50-68		50-63		
AML cytogenetic risk							0,83
Favorable	5	5	4	7	1	3	
Intermediate	69	72	42	71	27	73	
Unfavorable	15	16	9	15	6	16	
Unknown	7	7	4	7	3	8	
Disease status							0,668
Early CR	68	71	40	68	28	76	
Advanced	28	29	19	32	9	24	
Donor age, years							< 0,001
Median	49		55		32		
Range	20-68		24-68		20-58		
Donor/recipient sex match							0,53
Male/male	24	25	10	17	14	38	
Male/female	28	29	18	30	10	27	
Female/male	16	17	11	19	5	13	
Female/female	28	29	20	34	8	22	
Donor/recipient CMV match							
Negative/negative	4	4	3	5	1	3	0,57
Mismatch (-/+ or+/-)	24	25	5	9	19	51	< 0,001
Positive/positive	60	63	45	76	15	41	< 0,001
Unknown	8	8	6	10	2	5	0,623
Graft type							0,37
Bone marrow	5	5	2	3	3	8	
Peripheral blood	91	95	57	97	34	92	
Conditioning intensity							0,83
Myeloblative	36	38	23	39	13	35	
Reduced intensity	60	62	36	61	24	65	
CD 34+ cells transplanted x 10^6/kg							0,004
Median	5,2		4,7		6,5		
range	1,0-18,3		1,0-9,6		2,0-18,3		

causes of death were transplant-related causes in 25 (51%) and relapse in 24 (49%).

Patients transplanted with sibling donor had OS and DFS rates at 2-year of 48% and 42%, respectively, whereas for patients with MUD the corresponding figures were 42% and 42%. The differences in OS and DFS between sibling and MUD cohorts were insignificant (Figure 1). The strongest survival predictors in univariate analysis (see table 2) were intermediate/favourable (RR = 0.45; CI 0.23-0.86; P = 0.016) or unfavorable cytogenetics (RR = 3.13; CI 1.55-6.33; P = 0.001) and disease status pre-SCT (patients with advanced disease RR = 2.14; CI 1.13-4.04; P = 0.02). Other transplant variables (donor type, conditioning, CMV status, donor gender etc) did not impact survival. The same variables were identified as significant predictors of DFS.

Nonrelapse mortality. The overall non-relapse mortality was 26% (25 patients). The incidencies of NRM were not different between the SIB and MUD cohorts (20% versus 35%; p = 0.245). Univariate analyses do not reveal any statistically significant prognostic variables associated with NRM (table 2).

Relapse or disease progression. A total of 27 patients suffered a relapse, 20 in the SIB group and 7 in MUD group. There was no significant difference in rate of disease progression or relapse between the SIB and MUD cohorts (34% vs. 19%; p = 0.162). The only significant variables influencing



	OS		DFS	
	SIB N = 59	MUD N = 37	SIB N = 59	MUD N = 37
Median survival; months (CI)	17.0 (0.0; 59.1)	16.0 (0.0; 33.5)	12.0 (0.0; 25.1)	19.0 (1.1; 36.9)
Survival at 12 months; % (CI)	55.4 (42.3; 68.5)	53.3 (36.5; 70.2)	50.0 (36.8; 63.2)	53.7 (36.9; 70.5)
Survival at 24 months; % (CI)	48.0 (34.2; 61.8)	41.8 (24.1; 59.4)	41.9 (27.9; 55.9)	42.4 (24.8; 60.0)

Figure 1. Survival of ≥ 50 years old allografted AML patients according to type of allogeneic HSCT (SIB = sibling donors; MUD = matched unrelated donors).

Table 2. Univariate analysis for outcomes

	OS			DFS			NRM			Relapse rate		
Variable	**RR**	**95 % CI**	**P**	**RR**	**95 % CI**	**P**	**OR**	**95 % CI**	**P**	**OR**	**95 % CI**	**P**
Patient age (years)	0.99	(0.92-1.06)	0.760	0.97	(0.90-1.04)	0.330	1.13	(0.97-1.32)	0.120	0.87	(0.76-0.99)	**0.038**
Intermediate/favorable risk cytogenetics	0.45	(0.23-0.86)	**0.016**	0.44	(0.24-0.83)	**0.011**	1.67	(0.45-6.13)	0.442	0.29	(0.10-0.86)	**0.025**
High risk cytogenetics	3.13	(1.55-6.33)	**0.001**	2.84	(1.43-5.66)	**0.003**	0.93	(0.24-3.58)	0.920	2.57	(0.76-8.72)	0.129
Disease status at HCT – advanced disease	2.14	(1.13-4.04)	**0.020**	2.16	(1.16-4.00)	**0.015**	0.49	(0.13-1.78)	0.278	4.19	(1.41-12.44)	**0.010**
Unrelated donor	1.06	(0.57-1.98)	0.852	0.90	(0.49-1.66)	0.736	2.57	(0.71-9.27)	0.150	0.43	(0.15-1.26)	0.125
Donor age	1.0	(0.97-1.02)	0.820	1.00	(0.97-1.02)	0.730	0.98	(0.94-1.03)	0.444	1.01	(0.97-1.04)	0.787
Type of graft-bone marrow	0.99	(0.30-3.21)	0.982	0.90	(0.28-2.91)	0.855	2.00	(0.17-23.96)	0.584	0.61	(0.06-5.80)	0.670
Myeloablative conditioning	1.11	(0.58-2.10)	0.756	1.13	(0.61-2.10)	0.693	0.31	(0.08-1.19)	0.087	2.63	(0.96-7.20)	0.060
Number of CD34+ cells transplanted	0.97	(0.88-1.08)	0.603	0.96	(0.87-1.06)	0.460	1.15	(0.90-1.48)	0.256	0.86	(0.71-1.05)	0.140

relapse in univariate analyses (table 2) were age of the patient (OR 0.87; CI 0.76 - 0.99; p = 0.038), intermediate/favourable risk cytogenetics (OR 0.29; CI 0.10 - 0.86; p = 0.025) and advanced disease status pre-SCT (OR 4.19; CI 1.41 - 12.44; p = 0.010)

Acute and chronic GVHD. In the entire cohort, the overall incidence of acute GVHD was 44.8%, whereas the incidence of grades III-IV was 14.6%. The incidences comparing SIB and MUD donors were similar both for overall and for gr. III-IV aGVHD (42.4 versus 44.6%; p = 0.674 and 13.6 versus 16.2%; p = 0.771, respectively). Among 45 SIB and 29 MUD patients who were alive at day+100 chronic GVHD was documented in 22 (49%) SIB and 12 (41%) MUD (p = 0.569). Similar incidence between SIB and MUD cohorts was observed also for extensive cGVHD which was 27% for the whole group and 26.7% for SIB and 27.6% for MUD (p = 0.999).

Multivariate analysis. The results of multivariate analysis of 3-year outcomes are shown in Table 3. The transplantation

Table 3. Multivariate analysis for outcomes

Variable	RR/OR	95 % CI	Overall P
Overall Survival			
Unfavourable cytogenetics	3.36	1.66 - 6.83	0.001
Advanced disease stage	2.30	1.21 - 4.37	0.011
Disease free survival			
Unfavourable cytogenetics	3.00	1.50 - 5.99	0.002
Advanced disease stage	2.27	1.22 - 4.22	0.009
Relapse			
Advanced disease stage	4.61	1.48 - 14.36	0.008
Myeloablative conditioning	2.95	1.01 - 8.65	0.048

with advanced disease (OR 4.61; CI 1.48-14.36; p = 0.008) and use of myeloablative regimen (OR 2.95; CI 1.01-8.65; p = 0.048) were associated with increased relapse rate. No significant independent variable influencing NRM was identified in multivariate analysis. The only major independent variables associated with an inferior OS were unfavourable risk cytogenetics (RR 3.36; CI 1.66-6.83; p = 0.001) and advanced disease status at the time of HSCT (RR 2.30; CI 1.21-4.37; p = 0.011). Unfavourable cytogenetics (RR 3.00; CI 1.50-5.99; p = 0.002) and advanced disease at the time of SCT (RR 2.27; CI 1.22-4.22; p = 0.009) were also the only independent variables associated with inferior DFS.

Discussion

In this registry based, retrospective study we present the results of data analysis of the cohort of AML patients ≥50 years that received an allogeneic SCT as a part of curative intent therapy. The contribution of recipient age toward the AML patient suitability for SCT, including with MUD has been a subject of debate in recent years.

We demonstrate that SCT in AML patients above 50 years provides sustained remission survival exceeding 40% regardless of the donor type. The adjusted relative risk of OS and DFS for patients with MUDs compared with SIB was 1.06 (CI 0.57-1.98) and 0.90 (CI 0.49-1.66). Similarly, the type of donor did not significantly affect NRM and rate of relapse. Higher (yet insignificant) relative risk of NRM with MUDs was offset by the trend for lower relapse rate. Moreover, we did not observed statistically significant differences in acute and chronic GVHD incidences.

This finding supports two main conclusions. First, it confirms the feasibility of SCT in our elderly patient population. Second, patients transplanted with unrelated donors have similar outcomes with regard to OS, DFS, NRM and relapse. These conclusions related to survival are consistent with the recently published data. Undoubtedly, there is currently firm evidence to consider both type of donor equivalent at least for younger patients [10-12] even in first remission [21]. Our observation confirms and extends available data for older AML patients. In analogous retrospective study of 368 AML patients with very similar characteristics (similar median age, various conditioning intensity and disease status), Schetelig at al. reported identical transplant outcomes - 40 and 35% OS/EFS at 2 years with no difference between related and unrelated donors [13]. Similarly, no impact of donor type on the outcome was observed in the multicenter study of 274 AML patients with median age of 60 years transplanted by uniform RIC SCT [22]. McClune et al. in CIBMTR study evaluated the impact of age in 545 patients above 40 years undergoing RIC SCT for AML in CR1. Comparing to our study he has found similar two year survival with only modest difference across the age groups (34% to 50%) and again he has detected no influence of donor type, even in the oldest subsets. On the other hand the greater HLA disparity in the MUD cohort adversely affected 2-year NRM, DFS, and OS [23]. Interestingly in multivariate analysis he has reported worse DFS with older donor age. As the donors were predictably significantly younger in our MUD cohort (median 32; range 20-58 vs 55; range 24-68; p< 0,001), one could speculate whether the younger donor age of MUD compensates for the possible negative impact of inherent higher immune incompatibility in comparison to related donors. The advanced donor age was associated with some impairment of stem cell function [24] and Mehta et al. reported the donor age above 45 years adversely influences OS and DFS and increases the risk of relapse and TRM [25] in patients transplanted after RIC. The Cox model in our study did not reveal the effect of donor age on survival, NRM and relapse (see table 2), however the heterogeneity of our group with regard to type of conditioning and graft source may limit our finding.

Historically there was legitimate reluctance to refer older patients for unrelated SCT to patients above 50 years of age due to the presumed excess of NRM linked to higher rate of GVHD. Lim et al. in retrospective EBMT study of 1333 patients older than 50 years with MDS/secondary AML reported that use of unrelated donor was independent variable associated with nonrelapse mortality [26]. Our analysis reveal only insignificant trend for higher NRM with MUD

(OR 2.57; CI 0.71-9.27; p = 0,150). Again, the relatively small number of our patients in MUD cohort might confound our results.

The multivariate analysis for main transplant outcomes reveals unexpected finding the myeloablative conditioning was marginally significantly associated with risk of relapse (HR 2.95; CI 1.01-8.65; p = 0.048) despite the number of patients with advanced disease at SCT and cytogenetic risk distribution were similar between RIC and myeloablative group (data not shown). This is in contrast with most of other studies showing higher relapse rate using RIC regimens [27-29]. The significantly higher portion of patients with unknown cytogenetics in the myeloablative cohort (17% vs. 2% for the RIC, p = 0,037) together with smaller number of patients in myeloablative cohort (n = 36) might contribute to the finding. Khabori et al. recently compared the outcomes of RIC and conventional conditioning in 101 AML/MDS patients and he has not found significant difference for OS, EFS, TRM and relapse between the two cohorts [30]. He reported only disease risk was significantly associated with OS, EFS and cumulative relapse (HR 3.24; CI 1.08-10.12). Similarly Lim et al. [26] and Krauter et al. [31] concluded that disease status at transplantation is the most important prognostic factor for SCT success in elderly AML patients. As shown by univariate and multivariable analysis our data supports these. The only significant predictors of survival univariate analysis proved to be cytogenetics (RR = 0.45; CI 0.23-0.86; P = 0.016 for intermediate/favorable and RR = 3.13; CI 1.55-6.33; P = 0.001 for unfavourable cytogenetics, respectively) and disease status at SCT (RR = 2.14; CI 1.13-4.04; P = 0.02 for patients with advanced disease at SCT).

In the multivariable Cox model the only factors consistently statistically significant for OS, EFS and relapse were advanced disease stage and (as mentioned above with exception for relapse) unfavourable cytogenetics (table 3). Overall, these results are in accordance with the recent reports [13, 26, 30-31] where the main independent factor predicting SCT outcome in similar AML population was disease risk.

Our analysis is a retrospective study and as such it has inherent important limitations. It is naturally susceptible to bias in patient selection. With regards to heterogeneity of the population, the sample size is relatively small, especially for unrelated cohort. Because of the unavailability for many patients we were not able to assess the SCT comorbidity index scoring and thus the results of our study can be influenced by differences in patient comorbidities that drive the decision to type of donor or type of conditioning.

In summary our analysis indicates that outcomes of allografted AML patients aged ≥ 50 years are mainly determined by disease biology, i.e. cytogenetic risk category and disease status at transplantation. Age alone and absence of related donor should not be the basis for excluding AML patient from potentially curative allogeneic SCT. Rather, transplantation either from related or unrelated donors should be considered early in the disease course, primarily in patients with poor cytogenetics.

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