The role of matched sibling donor allogeneic stem cell transplantation in pediatric high-risk acute myeloid leukemia: results from the AML-BFM 98 study

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The online version of this article has a Supplementary Appendix.

ABSTRACT

Background

The role of allogeneic stem cell transplantation in post-remission management of children with high-risk acute myeloid leukemia remains controversial. In the multi-center AML-BFM 98 study we prospectively evaluated the impact of allogeneic stem cell transplantation in children with high-risk acute myeloid leukemia in first complete remission.

Design and Methods

HLA-typed patients with high-risk acute myeloid leukemia, who achieved first complete remission (n=247), were included in this analysis. All patients received double induction and consolidation. Based on the availability of a matched-sibling donor, patients were allocated by genetic chance to allogeneic stem cell transplantation (n=61) or chemotherapy-only (i.e. intensification and maintenance therapy; n=186). The main analysis was done on an intention-to-treat basis according to this allocation.

Results

Intention-to-treat analysis did not show a significantly different 5-year disease-free survival (49±6% *versus* 45±4%, $P_{\text{log rank}}$=0.44) or overall survival (68±6% *versus* 57±4%, $P_{\text{log rank}}$=0.17) between the matched-sibling donor and no-matched-sibling donor groups, whereas late adverse effects occurred more frequently after allogeneic stem cell transplantation (72.5% *versus* 31.8%, P_{Fischer}<0.01). These results were confirmed by as-treated analysis corrected for the time until transplantation (5-year overall survival: 72±8% *versus* 60±4%, $P_{\text{Mantel-Byar}}$ 0.21). Subgroup analysis demonstrated improved survival rates for patients with 11q23 aberrations allocated to allogeneic stem cell transplantation (5-year overall survival: 94±6% *versus* 52±7%, $P_{\text{log-rank}}$=0.01; n=18 *versus* 49) in contrast to patients without 11q23 aberrations (5-year overall survival: 58±8% *versus* 55±5%, $P_{\text{log-rank}}$=0.66).

Conclusions

Our analyses defined a genetic subgroup of children with high-risk acute myeloid leukemia who benefited from allogeneic stem cell transplantation in the prospective multi-center AML-BFM 98 study. For the remainder of the pediatric high-risk acute myeloid leukemia patients the prognosis was not improved by allogeneic stem cell transplantation, which was, however, associated with a higher rate of late sequelae. *(ClinicalTrials.gov Identifier: #NCT00111345)*

Key words: acute myeloid leukemia, AML, stem cell transplantation, SCT, *MLL* childhood, post-remission therapy.

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Introduction

The role of allogeneic stem cell transplantation (SCT) in the management of pediatric acute myeloid leukemia (AML) during the first complete remission is a subject that is under debate, as reviewed by Niewerth *et al.*[1] Although allogeneic SCT is widely accepted as a curative and effective treatment option for consolidation in children with AML, it is associated with a higher risk of treatment-related mortality, morbidity, and long-term sequelae than chemotherapy alone.[2] Among this pediatric population, late sequelae such as endocrine dysfunction, impaired growth and fertility, severe bone disorders and secondary malignancies are particularly relevant.[3] Recent intensified chemotherapy protocols in conjunction with improved supportive care and effective treatment options in relapse have enabled 5-year overall survival rates of more than 60% in AML.[4] Thus, allogeneic SCT has to be superior in terms of event-free survival and overall survival to chemotherapy only in order to be considered as first choice therapy for patients with pediatric AML in first complete remission. A clear definition of subgroups of patients who could benefit from allogeneic SCT remains a long sought after goal, which could spare unnecessary toxicity for those patients in whom chemotherapy alone could achieve equal or better survival rates.

Previous multicenter trials preferentially recommended matched sibling donor (MSD) SCT in first complete remission.[5-7] To date, most study groups agree that patients with acute promyelocytic leukemia [APL, AML FAB M3, t(15;17)], myeloid leukemia in Down syndrome, as well as patients with AML and favorable cytogenetics, e.g. t(8;21) or inv(16), should be treated with chemotherapy-only as consolidation therapy.[1] In all other patients the significance of allogeneic SCT in first complete remission has not been clearly defined. Several multi-center and single center studies have produced conflicting results regarding the benefit of allogeneic SCT,[1,8-11] but only a few studies tested the impact of allogeneic SCT in first complete remission prospectively on an intention-to-treat basis based on the availability of a suitable donor.[1] The evaluation of the impact of SCT is hampered by methodological difficulties,[12] including the necessity to achieve and remain in remission until SCT, exclusion of patients with expected severe side effects from SCT, availability of a compatible sibling for eligible patients, and the correlation of outcome with the availability of a donor. Therefore, at best, studies examining this utilize biological randomization with intention-to-treat analyses (level of evidence, 2++).[13]

Here, we report the results of the prospective AML-BFM 98 trial, which aimed to determine the role of allogeneic SCT - assigned on the basis of genetic chance – as treatment for children with high-risk AML in first complete remission.

Design and Methods

Patients

The AML-BFM 98 study was a randomized, controlled phase III study running in 75 centers in Germany, Austria, Switzerland, and the Czech Republic, which opened in July 1, 1998 and closed in June 30, 2003. The final protocol was approved by the protocol review committee of the German Cancer Society, and by the ethics committee of the University of Münster. Between July 1, 2003 and April 30, 2004 the AML-BFM 98 Interim Study, continuing the best arm of the AML-BFM 98 trial, recruited further patients. Simultaneously, centers in Germany, Austria and Switzerland (BFM-Core group) participated in a prospective study on allogeneic SCT versus chemotherapy for high-risk childhood AML in first complete remission (AML CR1 HLA id) on behalf of the European Bone Marrow Transplantation (EBMT) Pediatric Working Party and the International BFM Study Group (I-BFMSG), which was approved by the ethics committee of the University of Tübingen.

In total, 555 children and adolescents (0 to 18 years) with newly diagnosed and centrally ensured primary AML according to WHO criteria and with written informed consent were enrolled. The French-American-British (FAB) classification was used for the initial diagnosis of AML.[14,15] The diagnoses of the FAB M0 and M7 subtypes required confirmation by immunological methods.[15,16] Patients with myelosarcoma (<30% blasts), biphenotypic leukemia, secondary AML, Down syndrome and AML (n=62) and syndromes such as Shwachman-Diamond or Fanconi anemia, which prevent sufficient therapy, were not eligible for inclusion in the AML CR1 HLA id study and were, therefore, excluded from further analysis. The remaining 493 protocol patients were stratified into a standard-risk group (n=176) and a high-risk group (n=317) based on the results of the AML-BFM 83/87 studies.[17]

The standard-risk group included all patients with AML FAB M1/2 and Auer rods, M3, M4eo, t(15;17), t(8;21) or inv(16). Patients with FAB M1/2, t(8;21), M4eo or inv(16) and more than 5% blasts in the bone marrow at day 15 (centrally reviewed) were shifted to the high-risk group. The high-risk group comprised those patients and patients with all other subtypes. The results for the high-risk patients are reported here. High-risk patients and family members were required to undergo HLA typing after assignment to the risk group. All high-risk patients with a matched sibling donor were eligible for allogeneic SCT in first complete remission.

Therapy

The study design and treatment details of the AML-BFM 98 study have already been reported.[18] In brief, all patients received double induction with AIE (cytarabine, idarubicin, etoposide) and HAM (high-dose cytarabine, mitoxantrone), and then consolidation (Figure 1). For consolidation, patients of the AML-BFM 98 study were randomly assigned to two short chemotherapy cycles, i.e. AI (cytarabine, idarubicin, intrathecal cytarabine) and haM (high-dose cytarabine, mitoxantrone, intrathecal cytarabine) or the BFM-type 6-week consolidation (6-thioguanine, prednisone, vincristine, idarubicin, cytarabine, cyclophosphamide, intrathecal cytarabine).[19] The cumulative dose of anthracyclines was similar in both arms.

According to the AML CR1 HLA id protocol, allogeneic SCT was to be performed in first complete remission after consolidation. Children who were not transplanted in first complete remission received one course of HAE (high-dose cytarabine and etoposide) as intensification therapy and maintenance therapy for 12 months (thioguanine, cytarabine, intrathecal cytarabine).

Allogeneic SCT was performed in 23 SCT centers. The recommended standard conditioning regimen for allogeneic SCT in first complete remission was busulfan [4 mg/kg/day (5 mg/kg/day for children <3 years of age); days -7 to -4] and cyclophosphamide (60 mg/kg/day; days -4 to -2). Cyclosporine A 0.5 mg/kg *b.i.d.* i.v. was administered, starting on day -1, for graft-*versus*-host disease (GvHD) prophylaxis. Children older than 16 years of age additionally received methotrexate (10 mg/m^2/day; days +1, +3 and +6) with folinic acid rescue (15 mg/m^2/day; days +2, +4 and +7). Cyclosporine A serum levels were monitored in the case of hepat-

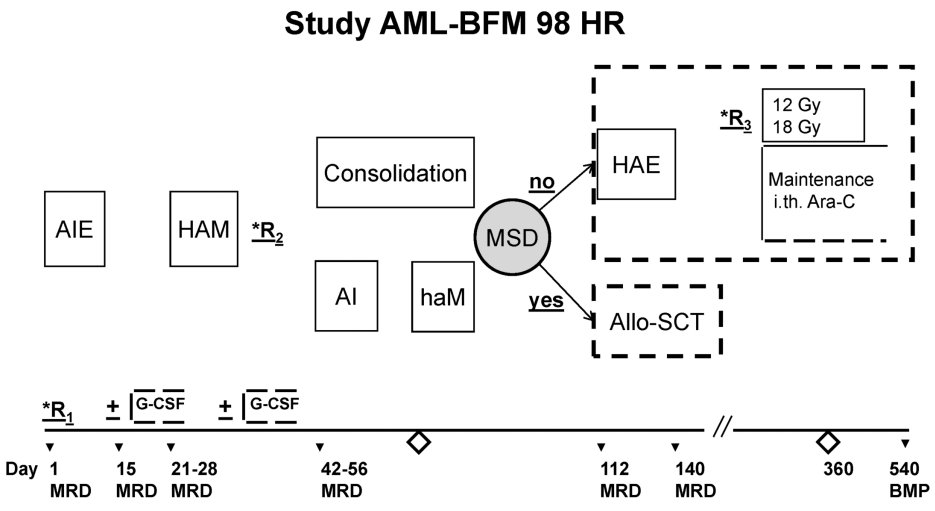

Figure 1. Treatment schedule of the Acute Myeloid Leukemia Berlin-Frankfurt-Muenster (AML-BFM 98) study for high risk (HR) patients: AIE, cytarabine/ idarubicin/ etoposide; AI, cytarabine/ idarubicin; HAM, high-dose cytarabine (3 g/m² q12 h over 3 days)/ mitoxantrone; haM, high-dose cytarabine (1 g/m² q12 h over 3 days)/ mitoxantrone; consolidation, 6-thioguanine/ prednisone/ vincristine/ idarubicin/ cytarabine/ cyclophosphamide; HAE, high-dose cytarabine (3 g/m² q12 h over 3 days)/ etoposide; CNS irradiation; maintenance, 12 months thioguanine/ cytarabine. R1, first random assignment; R2, second random assignment; R3, third random assignment. MSD, matched sibling donor.

ic or renal dysfunction, but no adjustment of dosing was intended.

Until October 2001 relapse treatment was performed according to the AML-BFM Relapse Study 97 and from November 2001 to March 2009 according to the international AML Relapse Study 2001/01.[20] Allogeneic SCT was recommended for all patients in second complete remission.

Cytogenetic and molecular genetic analyses

Cytogenetic analyses were carried out and centrally reviewed in the AML-BFM reference laboratory in Giessen, Germany, as previously described.[21] Comprehensive cytogenetic data from 88% (n=217) of the included patients (n=247) were available. Complete karyotypes were described according to the International System of Human Cytogenetic Nomenclature.[22]

Statistical methods/ definitions

Complete remission was defined by fulfillment of the Cancer and Leukemia Group B (CALGB) criteria.[23] Early death was defined as death before or within the first 6 weeks of treatment. Event-free survival was defined as the time from diagnosis to the date of last follow-up or first event. Events were early death, resistant leukemia, relapse, secondary malignancy, or death from any cause. Failure to achieve remission was considered as an event on day 0. Survival was defined as the time of diagnosis to death from any cause. The 5-year overall survival was calculated from date of diagnosis to death, and disease-free survival from the date of remission to first event (relapse, secondary malignancy, or death). The Kaplan-Meier method was used to estimate survival rates;[24] differences were compared with a two-sided log-rank test.[25] Standard errors were obtained using Greenwood's formula. Cumulative incidences of relapse and death in complete remission were calculated by the method of Kalbfleisch and Prentice and compared with Gray's test. The Cox proportional hazards model was used to obtain the estimates and 95%-confidence interval of the relative risk for prognostic factors.[26] Differences in the distribution of individual parameters among subsets of patients were analyzed using the χ^2 or Fisher's exact test for categorized variables and the Mann-Whitney U test for continuous variables. The effect of SCT on survival was tested using the Mantel-Byar method for comparisons of patients treated or not treated with SCT. For the graphic presentations, patients without SCT and an event-free survival below the median time to transplantation (0.43 years) were excluded. The follow-up data are those as of August 2011. Computations were performed using SAS (Statistical Analysis System Version 9.1; SAS Institute, Cary, NC, USA).

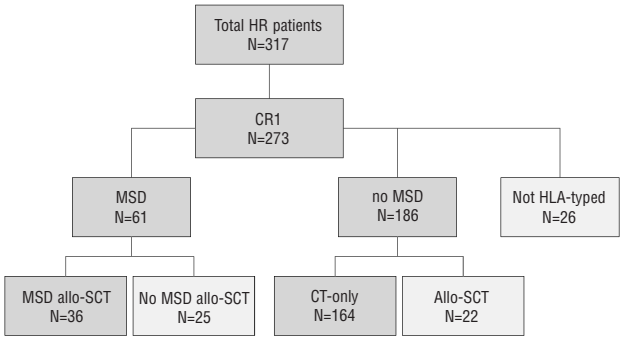

Figure 2. Flow chart of high-risk (HR) AML patients and their post-remission management in first complete remission in the AML-BFM 98 trial. CR1, first complete remission. MSD, matched sibling donor. Allo-SCT, allogenic stem cell transplantation.

Results

Patients' characteristics

Between July 1998 and April 2004 317 children and adolescents with high-risk AML were enrolled in the AML-BFM 98 and AML-BFM 98 Interim clinical trials. These children included patients who were eligible for allogeneic SCT in first complete remission (Figure 2). Overall, 273 achieved first complete remission (86%). In 26 patients (9.5%) HLA typing was either missing (n=15; 5.5%) or refused (n=11; 4%). These patients were, therefore, excluded from subsequent analyses (Figure 2). Of the remaining 247 patients, 61 patients (25%) had a MSD and were allocated to allogeneic SCT, while 186 (75%) had no MSD (intention-to-treat groups: MSD *versus* no-MSD).

Allogeneic SCT was refused by the guardians/local physician in six cases, resulting in a compliance rate of 90.1%. Two children were transplanted from a matched unrelated donor although a MSD was available and were, therefore, excluded from the as-treated analysis. In 23 children with an available donor, allogeneic SCT could not be carried out in first complete remission because of early relapse (n=7), death in complete remission (n=2) or poor clinical condition (n=8). Thus, in total, 36 patients (59%) with a MSD (n=61) actually received a MSD allogeneic SCT in first complete remission (=as-treated group).

Together with two patients who were transplanted from a matched unrelated donor, 38 patients (62%) received allogeneic SCT in first complete remission. This rate is within the range occurring in previous studies.[27,28]

One hundred and sixty-four of 186 (88%) patients without a MSD received chemotherapy only (=as-treated group). Twenty-two children (12%) were transplanted from an unrelated donor (n=17), mismatched family donor (n=2) or haploidentical donor (n=3).

The characteristics of the patients in the intention-to-treat and as-treated groups are summarized in Table 1.

Treatment outcome

Patients in the MSD group (n=61) did not have a significantly better 5-year disease-free survival (49±6% *versus* 45±4%; $P_{log\text{-}rank}$=0.44; Figure 3A) or 5-year event-free survival (49±6% *versus* 45±4%; $P_{log\text{-}rank}$ =0.51) than patients in the no-MSD group (n=186). Likewise, the 5-year overall

Table 1. Patients' characteristics.

	intention-to-treat analysis							As-treated analysis						
	no MSD (n=186)		MSD (n=61)					CT-only (n=164)		allo-SCT (n=36)				
	N	(%)	N	(%)	Total	(%)	P	N	(%)	N	(%)	Total	(%)	P
Gender														
male	98	52.7	31	5.8	129	52.2		90	54.9	17	47.2	107	53.5	
female	88	47.3	30	49.2	118	47.8	0.88	74	45.1	19	52.8	93	46.5	0.46
Age, years														
younger than 2	69	37.1	15	24.6	84	34.0		61	37.2	8	22.2	69	34.5	
2-9	47	25.3	24	39.3	71	28.7		42	25.6	17	47.2	59	29.5	
at least 10	70	37.6	22	36.1	92	37.2	0.07	61	37.2	11	3.6	72	36.0	0.03
White blood cell, $\times 10^9$/L														
less than 20	100	53.8	41	67.2	141	57.1		86	52.4	24	66.7	110	55.0	
20-100	46	24.7	11	18	57	23.1		43	26.2	7	19.4	50	25.0	
at least 100	40	21.5	9	14.8	49	19.8	0.29	35	21.3	5	13.9	40	2.0	0.29
French-American-British subtype														
M0	12	6.5	4	6.6	16	6.5		12	7.3	2	5.6	14	7.0	
M1	1	0.5	.	.	1	.4		1	.6	.	.	1	.5	
M1 Au-	19	1.2	6	9.8	25	1.1		18	11	3	8.3	21	1.5	
M1 Au+	5	2.7	.	.	5	2.0		4	2.4	.	.	4	2.0	
M2 Au-	12	6.5	1	1.6	13	5.3		11	6.7	1	2.8	12	6.0	
M2 Au+	10	5.4	4	6.6	14	5.7		8	4.9	3	8.3	11	5.5	
M4	35	18.8	8	13.1	43	17.4		31	18.9	3	8.3	34	17.0	
M5	61	32.8	25	41	86	34.8		57	34.8	15	41.7	72	36.0	
M6	5	2.7	7	11.5	12	4.9		4	2.4	4	11.1	8	4.0	
M7	23	12.4	4	6.6	27	1.9		16	9.8	3	8.3	19	9.5	
other	1	0.5	2	3.3	3	1.2		.	.	2	5.6	2	1.0	
not classified	2	1.1	.	.	2	0.8	0.08	2	1.2	.	.	2	1.0	0.04
Central nervous system involvement														
no	159	87.8	57	96.6	216	9.0		142	89.3	32	94.1	174	9.2	
yes	22	12.2	2	3.4	24	1.0	0.08	17	1.7	2	5.9	19	9.8	0.54
Bone marrow day 15, % of blasts														
less than or equal 5	125	67.2	38	62.3	163	66.0		115	7.1	21	58.4	136	68.0	
more than 5	30	16.1	18	29.5	48	19.4		23	14.0	12	33.3	35	17.5	
no data	31	16.7	5	8.2	36	14.6	0.06	26	15.9	3	8.3	29	14.5	0.02
Cytogenetics														
normal	39	21.0	17	27.9	56	22.7		34	2.7	8	22.2	42	21.0	
11q23-aberrations	49	26.3	18	29.5	67	27.1		41	25.0	14	38.9	55	27.5	
t(8;21)(q22;q22)	3	1.6	3	4.9	6	2.4		3	1.8	2	5.6	5	2.5	
-7/7q-	7	3.8	2	3.3	9	3.6		4	2.4	1	2.8	5	2.5	
-5/-5q	1	0.5	1	1.6	2	.8		1	0.6	.		1	0.5	
-Y/-X	1	0.5	.		1	.4		1	0.6	.		1	0.5	
t(1;22)(p13;q13)	2	1.1	.		2	.8		2	1.2	.		2	1.0	
t(16;21)(p11;q22)	1	0.5	.		1	.4		1	0.6	.		1	0.5	
der(1q)	1	0.5	.		1	.4		1	0.6	.		1	0.5	
der(12p)	3	1.6	2	3.3	5	2.0		3	1.8	.		3	1.5	
+8	7	3.8	2	3.3	9	3.6		7	4.3	1	2.8	8	4.0	
+21	.		1	1.6	1	0.4		.		1	2.8	1	0.5	
hyperdiploid	1	0.5	.		1	0.4		1	0.6	.		1	0.5	
complex	1	0.5	.		1	0.4		1	0.6	.		1	0.5	
other	47	25.3	8	13.1	55	22.3		43	26.2	4	11.1	47	23.5	
no data	23	12.4	7	11.5	30	12.1	0.66	21	12.8	5	13.9	26	13.0	0.46

CT: chemotherapy; allo-SCT: allogeneic stem cell transplantation.

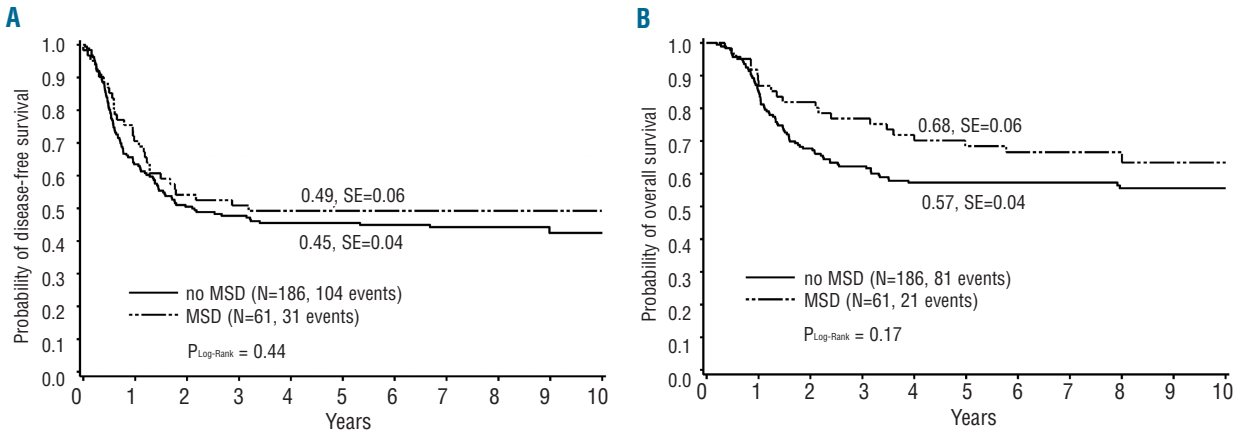

Figure 3. Outcome of high-risk-AML patients assigned to allogeneic SCT (with MSD) or chemotherapy-only (no MSD) (A) Disease-free survival. (B) Overall survival. 5-year probabilities are given.

survival rates were not significantly different between the two groups (68±6% *versus* 57±4%; $P_{\text{log-rank}}$=0.17, Figure 3B). Additionally, Cox regression analysis did not demonstrate a significantly reduced risk ratio (RR) for the MSD group considering 5-year disease-free survival [RR=0.89; 95% confidence interval (CI) 0.69-1.15; *P*=0.37] or 5-year overall survival (RR=0.86; 95% CI 0.64-1.17; *P*=0.34).

To exclude the possibility that intention-to-treat analysis masked the therapeutic effect of allogeneic SCT due to non-compliance, we also performed an as-treated analysis corrected for the time until transplantation (median, 0.43 years; range, 3-8 months).[29] Those children with a MSD who underwent MSD-allogeneic SCT in first complete remission (n=36) had a 5-year disease-free survival of 61±8% whereas those children without a MSD treated with chemotherapy only (n=164) had a 5-year disease-free survival of 49±4% ($P_{\text{Mantel-Byar}}$=0.35) (*Online Supplementary Figure S1A*). The difference in 5-year overall survival between the chemotherapy-only group and the allogeneic SCT group was not statistically significant (72±8% *versus* 60±4%, $P_{\text{Mantel-Byar}}$=0.22) (*Online Supplementary Figure S1B*). This finding strongly supported the results obtained in the intention-to-treat analysis. When including all patients who underwent allogeneic SCT from either a MSD or matched unrelated donor (n=36 and n=24, respectively) or received chemotherapy-only (n=172) in the as-treated analysis the results were similar (5-year overall survival: 66±6% *versus* 61±4%, $P_{\text{Mantel-Byar}}$=0.74; *Online Supplementary Figure S2*). Of note, we did not observe significant differences between the MSD and no-MSD groups regarding the cumulative incidences of relapse and death in complete remission (*Online Supplementary Table S1*).

Toxicity and late sequelae

In order to evaluate late sequelae after allogeneic SCT and chemotherapy-only, we analyzed the follow-up data after 2 years or more of all children who underwent allogeneic SCT in first complete remission (including those without a MSD) or who received chemotherapy only (including those with a MSD but who did not undergo SCT in first complete remission) together. After 2 years, there were 44 and 131 survivors in the respective groups. We observed a higher rate of late sequelae (including cardiomyopathy, liver dysfunction or cirrhosis, skeletal anomalies, necessity for hormone replacement therapy; *Online Supplementary Table S2*) among the allogeneic SCT patients. One or more of these late sequelae occurred in 72.5% (n=29) of all children undergoing allogeneic SCT in first complete remission and in 31.8% (n=42) of the children who received chemotherapy only in first complete remission (including those who went on to undergo SCT in second complete remission; P_{Fischer}<0.01).

For 33 patients who underwent allogeneic SCT, data were available about the occurrence of GvHD. Acute GvHD was observed in 19 patients (57%). Eleven patients had grade II (33%), and four patients had grade III or higher (12%). Chronic GvHD was observed in four patients (12%).

Subgroup analysis

There was heterogeneity between study groups in risk group stratification. The AML-BFM 98 HR group included patients who were considered as intermediate-risk and poor-risk by a recent meta-analysis.[30] The poor-risk subgroup was defined by monosomy 7, monosomy 5, deletions of 5q, or more than 15% blasts after the first course of chemotherapy. All other patients were stratified as intermediate-risk. To achieve comparability between reports, we determined *post hoc* the risk of those defined subgroups. Regarding intermediate-risk patients (n=185), we did not find that the 5-year disease-free survival of the MDS group was significantly better than that for the no-MSD group (48±8% *versus* 45±4%, $P_{\text{log-rank}}$=0.52) (*Online Supplementary Figure S3A*). The 5-year overall survival was better in the MSD group than in the no-MSD group (69±7% *versus* 56±4%), but the difference was not statistically significant ($P_{\text{log-rank}}$=0.16; *Online Supplementary Figure S3B*), possibly because of the small numbers of patients and the resulting limited statistical power. In the small group of poor-risk patients (n=30), 5-year disease-free survival (45±15% *versus* 32±11%, $P_{\text{log-rank}}$=0.48) and 5-year overall survival (73±16% *versus* 42±13%, $P_{\text{log-rank}}$=0.15) were not significantly different between the MSD and the no-MSD groups (*Online Supplementary Figure S4A,B*. An as-treated analysis also yielded similar results (*Online Supplementary Figures S5 and S6*).

Table 2. Disease-free survival of defined subgroups.

	No MSD (n=186)			MSD (n=61)				All (n=247)			
	N	Events	5yr-DFS (%)	N	Events	5yr-DFS (%)	*P*	N	Events	5yr-DFS (%)	*P*
Gender											
male	98	55	45±5	31	18	42±9	0.93	129	73	45±4	
female	88	49	45±5	30	13	57±9	0.24	118	62	48±5	0.58
Age, years											
younger than 2	69	38	46±6	15	7	53±13	0.53	84	45	47±5	
2-9	47	26	47±7	24	13	46±10	0.88	71	39	46±6	
at least 10	70	40	44±6	22	11	50±11	0.57	92	51	46±5	1.00
White blood cell count, $\times 10^9$/L											
less than 20	100	61	42±5	41	22	46±8	0.40	141	83	43±4	
20-100	46	22	52±7	11	4	64±15	0.47	57	26	54±7	
at least 100	40	21	47±8	9	5	44±17	0.74	49	26	47±7	0.34
French-American-British subtype											
M0/M6/M7	40	24	42±8	15	10	33±12	0.99	55	34	40±7	
M1/M2	47	26	47±7	11	4	64±15	0.38	58	30	50±7	
M4	35	16	54±8	8	4	50±18	0.90	43	20	53±8	
M5	61	36	43±6	25	12	52±10	0.32	86	48	45±5	0.50
Central nervous system involvement											
no	164	91	46±4	57	31	46±7	0.86	221	122	46±3	
yes	21	13	38±11	2	0	100±0	0.17	23	13	43±10	0.66
Bone marrow day 15, % of blasts											
less than or equal 5	146	77	49±4	42	21	50±8	0.67	188	98	49±4	
more than 5	31	22	29±8	18	9	50±12	0.16	49	31	37±7	0.26
Cytogenetics											
normal	39	23	44±8	17	11	35±12	0.82	56	34	41±7	
11q23-aberrations	49	30	38±7	18	6	67±11	0.04	67	36	46±6	
other	75	42	47±6	19	11	42±11	0.68	94	53	46±5	0.87

5 yr-DFS: 5-year disease-free survival.

We also investigated, in a *post hoc* analysis, whether subgroups within our cohort of high-risk AML patients might have a benefit from allogeneic SCT. We did not observe a significantly different 5-year disease-free survival after allocation to allogeneic SCT or chemotherapy only for patients grouped according to gender, age, white blood cell count at diagnosis, FAB subtype (M0/M6/M7, M1/M2, M4 and M5), central nervous system involvement, or response on day 15 (Table 2). Translocations involving chromosome 11q23 were present in 31% (n=67) of cases in the subset of patients for whom cytogenetic data were available (88%, n=217), representing the largest cytogenetically defined subgroup in our study. Interestingly, those children with 11q23 aberrations had a significantly better 5-year disease-free survival when assigned to allogeneic SCT (67±11% *versus* 38±7%, $P_{\text{log-rank}}$=0.04; Figure 4A). This difference was even more apparent when the 5-year overall survival was considered (94±6% *versus* 52±7%, $P_{\text{log-rank}}$=0.01; Figure 4B). The as-treated analysis revealed similar results: both 5-year event-free survival (71±12% *versus* 38±8%, $P_{\text{Mantel-Byar}}$=0.03) and 5-year overall survival (92±7% *versus* 53±8%, $P_{\text{Mantel-Byar}}$=0.03) were significantly improved by allogeneic SCT. In contrast, patients without 11q23 rearrangement (n=150) had a 5-year disease-free survival of 39±8% *versus* 46±5% ($P_{\text{log-rank}}$=0.66; Figure 4A) and a 5-year overall survival of 58±8% *versus* 55±5% ($P_{\text{log-rank}}$=0.66; Figure 4B) in the MSD and no-MSD groups, respectively. Again, as-treated analysis revealed comparable results to the intention-to-treat analysis (5-year overall survival: 53±12% *versus* 59±5%, $P_{\text{Mantel-Byar}}$=0.89; 5-year disease-free survival: 47±12% *versus* 50±5%, $P_{\text{Mantel-Byar}}$=0.76; 5-year event-free survival: 47±12% *versus* 50±5%, $P_{\text{Mantel-Byar}}$=0.92 (allogeneic SCT *versus* chemotherapy only). Of note, the trends towards better disease-free and overall survival rates in the intermediate-risk patients in the MSD group were also abrogated when the patients with 11q23 rearrangement were excluded (5-year disease-free survival: MDS 35±9% *versus* no-MSD 47±5%, $P_{\text{log-rank}}$=0.36; 5-year overall survival: MDS 57±5% *versus* no-MDS 54±5%, $P_{\text{log-rank}}$=0.69).

Cox regression analysis with an interaction term for 11q23 and MSD yielded a reduced RR for this variable considering 5-year overall survival (RR=0.19; 95% CI 0.04-0.82; *P*=0.026) and 5-year disease-free survival (RR=0.42; 95% CI 0.17-1.05; *P*=0.063; *Online Supplementary Table S3*). Neither parameter alone (11q23 aberration or allogeneic SCT) independently affected the RR significantly (*Online Supplementary Table S3*). Additionally, a trend towards a reduced cumulative incidence of relapse was observed for patients with 11q23 aberration in the MSD group (33±12% *versus* 58±7%, P_{Gray}=0.07; *Online Supplementary Figure S7*).

Discussion

Our prospective study aimed to determine the role of allogeneic SCT in children with high-risk AML as post-remission treatment in first complete remission. High-risk AML patients were assigned to allogeneic SCT if a MSD was available, leading to a biological randomization. Here, we report that allogeneic SCT did not significantly

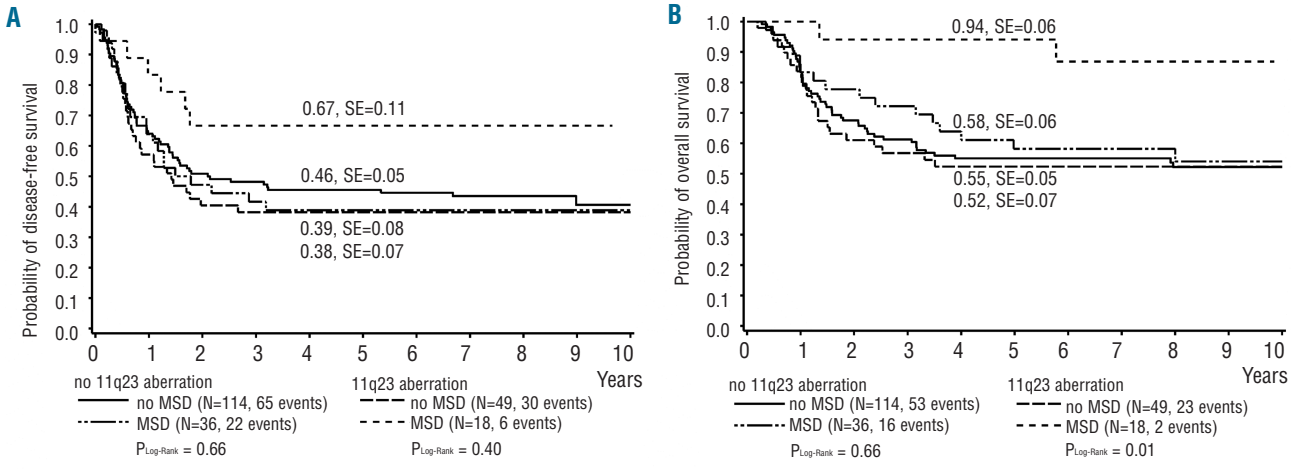

Figure 4. Outcome of high-risk-AML patients with or without an 11q23 aberration assigned to allogeneic-SCT (with MSD) or chemotherapy-only (no MSD). (A) Disease-free survival. (B) Overall survival: 5-year probabilities are given.

improve overall survival or disease-free survival in childhood high-risk AML, considering the whole group of patients. Neither intention-to-treat nor as-treated analysis corrected for the time until transplantation revealed a clear benefit from allogeneic SCT. The exceptions are patients with 11q23 aberrations, who formed a genetically distinct subgroup among the high-risk AML patients with improved survival (5-year overall and disease-free survival) after allogeneic SCT.

As reviewed by Niewerth *et al.*[1] most recent pediatric AML studies (newly diagnosed AML) with good results with chemotherapy only, which evaluated the role of allogeneic SCT using intention-to-treat analysis or as-treated analysis corrected for the time-to-transplantation, did not show an improved overall survival or disease-free survival after transplantation.[6,31-33] Based on those clinical trials, Niewerth *et al.*[1] did not recommend allogeneic SCT in first complete remission for pediatric AML in general. The differences between our results and those of prior studies that indicated a benefit from allogeneic SCT[34] may be attributable to more intensive and effective chemotherapy regimens.[1] However, the fact that a high proportion of children who receive chemotherapy only can be rescued after relapse by salvage therapy which includes allogeneic SCT implies that subgroups of AML patients can indeed benefit from allogeneic SCT.[20] A step towards the long sought after goal to identify those subgroups was made by Horan *et al.*[30] who recently combined data from 1,373 pediatric AML patients from the US Pediatric Oncology Group (POG)-8821, Children's Cancer Group (CCG)-2891, CCG-2961 trials and the European Medical Research Council (MRC)-10 trial in a meta-analysis. While Horan *et al.* did not observe significant differences for overall survival in the favorable- and poor-risk groups or in the non-risk stratified patients, allogeneic SCT did improve disease-free survival and overall survival for the intermediate-risk patients.[30,35] When stratifying our patients in accordance with their subgroup definitions, we found the same trend although in our study this did not reach statistical significance.

Most importantly this trend towards a better 5-year overall survival in the MSD group could be attributed to patients with 11q23 aberrations. Allogeneic SCT significantly improved the 5-year disease-free survival (67±11% *versus* 38±7%, $P_{log\text{-}rank}$=0.04) and 5-year overall survival (94±6% *versus* 52±7%, $P_{log\text{-}rank}$=0.01) for this cytogenetically defined subgroup (Figure 4). Conversely, when analyzing the children without 11q23 aberrations separately, the trend towards a better survival in the MSD group was abrogated both in the whole group of high-risk AML patients (5-year disease-free survival: MSD 39±8% *versus* no-MSD 46±5%, $P_{log\text{-}rank}$=0.66; 5-year overall survival: 58±8% *versus* 55±5%, $P_{log\text{-}rank}$=0.66) and in the intermediate-risk patients (5-year disease-free survival: MSD 35±9% *versus* no-MSD 47±5%, $P_{log\text{-}rank}$=0.36; 5-year overall survival: 57±5% *versus* 54±5%, $P_{log\text{-}rank}$=0.69) based on the stratification criteria used by Horan *et al.*[30] This clearly indicates that chemotherapy only is at least as effective as allogeneic SCT in those patients.

Patients with 11q23- or *MLL*-rearranged AML form a heterogeneous group considering translocation partners and prognosis.[21,36] Within our AML-BFM 98 study the prognosis (event-free survival, overall survival and cumulative incidence of relapse) of the whole group of 11q23- or MLL-rearranged patients was significantly worse than that of the remaining study cohort.[21] While patients with t(9;11)(p22;q23) and with t(11;19)(q23;p13) had a similar outcome to that of the other patients, the small subgroup of patients with *MLL* rearrangements other than t(9;11) and t(11;19) had an unfavorable outcome and a significantly higher cumulative incidence of relapse,[21] which might be improved by allogeneic SCT (5-year overall survival 92±8% *versus* 56±12%; $P_{log\text{-}rank}$=0.09 and 5-year disease-free survival 54±14% *versus* 33±11%; $P_{log\text{-}rank}$=0.23; n=13 *versus* n=18). In particular t(4;11), t(6;11) and t(10;11) were defined as a poor prognostic markers by others and by us.[21,36] Nevertheless, it remains to be determined through future studies by other study groups and by us whether our recommendations for subgroup utilization of allogeneic SCT in high-risk AML patients with 11q23 aberration should be broadly utilized.

In conclusion, our population-based, prospective multicenter study indicated the advantage of allogeneic SCT in the post-remission management of pediatric high-risk

AML with 11q23 aberrations compared to chemotherapy only. However, the specific 11q23 cytogenetic subgroups which might benefit from early allogeneic SCT have to be defined by future studies. In contrast, the remaining patients demonstrated no advantage from allogeneic SCT in first complete remission. Considering the higher toxicity and the higher rate of severe late adverse events, our data suggest that allogeneic SCT in patients with high-risk AML should be restricted to second complete remission.

Appendix

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