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Allogeneic stem cell transplantation for patients with acute myeloid leukemia or myelodysplastic syndrome who have chromosome 5 and/or 7 abnormalities

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Backgrounds and Objectives. Chromosome 5 and/or 7 abnormalities are cytogenetic findings indicative of a poor prognosis in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The only potential cure for such patients is allogeneic stem cell transplantation (SCT). As data on allogeneic SCT in this context are limited we did a retrospective study of allogeneic SCT in patients with AML or MDS who had chromosome 5 and/or 7 abnormalities.

Design and Methods. This was a retrospective study of 65 patients (16 children, 49 adults) with AML (n=33) or MDS (n=32) who had chromosome 5 and/or 7 abnormalities and who underwent allogeneic SCT in six Dutch Centers between 1983 and 2001. Data on all these patients are recorded in the Netherlands Stem Cell Transplant Registry (Typhon).

Results. The 3-year overall survival rate among all patients was 25%. Patients below the age of 40 years had significantly fewer relapses (40%) and better survival (38%) than those above the age of 40 (86% and 8%, respectively). Relapses were less frequent in recipients of unrelated grafts than in those whose grafts were from HLA-identical siblings (30% versus 69%). The development of acute graft-versus-host disease (GVHD) grades II-IV was independently associated with significantly higher transplant-related mortality (TRM). Patients with either chromosome 5 or chromosome 7 abnormalities had a significantly better survival than patients with both chromosome 5 and 7 abnormalities. These patients with poor-risk chromosome 5 and/or 7 abnormalities were compared with a group of patients with a secondary AML/MDS and normal cytogenetics and were found to have significantly more relapses and significantly worse survival but a similar TRM.

Interpretation and Conclusions. We conclude that patients with AML or MDS with chromosome 5 and/or 7 abnormalities do rather poorly after allogeneic SCT, mainly because of the very high relapse rate. Nevertheless, this is the only approach that can cure some of these patients.

Key words: acute myeloid leukemia, myelodysplastic syndrome, allogeneic transplantation, del(5q)/-5, del(7q)/-7.

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In recent years the karyotype of acute leukemia and myelodysplastic syndrome (MDS) has become the most important prognostic determinant both for initial response to induction therapy and for remission duration and overall survival.[1-9] Poor risk cytogenetics in patients with acute myeloid leukemia (AML) or MDS are especially abnormalities of chromosome 5 and/or 7 [excluding MDS type refractory anemia with del(5q)], quite often accompanied by other chromosome abnormalities.[1,6–15] The pathological significance of chromosome 5 and 7 abnormalities is still unknown.[16] In secondary MDS and AML the abnormalities of chromosome 5 and 7 are believed to be induced by prior treatment with alkylating antineoplastic agents.[17] With conventional intensive chemotherapy the outcome for patients with MDS who have chromosome 5 and/or 7 abnormalities is as poor as that for patients with AML having 5 and/or 7 abnormalities.[18,19] Currently, the only established therapy with curative potential for these poor-risk patients is allogeneic stem cell transplantation (SCT),[1,10,12,20,21] although this success is counterbalanced by a rather high transplant-related mortality as well as relapse.[7,12,22] As data on allogeneic SCT in myeloid leukemias with chromosome 5 and/or 7 abnormalities are limited and only published among those from patients with other poor-risk cytogenetic abnormalities we did a retrospective study of allogeneic SCT in 65 patients with AML or MDS who had chromosome 5 and/or 7 abnormalities. All patients were registered at the Netherlands Stem Cell Transplant Registry (Typhon).

Design and Methods

Patients

A cohort of 65 patients including 16 children and 49 adults with poor-risk AML or MDS who had chromosome 5 and/or 7 abnormalities and who were treated with allogeneic SCT at six Dutch centers were studied. The study period dated from 18 January 1983 until 4 October 2001. Forty-six patients received transplants from HLA-

identical sibling donors and 19 patients had HLA-matched unrelated donors (MUD). The diagnosis of MDS and AML was established by the centers according to the French-American-British (FAB) classification system. Twenty patients had MDS that was not treated with chemotherapy before the transplant procedure and 45 patients received induction chemotherapy for AML or MDS; 30 of these 45 patients achieved complete remission. Those in whom induction failed had less than 10% blasts in the bone marrow and none had blasts in the peripheral blood. Sixteen patients had secondary AML or MDS that had developed after treatment with chemotherapy for other malignancies. All patients had chromosome 5 and/or chromosome 7 abnormalities. Patients with del (5q) in the context of MDS-refractory anemia (5q- syndrome) were excluded. Table 1 shows the characteristics of the patients, their disease and transplant.

Preparative regimen and management of graft-versus-host disease (GVHD)

The conditioning regimen consisted of total body irradiation and cyclophosphamide in 38 patients and of busulfan and cyclophosphamide in 27 patients (12 with melphalan as well). GVHD prophylaxis consisted of T-cell depletion together with cyclosporine in 40 patients, and of T-cell depletion alone in 6 patients. Prophylaxis of GVHD in recipients of grafts that were not T-cell-depleted was the combination of cyclosporine and methotrexate (n=16) or cyclosporine monotherapy (n=3). Patients with acute GVHD grades II-IV and those with extensive chronic GVHD were treated with high-dose corticosteroids, sometimes combined with cyclosporine. All patients received post-transplant prophylaxis against infections for at least one year with cotrimoxazole and acyclovir.

Diagnosis and evaluation of GVHD

Acute GVHD (grades I-IV) and chronic GVHD (limited or extensive) were diagnosed clinically, confirmed pathologically by skin or mucosal biopsy and classified according to standard criteria.[23] Chronic GVHD was defined as GVHD present at day 100 onwards after transplantation.

Statistical analysis

The time intervals for survival, relapse incidence and transplant-related mortality were calculated from the day of stem cell transplantation (SCT) onwards. For the Kaplan-Meier curves (used in univariate descriptions) and Cox models (used to estimate hazard ratios) the relapsed patients were censored for transplant-related mortality at the time of relapse and *vice versa*. Univariate comparison of Kaplan-Meier curves was performed using the two-tailed log-rank test. The trend version of the log-rank test was used for ordered categorical variables. The association of various risk factors with the outcomes overall survival, relapse incidence and transplant-related mortality was quantified using hazard ratios estimated in Cox models. Multivariate analyses were based on proportional hazard models, calculated using a stepwise backward approach; predictors were removed when their p-value in the likelihood ratio-test was greater than 0.10. For the purpose of comparison with other published data and to obtain

Table 1. Underlying disease and characteristics of 65 patients.

Disease at transplantation		
Acute myeloid leukemia	33	(51%)
M0	1	(2%)
M1	5	(8%)
M2	10	(15%)
M4	7	(11%)
M5	6	(9%)
Unclassified	4	(6%)
Myelodysplastic syndrome	32	(49%)
RA	10	(16%)
RAEB	8	(12%)
RAEB-t	8	(12%)
CMMoL	6	(9%)
Secondary origin		
Acute myeloid leukemia	8	(12%)
Myelodysplastic syndrome	8	(12%)
Type of transplantation		
HLA-identical	46	(71%)
Unrelated	19	(29%)
Median age in years (range)	33	(1-60)
Gender		
Male	33	(51%)
Female	32	(49%)
Stem cell source		
Marrow	57	(88%)
Peripheral blood	7	(11%)
Cord blood	1	(1%)
T-cell depletion		
Yes	46	(71%)
No	19	(29%)
Cytogenetics		
Del(5q)/-5	6	(9%)
Del(5q)/-5 + other abnormalities	12	(18%)
Del(7q)/-7	22	(34%)
Del(7q)/-7 + other abnormalities	20	(31%)
Del(5q)/-5 + del(7q)/-7	5	(8%)
Monosomy	43	(66%)
Deletion	19	(29%)
Monosomy + Deletion	3	(5%)
Underlying disease and cytogenetics		
Chromosome 5 and 7 abnormalities		
Acute myeloid leukemia	32	(49%)
Myelodysplastic syndrome		
RA	8	(12%)
RAEB	6	(9%)
RAEB-t	8	(12%)
CMMoL	6	(9%)
Chromosome 5 or 7 abnormalities		
Acute myeloid leukemia	1	(2%)
Myelodysplastic syndromes		
RA	2	(3%)
RAEB	2	(3%)
RAEB-t	–	(0%)
CMMoL	–	(0%)

RA: refractory anemia: RAEB: refractory anemia with excess blasts; RAEB-t: refractory anemia with excess blasts in transfromation; cMMoL: chronic myelomonocytic leukemia.

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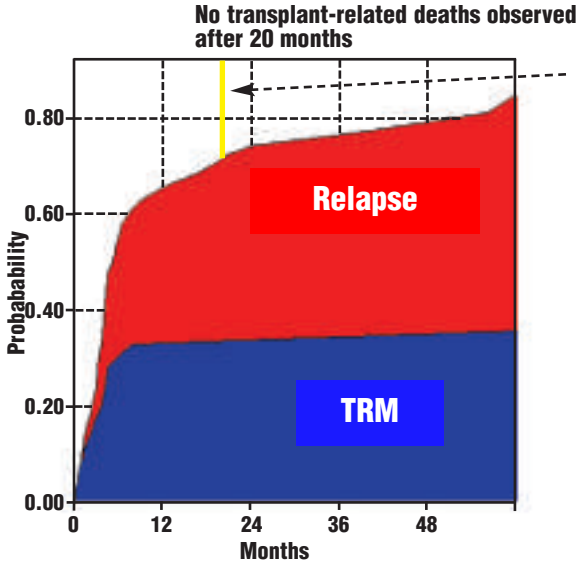

Figure 1. Cumulative incidence of relapse and transplant-related mortality (TRM) in a competing risk setting.

valid (non-biased) estimates for the actual probability of the competing risks of relapse and death in remission, estimates for relapse incidence and transplant-related mortality were made using cumulative incidence estimates. The sum of the cumulative incidences of relapse and transplant-related mortality is the complement of the relapse-free survival. Since the hazard ratios of the various risk factors involved in the analyses can be validly estimated using the Cox model, all inferences in univariate and multivariate analyses concerning such risk factors are performed in the framework of Cox models. The cumulative incidence approach is not really needed (nor currently feasible) when estimating the relative effect of the risk factor multivariately: only when estimating the height of the survival curve itself does one have to revert to the cumulative incidence estimate of that curve. As usual, p values < 0.05 were considered statistically significant. Calculations were performed in SPSS version 10. The cumulative incidences were calculated in NCSS version 2001. Variables tested were *age*: <40 years (n=40) or ≥40 years (n=25); *year of transplantation*: ≤1995 (n=24) or >1995 (n=41); *T-cell depletion*: yes (n=46) or no (n=19); *chromosome abnormalities*: chromosome 7 (n=42), chromosome 5 (n=18), chromosomes 5 and 7 (n=5); *monosomy*: yes [(n=46; chromosome 7 (n=36), chromosome 5 (n=6), chromosomes 5 and 7 (n=4)] or no [(n=19; chromosome 7 (n=6), chromosome 5 (n=12), chromosomes 5 and 7 (n=1)]; *deletion*: yes [(n=22; chromosome 7 (n=6), chromosome 5 (n=13), chromosomes 5 and 7 (n=3)] or no [(n=43; chromosome 7 (n=36), chromosome 5 (n=5), chromosomes 5 and 7 (n=2)]; *the interval between diagnosis and SCT*: ≤6 months (n=33) or >6 months (n=32); the interval between first complete remission and SCT: ≤3 months (n=19) or >3 months (n=11); *stage of disease at transplantation*: untreated [(n=20; refractory anemia n=9, refractory anemia with excess blasts n=7, chronic myelomonocytic leukemia n=4)], first complete remission [(n=30; AML n=20, refractory anemia n=1, refractory anemia with excess blasts n=1, refractory anemia with excess blasts in transformation n=6, chronic myelomonocytic leukemia n=1)] or complete remission not achieved after chemotherapy [(n=15; AML n=13, refractory anemia with excess blasts in transformation n=2)], *acute GVHD:* grades 0-I (n=50) or grades II-IV (n=15); *chronic GVHD*: none (n=39) or limited and extensive (n=13); type of SCT: HLA-identical sibling (n=46) or unrelated donor (n=19); *disease at transplantation*: AML (n=33) or MDS (n=32).

Results

There were no significant differences in relapse incidence, overall survival and transplant-related mortality between AML and MDS patients, therefore both groups were combined for the analyses.

Acute and chronic GVHD

No or only grade I acute GVHD was present in 50 patients (77%) whereas acute GVHD grades II-IV occurred in 15 patients (23%). Thirteen of 52 evaluable patients (25%) developed chronic GVHD, which was limited in eight cases (15%) and extensive in five (10%).

Responses and outcome

At 3 years after SCT the overall survival in all 65 patients was 25% (95% confidence interval [95% CI], 14-37%). The relapse incidence at 3 years was 58% (95% CI: 42-74%) by the Kaplan Meier method and 40% (95% CI: 30-55%) by cumulative incidence (Figure 1). The 20-month incidence of transplant-related mortality was 44% by Kaplan Meier (95% CI: 29-60%) and 36% (95% CI: 26-50%) by cumulative incidence (no transplant-related deaths occurred more than 20 months after SCT) (Figure 1).

Univariate analysis

All percentages are based on Kaplan-Meier curves. The hazard ratios follow from the Cox model. Patients under the age of 40 years old had a significantly lower incidence of relapse and better overall survival. The relapse incidence at 3 years was 40% in patients <40 years and 86% for patients ≥40 years, which corresponds to a hazard ratio of 3.2 (95% CI: 1.5-6.7; p=0.002) (Table 2) (Figure 2). The overall survival at 3 years in patients <40 years was 38% whereas for patients ≥40 years it was 8% with a hazard ratio of 1.8 (95%CI: 1.0-3.3; p=0.04) (Table 2). When patients <40 years were divided into two groups, between 0-20 years (n=16) and between 20-40 years (n=24), it

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Table 2. Univariate analysis for outcome at 3 years.

Outcomes	*Variables*	*HR*	*95%CI*	*p*
Overall survival	***Age***			
	< 40 yrs	1.0	1.0-3.3	0.04
	≥ 40 yrs	1.8		
	Stage			
	Untreated	1.0		0.9
	Complete remission	1.1	0.6-2.3	
	No complete remission	1.2	0.5-2.8	
	Type of SCT			
	HLA-identical sibling	1.0		
	Unrelated donor	0.6	0.3-1.3	0.2
	Acute GVHD			
	Grades 0-I	1.0		
	Grades II-IV	1.6	0.8-3.1	0.2
	Chromosome abnormality			
	5	1.0		0.03
	7	0.7	0.4-1.4	
	5+7	2.6	0.9-7.4	
Relapse incidence	***Age***			
	< 40 yrs	1.0		
	≥ 40 yrs	3.2	1.5-6.7	0.002
	Stage			
	Untreated	1.0		0.1
	Complete remission	3.5	1.0-11.9	
	No complete remission	3.4	0.9-13.1	
	Type of SCT			
	Identical sibling	1.0		
	Unrelated donor	0.4	0.1-1.1	0.05
	Acute GVHD			
	Grades 0-I	1.0		
	Grades II-IV	0.6	0.2-1.9	0.4
	Chromosome abnormality			
	5	1.0		0.08
	7	0.5	0.2-1.2	
	5+7	2.3	0.4-11.2	
Transplant-related mortality	***Age***			
	< 40 yrs	1.0		
	≥ 40 yrs	1.0	0.4-2.4	1.0
	Stage			
	Untreated	1.0		0.09
	Complete remission	0.4	0.1-1.0	
	No complete remission	0.5	0.2-1.6	
	Type of SCT			
	HLA-identical sibling	1.0		
	Unrelated donor	1.2	0.5-2.9	0.7
	Acute GVHD			
	Grades 0-I	1.0		
	Grades II-IV	2.8	1.2-6.4	0.01
	Chromosome abnormality			
	5	1.0		0.2
	7	1.2	0.4-3.4	
	5+7	3.5	0.8-15.1	

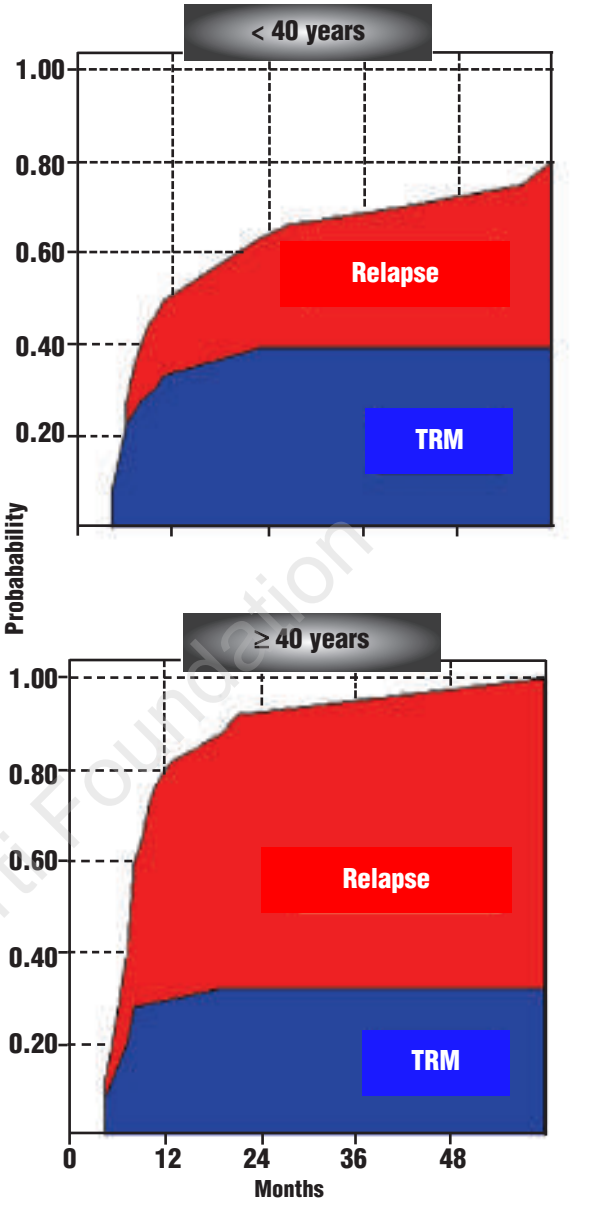

Figure 2. Cumulative incidence of relapse and treatment-related mortality in a competing-risk model, according to age < 40 years (n=40) and ≥ 40 years (n=25).

appeared that both subgroups had a significantly lower relapse incidence (p=0.006) than had patients ≥40 years. Although both subgroups also had a better overall survival, the differences were not significant (p=0.1). The development of acute GVHD grades II-IV was statistically significantly associated with higher transplant-related mortality. The 20-month incidence of transplant-related mortality was 32% among patients with acute GVHD grades 0-1 and 75% among those who developed grades II-IV, hazard ratio 2.8 (95%CI: 1.2-6.4; p=0.01) (Table 2). We also found a lower relapse incidence in recipients of grafts from unrelated donors than in recipients of grafts from HLA-identical siblings (p=0.05). The relapse incidence at 3 years in the group with unrelated donors was 30%, whereas it was 69% in the group with HLA-identical sibling donors, hazard ratio 0.4 (95%CI: 0.1-1.1) (Table 2). Furthermore, we found that patients who underwent SCT without their disease having been previously treated with chemotherapy fared better than those who had been treated with remission-induction chemotherapy. The relapse incidence at 3 years was 36% in untreated patients versus 66% for those in first complete remission following treatment, hazard ratio: 3.5 (95%CI: 1.0-11.9), versus 61%, hazard ratio: 3.4 (95%CI: 0.9-13.1) for those in whom induction treatment had failed (p=0.10) (Table 2). The same held true for overall survival at 3 years: 42% for untreated patients versus 23% for patients in

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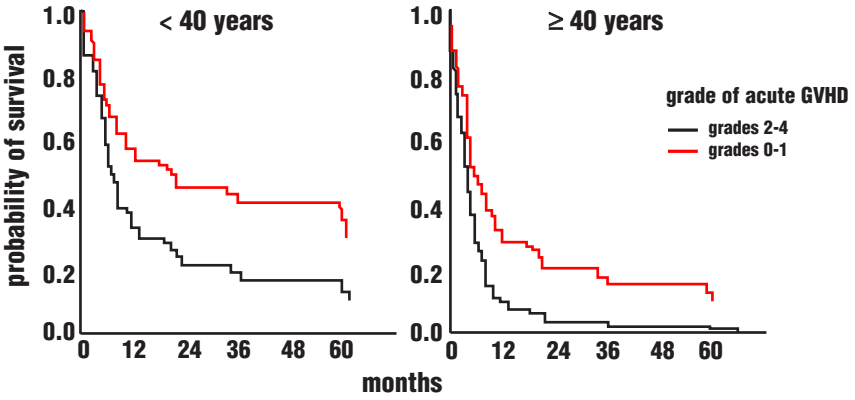

Figure 3. Survival according to acute GVHD and age based on a Cox model in which stage of disease at transplantation and type of SCT were removed because they were multivariately non-significant.

first complete remission with a hazard ratio of 1.1 (95%%CI: 0.6-2.3) versus 21% with a hazard ratio of 1.2 (95%CI: 0.5-2.8) for those in whom induction failed (p=0.90) (Table 2). Patients with both chromosome 5 and 7 abnormalities had a significantly poorer overall survival than did patients with either chromosome 5 or chromosome 7 abnormalities (p=0.03); no difference was seen for relapse incidence or transplant-related mortality. The overall survival at 3 years was 15% in patients with chromosome 5 abnormalities versus 33%, hazard ratio 0.7 (95%CI: 0.4-1.4) in patients with chromosome 7 abnormalities versus 0%, hazard ratio 2.6 (95%CI: 0.9-7.4) (already after an overall survival of 6 months) in patients with chromosome 5 and 7 abnormalities. Comparisons within the group of chromosome abnormalities were not significant because of the small number of patients with both chromosome 5 and 7 abnormalities (n=5) (Table 2).

No significant differences were seen for the other variables tested: year of transplantation (≤1995 or >1995), T-cell depletion or not, monosomy (yes or no), deletion (yes or no), those with or without chronic GVHD, interval between diagnosis or first complete remission and SCT (≤6 months and >6 months or ≤3 months and >3 months, respectively).

Multivariate analysis

In view of the results from the univariate analyses and the small number of patients the multivariate analyses for overall survival and relapse incidence were restricted to the variables found to be significant for overall survival, relapse incidence and transplant-related mortality: age, acute GVHD, stage of disease at transplantation, chromosome abnormalities and type of SCT. Age had an independent significant effect on overall survival and relapse incidence corresponding with a hazard ratio of 1.9 (95%CI: 1.0-3.4; p=0.05) (Figure 3) and 3.5 (95%CI: 1.5-7.8; p=0.003), respectively. Patients above the age of 40 years did far worse than patients under the age of 40 (Table 3). The chromosome abnormalities also had a significant effect on overall survival. Patients with both chromosomes 5 and 7 abnormalities had a worse survival than patients with 5 or 7 abnormalities (hazard ratio 3.2; 95%CI: 1.1-9.3; p=0.04) (Table 3). Finally, patients who developed grades II-IV acute GVHD had a worse overall survival than patients who developed grades 0-I (hazard ratio 2.2; 95%CI:1.1-4.6; p=0.03) (Figure 3). This contrasts with the results of the univariate analysis in which no difference was found in overall survival according to acute GVHD status (p=0.2) (Table 2). The relapse incidence was lower in untreated patients than in treated patients, whether these latter had or had not achieved a first complete remission (p=0.1) (Table 3).

Table 3. Multivariate Cox regression analysis for overall survival and relapse incidence.

Outcomes	*Variables*	*HR*	*95%CI*	*p*
Overall Survival	***Age***			
	< 40 yrs	1.0		
	≥ 40 yrs	1.9	1.0-3.4	0.05
	Acute GVHD			
	Grades 0-I	1.0		
	Grades II-IV	2.2	1.1-4.6	0.03
	Chromosome abnormality			
	5	1.0		0.04
	7	0.8	0.4-1.6	
	5+7	3.2	1.1-9.3	
Relapse Incidence	***Age***			
	< 40 yrs	1.0		
	≥ 40 yrs	3.5	1.5-7.8	0.003
	Stage			
	Untreated	1.0		0.1
	Complete remission	3.8	0.1-13.4	
	Not complete remission	2.8	0.7-11.3	

Comparative analysis

We compared the results in our AML/MDS patients with high-risk chromosome 5 and/or 7 abnormalities with the results in secondary AML/MDS patients with normal cytogenetics. Data for this normal cytogenetics group were obtained from the MDS study group of the EBMT Chronic Leukemia Working Party, March 2001, and kindly provided by Dr. T de Witte, Nijmegen, the Netherlands. The group consisted of 238 patients with secondary AML or MDS (sAML/MDS) with normal

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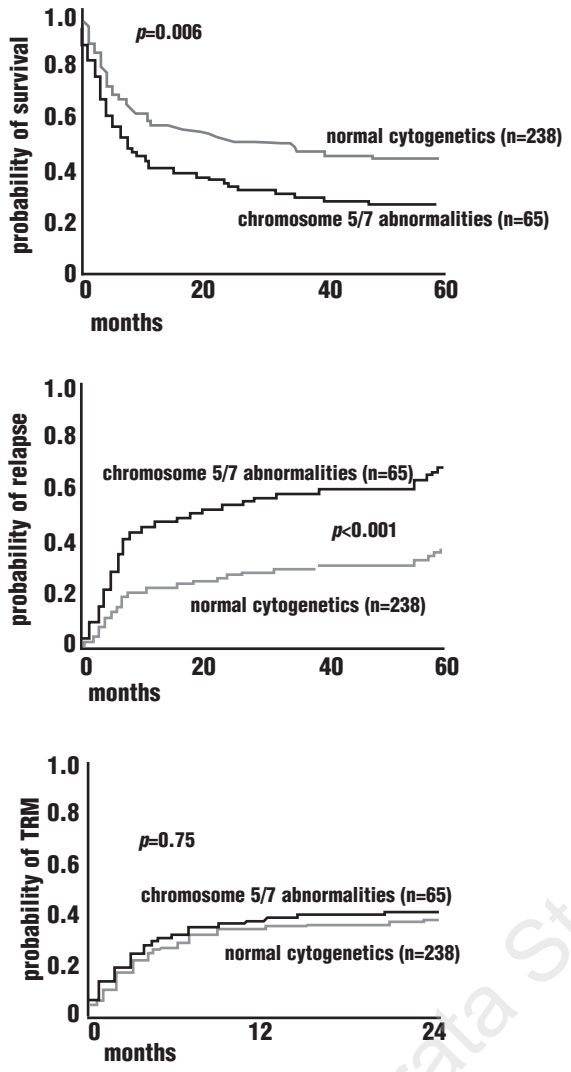

Figure 4. Probability of overall survival, relapse incidence and transplant-related mortality (TRM) for sAML/MDS patients with normal cytogenetics (n=238) and high-risk AML/MDS patients with chromosome 5/7 abnormalities (n=65).

cytogenetics. We performed a univariate Cox analysis. The univariate hazard ratios from Cox models comparing the study population with the control population were virtually identical to the hazard ratios obtained after a multivariate correction for age and disease status at transplant. Hence the univariate comparison is not affected in any way by the main risk factors of age and disease status.

The results showed a significantly better overall survival in the group with normal cytogenetics (p=0.006). The 3-year survival was 47% in the group with normal cytogenetics and 25% in our high-risk chromosome 5/7 AML/MDS population; the Cox model showed a hazard ratio of 1.6 (95%CI:1.1-2.2) (Figure 4). The relapse incidence also differed significantly between the group with normal cytogenetics and our high-risk chromosome 5/7 abnormalities group. At 3 years the relapse incidence was 30% in patients with normal cytogenetics, whereas it was 58% in the chromosome 5/7 group, corresponding to a hazard ratio of 2.5 (95%CI:1.6-4.0; p<0.001) (Figure 4). Transplant-related mortality did not differ significantly between the two groups. The transplant-related mortality at 20 months was 44% in our chromosome 5/7 group and 38% in the group with normal cytogenetics, corresponding to a hazard ratio of 1.1 (95%CI:0.7-1.7; p=0.75) (Figure 4).

Discussion

Our observation that only 25% of patients with AML/MDS and chromosome 5 and/or 7 abnormalities are still alive 3 years after a SCT is concordant with previous data from small series of such patients.[1,12] Age appeared to be a significant prognostic factor both in univariate and multivariate analyses. Patients below the age of 40 years had a significantly lower relapse incidence and better overall survival at 3 years than did those above the age of 40. Remarkably, transplant-related mortality was comparable among younger and older patients. This might have been caused by the (partial) T-cell depletion of the grafts used in most of the patients, which decreases GVHD and transplant-related mortality in older patients. Nevertheless, the transplant-related mortality rate of 44% is remarkably high, which might be due to the fact that this rate reflects the outcome of allogeneic transplants carried out in the 1980s and 1990s. More recent studies show lower transplant-related mortality rates in high-risk leukemia patients.[24]

Patients with chromosome 5 and 7 abnormalities appeared to have worse overall survival and also a higher relapse incidence and transplant-related mortality than did patients with either chromosome 5 or chromosome 7 abnormalities, although the number of patients for this analysis was limited. We did not find any significant differences between the group of patients with or without a deletion or monosomy. Another remarkable fact was that we did not find a lower relapse incidence and better survival for patients transplanted in complete remission compared to patients transplanted while not in complete remission, although none of these latter patients had more than 10% blasts in their marrow. In fact untreated patients had a tendency to better outcome both in univariate and multivariate analyses. This might be related to the fact that patients who received SCT in first complete remission had AML or refractory anemia with excess blasts in transformation whereas patients who received SCT for untreated disease generally had less advanced MDS.

To our knowledge this report of poor-risk AML/MDS patients with chromosome 5 and/or 7 abnormalities is

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one of the first studies analyzing a substantial number of such patients. The comparison of the results of our high-risk chromosome 5/7 AML/MDS group with the results of sAML/MDS patients with normal cytogenetics showed comparable transplant-related mortality in both groups but a significantly higher relapse incidence in the former group. We postulate that the poor outcome in our group of high-risk chromosome 5/7 patients is mainly or almost completely due to the increased relapse rate. We conclude that patients with AML and MDS with chromosome 5 and/or 7 abnormalities do rather poorly after allogeneic SCT, although this is the only approach that can cure some of these patients, especially the younger ones.

The poor survival of 25% at 3 years is mainly caused by the very high relapse rate in this group, although given that many of the patients were transplanted a decade (or more) ago, the transplant-related mortality might be expected to be decreased and survival increased nowadays. The better anti-leukemic effect of grafts from unrelated donors in these poor-risk patients underscores the importance of the allogeneic effect of this approach. In patients older than 40 years conventional SCT should be discouraged; non-myeloablative SCT might be a better approach. Another therapeutic option for this group of patients might be new inhibitors of DNA-methylation with a strong anti-leukemic effect, such as 5-azacitidine and 5-aza-2'-deoxycytidine.[25,26]

HMvdS: conception and design, analysis and interpretation of data, drafting the article; AvB: analysis and interpretation of data, statistical expertise, collecting and assembly of data; RB: analysis and interpretation of data, statistical expertise, collecting and assembly of data; AVMBS, RME, RMB, JJC, HCS, and GJO: provision of patients, revising the manuscript critically for important intellectual content; LFV: conception and design, analysis and interpretation of data, provision of patients, revising the manuscript critically for important intellectual content, final approval of the article. The authors declare that they have potential conflicts of interest.

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