Intensive treatment strategies in patients with high-risk myelodysplastic syndrome and secondary acute myeloid leukemia: a study towards a risk adapted approach

Intensive treatment strategies in patients with high-risk myelodysplastic syndrome and secondary acute myeloid leukemia: a study towards a risk adapted approach

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aan mijn ouders

TABLE OF CONTENTS

CHAPTER 1

Intensive treatment strategies in patients with high-risk myelodysplastic syndrome and secondary acute myeloid leukemia

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INTRODUCTION

The myelodysplastic syndromes (MDS) form a heterogeneous group of clonal stem cell disorders characterized by a hypercellular bone marrow, peripheral cytopenias and dysplastic features in blood and bone marrow. The spectrum of the disease may vary from an indolent course over several years to more rapid progression to acute myeloid leukemia (AML).[1] In this review leukemia evolving from MDS is named secondary acute myeloid leukemia (sAML).

MDS is predominantly diagnosed in elderly patients. In a population-based study in Germany the annual incidence of MDS in patients over 50 years was 4.9 per 100 000 persons compared to an incidence of 1.8 per 100 000 for acute myeloid leukemia in the same age-group.[2] In the last decades the incidence of MDS seems to increase. In part this may be due to a greater readiness to perform bone marrow examinations in elderly patients, but there is also some evidence for a real increase due to occupational and environmental exposure to chemicals like benzene and other organic solvents.[3-5] Furthermore, treatment with radiotherapy and/or certain chemotherapeutic agents promotes the development of therapy-related MDS and AML (tMDS/tAML). Alkylating substances have the strongest leukemogenic potential. The risk of developing MDS or AML after treatment for Hodgkin's disease is 7-8% and appears to be closely related to the cumulative dose administered.[6,7] Also drugs targeting at topoisomerase II are capable to induce tMDS and tAML even in young children in whom a diagnosis of MDS is rare.[8,9]

Since 1982 the myelodysplastic syndromes have been classified according to FAB (French-American-British) criteria.[10] Five subcategories have been described: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEBt) and chronic myelomonocytic leukemia (CMML). The clinical course of MDS is variable. Patients with RA and RARS have a low risk of developing sAML and their median survival is more than 30 months. The majority of these patients die of consequences of bone marrow failure or due to iron overload as a result of repeated blood transfusions. The median survival of patients presenting with RAEB and RAEBt is generally shorter than 12 months.

The FAB-classification has several limitations. There are significant differences in outcome of patients within each subcategory. The FAB classification is entirely based on morphological criteria and the number of blasts in blood and bone marrow, whereas other

clinical and biological variables have not been incorporated in this classification. Therefore, numerous other classification systems have been proposed to predict the prognosis of individual patients.[1,11-14] In 1997 an international workshop combined the data of seven previous reported studies [1,11-13,15-17] to generate an International Prognostic Scoring System (IPSS).[18,19] Greenberg et al. distinguished four risk groups for survival and AML evolution (low, intermediate-1, intermediate-2 and high risk) based on cytogenetic subgroup, percentage of bone marrow blasts and number of cytopenias (Table 1). Age was an additional prognostic factor for survival, but not for AML evolution.

Table 1. IPSS (International Prognostic Scoring System).

	Score values				
Prognostic variables	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias[a]	0/1	2/3			
Low risk group	Score 0				
Intermediate-1 risk group	Score 0.5-1.0				
Intermediate-2 risk group	Score 1.5-2.0				
High risk group	Score 2.5-3.5				
Good karyotype	Normal, -Y, del 5q, del 20q				
Intermediate karyotype	Other abnormalities				
Poor karyotype	Chromosome 7 or complex ($\geq$ 3) abnormalities				

[a]: Cytopenias: hemoglobin < 10 g/dl, platelets < 100 x 10^9/l, neutrophils < 1.8 x 10^9/l

The IPSS seems to be an improved classification system for evaluating prognosis in MDS.[20] However, Estey et al. applied the IPSS to 219 untreated patients referred to M.D. Anderson and reported a lower survival expectation in the low, intermediate-1 and intermediate-2 categories compared to the corresponding IPSS patients.[21] Furthermore, the IPSS has been derived from patients treated with transfusions, biologic response modifiers and low-dose oral chemotherapy. Patients treated with intensive chemotherapy including stem cell transplantation have been excluded from this analysis. It is still unknown whether the IPSS is also applicable to patients treated with intensive treatment strategies.[22]

Cytogenetic abnormalities occur in approximately 40-60% of patients with primary MDS, whereas more than 80 % of patients with therapy-related MDS have abnormal karyotypes.[23-25] Jotterand and Parlier collected data on 2372 patients from 18 studies.[26] The incidence of clonal defects in primary MDS was 52%. Abnormal clones occurred more frequently in RAEBt (67%) and RAEB (62%), compared with RA (49%), RARS (36%) and CMML (36%). Both structural and numeric changes are found in MDS patients. MDS is more often associated with chromosomal deletions as a primary karyotypic anomaly, whereas balanced translocations are the most typical changes found in de novo AML. In therapy-related MDS and AML after the use of alkylating agents, cytogenetic abnormalities involving chromosome 5 or 7 and complex abnormalities, which are also associated with primary MDS are frequently found. Balanced translocations to chromosome bands 11q23 and 21q22 occur after treatment with topoisomerase-II inhibitors.[9,27] Cytogenetic abnormalities are independent prognostic factors for both survival and progression to AML.[13,28-30] Table 2 shows the cytogenetic abnormalities found in the studies of Greenberg [18] and Solé [30] and the impact on survival.

In 1997 a new classification system for MDS has been proposed by the World Health Organization (WHO).[31] This classification recognizes several limitations of the FAB classification. The importance of cytogenetic abnormalities in MDS reflects the definition of the 5q- syndrome as cases with de novo isolated del(5q), less than 5% marrow myeloblasts and the characteristic morphologic finding of hypolobulated megakaryocytes as a distinct entity.[32] One of the major changes in the WHO classification compared to the FAB classification is lowering the blast percentage for the diagnosis of acute myeloid leukemia from 30% to 20%. Several studies have suggested that there is little difference between RAEBt and AML in terms of prognosis and response to chemotherapy.[33,34] As a consequence RAEBt (refractory anemia with excess of blasts in transformation) has been

eliminated from the MDS classification. The new WHO classification distinguishes MDS with morphologic dysplasia restricted to the erythroid lineage (RA: refractory anemia) from MDS with multilineage dysplasia (RCMD: refractory cytopenia with multilineage dysplasia). A German study reported a better outcome of patients with dysplasia restricted to one cell lineage [35], but this observation was not confirmed by Nosslinger et al.[36] Whether this finding is an independent prognostic factor for MDS remains unclear. The definition of chronic myelomonocytic leukemia (CMML) in the FAB is problematic. This definition is based primarily on the peripheral blood monocyte count with less consideration of the blast percentage in the bone marrow. Besides, many patients with CMML display both myeloproliferative and myelodysplastic features. The WHO classification removes CMML from MDS to a myeloproliferative-myelodysplastic overlap category.

The new classification system has been criticized for several reasons: (1) Lowering the blast percentage for a diagnosis of AML to 20% in stead of 30% is arbitrary as well and introduces difficulties in comparing future AML/MDS studies with historical controls. (2) The definition of MDS as a clonal stem cell disorder based solely on dysplasia in the erythroid lineage is precarious. (3) The prognostic value of cytogenetic abnormalities is inconsistently incorporated in the classification. Clearly the optimal classification system for MDS and AML cannot be based on clinical features only, but also on data on gene expression patterns and other biologic parameters. Insight gained from the molecular analysis of MDS provides the basis for a more refined classification and future revisions of the WHO proposal will be necessary.

The majority of MDS patients are older than 60 years. For these patients supportive care, including biologic response modifiers and low dose chemotherapy, is the mainstay of therapy.

This review will discuss intensive treatment strategies, mainly used with the aim to cure young patients with MDS. Other treatment strategies, such as treatment with hematopoietic growth factors or low dose cytostatics and immune-modulation are not discussed in this review.

Table 2. Cytogenetic abnormalities and impact on prognosis.

Source	Greenberg et al.[18]	Solé et al.[30]	
Karyotype	Frequency (%)	Frequency (%)	Median survival (yr.)
No abnormalities	489 (60)	313 (49)	4.2
Single	203 (25)	190 (29)	2.1
Double	43 (5)	49 (8)	1.1
Complex	81 (10)	88 (14)	0.5
Total	816	460	
Single abnormalities			
del 5q	48 (6)	32 (5)	3.9
-7/del 7q	10 (1)	24 (4)	1.4
+ 8	38 (5)	31 (5)	1.1
del 11q		6 (1)	5.4
del 12p		13 (2)	> 6
del 20q	16 (2)	8 (1)	3.2
- X		6 (1)	1.1
- Y	17 (2)	8 (1)	> 6
Miscellaneous single	74 (9)		

ALLOGENEIC STEM CELL TRANSPLANTATION

The primary curative option for patients with myelodysplastic syndromes is allogeneic stem cell transplantation (SCT). Disease-free survival (DFS) ranges from 29% to 40%, with corresponding treatment-related mortality (TRM) of 37% to 50% and rate of relapse ranging from 23% to 48% after transplantation with an HLA-identical sibling donor.[37-45] Alternative donors like genotypically non-identical related donors and voluntary unrelated donors have been used as well since only one-third of MDS patients have an HLA-identical sibling.

Risk factors having an impact on the outcome of transplantation include age, disease duration, disease stage at time of transplantation, percentage of blasts in the bone marrow, presence of cytogenetic abnormalities, source of stem cells, application of T-cell depletion of the graft, type of donor and pre-transplant conditioning.

Anderson et al. analysed the outcome of 250 consecutive patients who underwent allogeneic transplantation in Seattle.[44] Disease-free survival at 5-year was comparable for

patients with a matched related donor (N=147) and a partially matched or unrelated donor (N=103), namely 38% versus 39%. After partially matched or unrelated donor transplantation the advantage of a lower relapse risk (10% versus 24% for a matched related donor) is counterbalanced by a significantly higher non-relapse mortality (51% versus 39%). The European Group for Blood and Marrow Transplantation (EBMT) reported on 1378 patients, who received a transplant between 1983 and 1998.[43] A total of 885 patients were transplanted with an HLA-identical sibling. The 3-year actuarial probability of disease-free survival was 36%, overall survival 41%, treatment-related mortality 43% and relapse 36%. Age had a significant effect on outcome. The DFS was 45% for patients aged less than 20 years, 37% for patients aged between 20-40 years, and 31% for patients older than 40 years at time of SCT. These significantly better results can be explained by a lower treatment-related mortality in younger patients. The EBMT analysis shows that the results of allogeneic SCT have improved over the years, due to a decrease in treatment-related mortality. A report from the International Bone Marrow Transplant Registry (IBMTR) on 452 recipients of HLA-identical transplants between 1989 and 1997 showed a 3-year DFS of 40%, overall survival 42%, TRM 37% and relapse rate 23%.[45] In an attempt to lower the toxicity of the conditioning regimen Deeg et al. used busulfan at a targeted plasma concentration in combination with cyclophosphamide.[46] This approach resulted in a 3-year TRM of 28%, relapse rate 16% and DFS 56%. The majority of transplant centres consider allogeneic stem cell transplantation as a treatment option in patients aged less than 45 or 50 years, but the upper age limit for SCT gradually increased in recent years. A study from Seattle on 50 patients aged between 55 and 66 years, who underwent allogeneic SCT, showed the feasibility of this treatment in fit elderly patients.[47] Overall survival at 3-year was 46%, relapse-free survival 42%, TRM 39% and relapse rate 19%.

Table 3. Allogeneic bone marrow transplantation for MDS and sAML.

Source	Number of patients	Median age (years)	Outcome calculated at N yr.	DFS or EFS (%)	Relapse (%)	TRM (%)
HLA-identical sibling						
Anderson 1995 [39]	93	30	5	40	29	44
Sutton 1996 [40]	71	37	7	32	48	39
Runde 1998 [42]	131	33	5	34	39	44
Nevill 1998 [41]	60	40	7	29	42	50
Anderson 2000 [44]	147	38	5	38	24	39
De Witte 2000 [43]	885	33	3	36	36	43
Sierra 2002 [45]	452	38	3	40	23	37
Deeg 2002 [46]	41	46	3	56	16	28
Anderson 1997 [53 a]	46	42	5	24	31	44
Yakoub-Agha 2000 [55 a]	70	37	2	28	42	49
Witherspoon 2001 [57 a]	69	--	5	11	32	58
Voluntary Unrelated Donor						
Anderson 1996 [70]	52	33	2	38	28	48
Arnold 1998 [71]	118	24	2	28	35	58
Anderson 2000 [44]	103	38	5	39	10	51
De Witte 2000 [43]	198	--	3	25	41	58
Deeg 2002 [46]	64	46	3	59	11	30
Witherspoon 2001 [57 a]	41	--	5	24	32	44
Castro-Malaspina 2002 [73]	510	38	2	29	14	54
Reduced Intensity Conditioning						
Martino 2002 [63]	37	57	1	66	28	5
Ho 2004 [67]	24	56	1	61		5
Ho 2004 [67] (VUD)	38	52	1	59		21

[a]: Transplantation for therapy related MDS and AML (tMDS/tAML)
[41]: Including 22 unrelated donors
[46]: Age 46 years overall
[53]: Including 17 tAML and 29 sAML patients
[55]: Including 8 unrelated donors, 3 mismatched related donors
[44]: Age 38 years overall, 70 unrelated donors, 33 non-identical family donors
[63]: Including 17 AML patients

Disease stage

Patients with less advanced stages of MDS such as RA and RARS may profit optimally from allogeneic stem cell transplantation with a myeloablative regimen, with long-term disease-free survival in more than 50% of patients,[48,49] owing largely to the substantially lower relapse rate compared to patients with more advanced disease.[43,49] Older age and longer disease duration before transplantation are associated with an increased risk of death after transplantation.[49] Therefore, the intention should be to transplant these patients early in the course of the disease before sensitisation due to transfusions and before development of iron overload and opportunistic infections. Transplantation may be postponed in selected patients without life-threatening cytopenias and cytogenetic abnormalities.

Data on allogeneic stem cell transplantation in CMML patients are limited.[37,50,51] Prognostic modelling shows that marrow infiltration with more than 5% monoblasts, a neutrophil count of more than 16 x 10^9/l and/or a monocyte count of more than 2.6 x 10^9/l are associated with an unfavourable prognosis and therefore patients with these features should be considered for allogeneic transplantation. In an analysis of 50 CMML patients reported to the EBMT registry, the estimated 2-year DFS was 18% with a relapse risk of 42%.[51]

The outcome after stem cell transplantation in patients with RAEB and RAEBt is less favourable than the outcome in patients with RA(RS), due largely to a higher risk of relapse. The European Group for Blood en Marrow Transplantation (EBMT) reported a 5-year actuarial relapse-rate of 44% and 52% in 35 RAEB patients and 28 RAEBt patients, who underwent allogeneic transplantation without prior remission induction chemotherapy.[42] The Fred Hutchinson Cancer Research Center (FHCRC) reported on a group of 93 MDS patients.[39] The 5-year actuarial disease-free survival, relapse and non-relapse mortality rates were 40%, 29% and 44% respectively. For the 47 patients with excess of blasts the relapse rate was 49% versus 4% for the 40 patients without excess of blasts, with actuarial disease-free survival of 31% versus 54%, respectively. The EBMT published the long-term results of 1378 patients transplanted for MDS.[43] A total of 885 patients were transplanted with an HLA-identical sibling. Both age and disease stage had independent prognostic significance for all three end-points.

In patients with secondary AML after MDS, most European transplant centres have adopted the strategy of stem cell transplantation after remission-induction chemotherapy, based on the high failure rate of transplantation in patients with active leukemia.[40,52,53]

Sutton et al. transplanted 11 patients with overt AML at time of transplantation. Treatment-related mortality was 60%, all patients relapsed and there were no long-term survivors.[40] The EBMT reported a 2-year disease-free survival of 18% in 13 untreated sAML patients in contrast with a 60% DFS in 16 patients transplanted in first CR.[52] In a report from Seattle on 46 patients with sAML (29 patients) and tAML (17 patients) who underwent transplantation as front line treatment the 5-years actuarial DFS, relapse rate and non-relapse mortality were 24%, 31% and 44% respectively.[53] A higher blast percentage before transplantation was associated with a significantly higher incidence of relapse. Younger age and shorter time from diagnosis to transplantation were associated with decreased non-relapse mortality. The results of these 46 previously untreated patients have been compared with a group of 20 patients (8 sAML, 12 tAML) who received induction chemotherapy before transplantation. There were no statistically significant differences in outcome for the patients who received induction chemotherapy before transplantation compared to the patients who did not. However, these results should be interpreted with caution since the decision to use chemotherapy before transplantation was made by the treating physician before referring patients to the transplant centre.

Whether patients with advanced stages of MDS or sAML benefit from chemotherapy prior to transplantation is still unresolved. The superior outcome of patients with a lower blasts percentage supports the use of chemotherapy to lower the disease burden before transplantation. Only prospective randomised studies analysed based on an intention-to-treat principle may circimvent the selection biases associated with retrospective analyses. This issue is addressed in a recently launched EBMT study.

Cytogenetic abnormalities

Cytogenetic abnormalities have a major influence on the outcome after stem cell transplantation. A French study reported a 7-year relapse rate of 83% in patients with complex anomalies.[40] Nevill et al. categorized patients according to the cytogenetic risk categories proposed by the IPSS.[18] Event-free survival for the entire group was 29%. Event-free survival for the poor-risk, intermediate-risk en good-risk groups were 6%, 40% and 51%, respectively, with actuarial risk of relapse 82%, 12% and 19%, respectively.[41]

Therapy-related MDS/AML

Ballen et al. treated 18 patients with therapy-related MDS/AML and 25 patients with primary MDS.[54] DFS and relapse rate were 43% and 8% for primary MDS and 24% and 22% for therapy-related MDS. These differences did not reach statistical significance. The EBMT analysis reported 67 patients who underwent allogeneic stem cell transplantation for therapy-related MDS and AML.[43] The 3-year DFS of 35% and relapse rate of 36% were identical to the outcome of patients with primary MDS. A French report involving 70 patients with therapy-related MDS and AML included 34% of patients in complete remission at the time of transplantation.[55] Two-year event-free survival, relapse and TRM rates were 28%, 42% and 49%, respectively. Only five of the 46 patients with active disease at the time of transplantation were long-term survivors. A large study from Seattle reported on 99 patients (47 tMDS, 52 tAML). Sixty-five patients received marrow from a family member and 34 received marrow from an unrelated donor. The probability of survival, relapse and non-relapse mortality was 13%, 47% and 78%, respectively. Non-relapse mortality was a significant impediment to survival: death from infection occurred in 27% and death from organ failure in 24% of patients.[56] In a later report a conditioning regimen with cyclophosphamide (CY) and targeted dose busulfan (BU) predicted for a better DFS. The 5-year DFS for the entire group was 16% versus 30% for a regimen with targeted BU/CY. The incidence of relapse was strongly affected by the stage of the disease at transplantation. In 12 patients with RA and RARS no relapses were observed. This finding argues for transplantation early in the disease evolution.[57]

T-cell depletion

Mattijssen et al. showed in a single centre study a 39% DFS at 2 years after transplantation with T-cell depleted grafts from HLA-identical siblings using elutriation in 35 patients. In 11 RA patients DFS was 73%, similar to the results for comparable patients receiving non-T-cell depleted grafts.[58] However the risk of GVHD is lower after T-cell depletion, which may reduce long-term morbidity and mortality. An EBMT analysis showed no differences in survival and DFS after T-cell depletion, but an increased risk of relapse was reported with a hazard ratio of 6.30.[42]

Bone marrow stem cells versus peripheral blood stem cells

In the setting of autologous transplantation peripheral blood stem cells have largely replaced bone marrow stem cells because of more rapid hematological repopulation and lower requirements for supportive therapy. Also, after allogeneic stem cell transplantation the use of peripheral blood stem cells resulted in a faster hematopoietic recovery in a prospective study.[59] In an EBMT survey in 234 MDS patients comparing marrow and G-CSF mobilized peripheral blood stem cells (PBSC) the use of PBSC reduced the median duration of neutropenia and thrombocytopenia by 4 and 12 days, respectively.[60] A lower treatment failure incidence (relapsed disease and refractory disease) was found when PBSC were used as stem cell source (38% versus 13%). There was a trend towards more chronic Graft-versus-host-disease (GVHD) among patients who received PBSC in univariate analysis, but the use of PBSC was not significantly associated with an increased risk for chronic GVHD in multivariate analysis. The treatment-related mortality was reduced with PBSC except for patients with RA and patients with high-risk cytogenetic abnormalities. The low treatment failure observed with PBSC in more advanced stages of MDS suggests that a graft-versus-MDS effect exists and that it could be enhanced by the use of G-SCF mobilized PBSC. The Spanish registry compared the outcome of 45 patients receiving bone marrow stem cells with 36 patients receiving peripheral blood stem cells.[61] Patients who received PBSC displayed a faster engraftment and showed a significantly reduced TRM at day 100 (14% versus 42%). In high-risk MDS (RAEB, RAEBt) overall survival and event-free survival appeared significantly longer after the use of PBSC.

Reduced Intensity Conditioning (RIC)

The principle idea of reduced intensity conditioning regimen is to minimize toxicity associated with conventional myeloablative regimens and to harness the graft-versus-MDS effect of the infused donor lymphocytes. The RIC regimens largely depend upon intensive immune suppression either during conditioning and/or after stem cell infusion in order to facilitate donor engraftment and to establish complete donor chimerism. Reduced intensity conditioning regimens have been tested in view of the high treatment-related mortality in older patients after conventional marrow ablative conditioning regimens. RIC regimens might also be of interest in patients with high blast counts particularly, if debulking with chemotherapy before transplantation is successful. Kröger et al. reported 37 patients with MDS or secondary AML, half of whom had a related

donor, who were ineligible for conventionally conditioned transplants.[62] The reduced intensity conditioning consisted of fludarabine, busulphan and antithymocyt globulin. Overall TRM was 27%, with significantly higher mortality in those with poor risk cytogenetics (75% versus 29%) or with an HLA-matched unrelated donor (45% versus 12%). In total, 32% of patients relapsed, and actuarial DFS at 3 years was 38% with a median follow-up of 20 months. A Spanish study showed a TRM of only 5% after transplantation of 37 patients with MDS and AML utilizing a regimen based on fludarabine and busulfan.[63] The 1-year progression-free survival was 66%. The incidence of grade II-IV acute GVHD was 19% and the 1-year incidence of chronic extensive GVHD was 46%. In multivariate analysis including GVHD, achievement of complete donor chimerism within 100 days and disease phase, only GVHD showed a protective effect on disease progression. The estimated DFS in patients with GVHD was 58% compared with 13% for those without GVHD. These results support the notion that a graft-versus-MDS/AML response is critical in reducing the risk of relapse after an RIC transplant. Parker et al. compared outcome of 23 MDS patients conditioned with reduced-intensity regimen consisting of fludarabine, busulfan and alemtuzimab (Campath-1H) with 29 patients treated with a myeloablative regimen.[64] The patients treated with RIC were considered ineligible for standard conditioning due to age (median 48 year) and co-morbidity. Contrary to the findings of Martino et al., acute and chronic GVHD appeared low after reduced intensity regimen (17% and 15%), due to the adding of Campath-1H. The 2-year DFS rates were 39% after RIC and 44% after standard conditioning with a reported TRM of 31% and 50%, respectively. Stuart et al. described the results of 91 patients with a diagnosis of MDS (77 patients) or MPD (myeloproliferative disorder) (14 patients) who were conditioned with fludarabine and a single fraction of total body irradiation (2 Gy) followed by infusion of stem cells from an HLA-matched related (N=49) or unrelated (N=42) donor.[65] Patients with low risk MDS (RA, RARS, RAEB) at the time of transplant (N=33) had an 18 month relapse rate of 32% ± 18%, resulting in overall survival rates at 18 months of 40% ± 18%. This relatively high relapse risk is in line with the observations of a recent EBMT study. The EBMT analysis showed a low TRM (16%), but a 54% relapse risk for the 24 patients transplanted with RIC protocols.[66]

The King's College Hospital group from London reported more favourable results following conditioning with fludarabine, busulphan and Campath-1H in 62 patients with MDS (24 matched sibling donors and 38 unrelated donors).[67] One-year DFS was 61% and 59% in patients transplanted with sibling and unrelated donors, respectively.

Nevertheless, no long-term surviving patients were observed in patients with progressive disease. The favourable results may be explained by the low estimated 1-year treatment-related mortality of 15% (5% sibling, 21% VUD), the relatively high number of patients transplanted with less than 5% marrow blasts at the time of transplant conditioning (> 75% of the patients), the high number of patients who received donor lymphocyte infusions (67% of sibling recipients and 26% of VUD recipients) and the relatively short period of follow-up. Late events occur often after RIC and survival curves do not begin to plateau until after day 200, with a suggestion that the curves may merge after 3 to 4 years.[68]

Transplantation with alternative donors

Through lack of HLA-identical family donors in the majority of young MDS patients, alternative donor sources have been used. Demuynck et al. treated 8 out of 24 patients with alternative donors (five HLA non-identical family donors and three unrelated donors).[69] There was only one long-term survivor after alternative donor transplantation. Infections and graft-versus-host disease were the main causes of death. Despite T-cell depletion severe acute GVHD $\geq$ grade 2 was noticed in 6 out of 8 patients. Among patients with MDS treated in Seattle with an unrelated donor following myeloablative conditioning, 2-year disease-free survival was 38%, with a relapse rate of 28%, and non-relapse mortality of 48%.[70] Both older age and longer disease duration were associated with a greater risk of death from non-relapse causes. The EBMT collected data on 118 patients treated with an unrelated donor.[71] Disease-free survival at 2 years, relapse risk and transplant-related mortality were 28%, 35% and 58% respectively. The transplant-related mortality was significantly influenced by age (younger than 18 years: 40%; 18-35 years: 61%; older than 35 years: 81%). Patients with more severe acute graft-versus-host disease experienced a lower relapse risk, suggesting an increased graft-versus-MDS effect in these patients. A later EBMT survey reported 198 patients, who underwent voluntary unrelated donor (VUD) transplantation. The reported DFS, survival, relapse rate and TRM at 3 year were 25%, 26%, 41% and 58% respectively.[43] This analysis also showed data of 91 patients transplanted with stem cells from a genotypically non-identical related donor. The 3-year DFS, survival and relapse rate were 28%, 31% and 18% respectively. Noteworthy the treatment related mortality was 66%, higher than in any other type of transplantation. De Witte et al. compared outcome of 58 patients transplanted with mismatched family donors and 78 patients transplanted with unrelated donors, matched for stage of disease and age at transplantation.[72] The 3-year DFS,

relapse risk and TRM after mismatch family transplantation were 23%, 18%, and 72% versus 28%, 29% and 61% after unrelated donor transplantation. The American National Marrow Donor Program (NMDP) presented data on 510 patients receiving a transplant from an unrelated donor.[73] The incidence of relapse at 2 years was 14%. A higher relapse rate was associated with advanced MDS and no GVHD. The 2-year DFS was 29% and TRM 54%. Improved DFS was associated with less advanced MDS, higher cell dose, recipient CMV seronegativity, shorter interval from diagnosis to transplantation and transplantation in recent years.

Table 3 shows a summary of studies published in the past years on allogeneic BMT for MDS and sAML.

INTENSIVE CHEMOTHERAPY AND AUTOLOGOUS TRANSPLANTATION

For those patients lacking a suitable donor, intensive chemotherapy with AML-like schedules may be an alternative approach. Complete remission rates have improved in recent years, ranging between 15% and 65%.[34,74-78] Remission duration, however, is brief due to the high rate of relapse. Karyotype is the most important prognostic factor influencing disease-free survival with a median of 16.5 months for patients with a normal karyotype compared to 4 months in those with an abnormal karyotype.[76] In 1995 the Leukemia Cooperative Group of the European Organisation for the Research and Treatment of Cancer (EORTC) reported results of the first prospective multicenter study using cytarabine and idarubicin as remission-induction treatment in patients with high-risk MDS and sAML.[77] There was no difference in remission rates between patients with MDS (50%) and sAML patients (63%). Again the outcome of patients without cytogenetic abnormalities was better than the outcome of patients with an abnormal karyotype. In an analysis of 158 patients with high-risk RAEB and RAEBt and 372 AML patients treated at the MD Anderson Cancer Center, remission rates were comparable for RAEB, RAEBt and AML, but event-free survival and overall survival were inferior in RAEB compared to AML or RAEBt.[34] Multivariate analysis indicated that the poorer outcome was due to the association between RAEB and poor prognostic features particularly complex cytogenetic abnormalities rather than to the diagnosis itself. A recent study investigated the value of fludarabine in addition to cytarabine and G-CSF in 91 MDS and 43 AML patients.[79] Combining cytarabine and fludarabine did not improve overall survival (39% FLAG vs. 24% AG) and DFS (23% FLAG vs. 16% AG).

Several studies combined chemotherapy with hematopoietic growth factors in an attempt to improve the outcome.[80,81] The reason for this approach is a reduction of the hypoplastic period and sensitising of the malignant cells for chemotherapy by recruiting these cells into the cell cycle. In an Italian study on 105 MDS and sAML patients, the CR rate was not affected by the use of G-CSF (33% versus 43%). Also, the use of G-CSF did not prolong remission duration and survival.[80] The HOVON cooperative group reported a 73% response rate for patients assigned to the G-CSF arm compared to 52% in the standard arm (p=0.08). The neutrophil recovery was significantly shorter after the use of G-CSF and this resulted in a reduced interval of 9 days between the induction and consolidation course.[81] Again no differences in overall survival and DFS were observed. Wattel et al. studied the use of quinine as multidrug resistance (mdr) modulator.[82] In a subgroup of 42 P- glycoprotein (Pgp) positive patients both CR rate and median survival were higher in patients receiving quinine.

In view of the high relapse rate after chemotherapy only, transplantation with autologous stem cells has been applied in an attempt to intensify the post-remission therapy. In a French study 7 patients with sAML received an autograft in CR after remission-induction chemotherapy.[83] One patient died before engraftment, for the other patients the median time to engraftment for the white blood cells was 41 days, in two patients engraftment for platelets did not occur, in the five other patients median time to engraftment was 120 days. In 1997 the European Group for Blood and Marrow Transplantation (EBMT) reported the results of 79 patients autografted for MDS and sAML in first complete remission.[84] Two-year survival, disease-free survival and relapse rate were 39%, 34% and 64%, respectively. Patients younger than 40 years showed a significantly better DFS (39%) than patients older than 40 years (25%). A cohort of 55 patients was compared with a matched control group of 110 patients with de novo AML. The MDS/sAML cohort showed a lower DFS (28%) when compared with de novo AML patients (51%), due to a higher relapse rate. The treatment-related mortality rate was less than 10%. In 1999 the first prospective study on autologous stem cell transplantation in myelodysplastic syndromes was published.[85] A complete remission was attained in 42/83 patients (51%). In 24 out of 39 patients (62%) transplantation with autologous bone marrow cells (ABMT: 16 patients) or autologous peripheral stem cells (APSCT: 8 patients) was performed. Hematological reconstitution occurred in all autografted patients. However, this study, perhaps given its size limitation, did not confirm a faster hemopoietic recovery for peripheral blood stem cells compared to bone marrow cells, as has been demonstrated in

primary AML.[86] The median DFS of the autografted patients was 29 months from transplantation. A multicenter study of the EORTC, EBMT, SAKK and GIMEMA included 197 patients with high-risk MDS and sAML.[87] The CR rate after remission-induction chemotherapy was 54%. Both allogeneic and autologous stem cell transplantation were employed as post-consolidation treatment, depending on the donor availability. The overall survival and DFS at 4-years were 26% and 29% respectively. Sixty-one percent of the patients without a donor (36/59) received an autologous stem cell transplantation in first CR and 72% of the patients with a donor (28/39) were allografted in first CR. The EBMT report included 173 patients, who underwent autologous transplantation.[43] Outcome of patients transplanted in first complete remission (N=126) was significantly better than outcome of patients transplanted in more advanced disease stage (N=47). In CR-1 the reported 3-year OS, DFS, TRM and relapse rate were 38%, 33%, 25%, and 55% versus 14%, 18%, 51%, and 64% after no CR-1.

The results of several studies employing intensive chemotherapy with or without stem cell transplantation are summarised in Table 4.

Stem cell mobilization

Since MDS is a clonal stem cell disorder, there remains concern regarding contamination of the graft by residual malignant cells and regarding the presence of sufficient residual normal stem cells to support rapid reconstitution. However, several studies reported that patients with an abnormal karyotype can achieve a cytogenetic remission if a morphological remission is reached after chemotherapy.

Delforge et al. demonstrated that polyclonal immature hematopoietic progenitors can be mobilized and harvested in patients with high-risk MDS after treatment with intensive chemotherapy.[88] Clonality analysis was performed in females heterozygous for the X-linked human androgen-receptor (HUMARA) gene, demonstrating a polyclonal pattern in the $CD34^+$ cell population in 4 of 5 patients.

In a separate report involving 11 patients in CR after chemotherapy, stem cell mobilization was attempted either with G-CSF alone or with G-CSF after recovery from the consolidation course. In 7/11 patients sufficient cell numbers were harvested resulting in a CD 34 progenitor cell yield > 1 x 10^6/kg.[89] Carella et al. were able to collect normal progenitor cells in 6/9 patients who presented with an abnormal karyotype.[90] In our own experience stem cell mobilization was feasible in about 50% of patients in the recovery phase after chemotherapy with G-CSF.[91]

Table 4. Intensive chemotherapy with or without autologous SCT in MDS and sAML.

Source	Number of patients	Median age (years)	Induction chemotherapy	CR (%)	Number of patients transplanted	Outcome
Fenaux 1991 [76]	MDS 31 sAML 16	54	Z + A	47	--	DFS: 11 mo OS: 14 mo
De Witte 1995 [77]	MDS 34 sAML 16	46	I + A	54	--	DFS: 11 mo OS: 15 mo
Parker 1997 [78]	MDS 13 sAML 3	44	I + A + F + G-CSF	63	6[a]	
Estey 1997 [34]	MDS 158	60	I + A or F + A ± G-CSF	65	--	DFS: 5-12 mo (RAEB/RAEBt)
Ossenkoppele 1999 [81]	MDS 64	62	D + A ± G-CSF	63	--	OS: 29-16%
Ossenkoppele 2004 [79]	MDS 91 AML 43	65 / 69	A + G-CSF ± F	68	--	DFS: 23-16% OS: 39-24%
De Witte 1997 [84 b]	MDS 19 sAML 60	39		--	79	DFS: 34% OS: 39% relapse: 64%
Wattel 1999 [85]	MDS 37 sAML 46	45	M + A ± Q	51	24	DFS: 29 mo OS: 33 mo[c]
De Witte 2001 [87]	MDS 138 sAML 46	47	I + A + E	54	36 auto CR-1 28 allo CR-1	DFS: 29% OS: 26%

A = cytarabine, Z = zorubicine, I = idarubicin, F = fludarabine, D = daunomycin, M = mitoxantrone, Q = quinine, E = etoposide

[a]: 3 allogeneic BMT, 3 autologous stem cell transplantation

[b]: Report on 79 patients transplanted in first CR

[c]: Calculated from transplantation

CONCLUSIONS

Allogeneic stem cell transplantation is the treatment of choice for the majority of young patients with MDS or sAML who have an HLA-identical sibling donor. Overall, approximately 40% of patients are likely to be cured with allogeneic stem cell transplantation. Long-term disease-free survival can be attained if transplantation is performed early in the disease course. An increased blast percentage and poor prognostic cytogenetic features are associated with an increased risk of relapse and, thereby, shorter disease-free survival. Longer disease duration, advanced patient age, therapy-related MDS, and the use of alternative donors are associated with increased non-relapse mortality.

Since outcome of transplantation is superior for patients with a low blast percentage, this supports the use of chemotherapy prior to transplantation in patients with high blast marrow infiltration. The issue whether patients with a blast percentage over 5% may benefit from remission-induction chemotherapy prior to transplantation, is addressed in a recently launched EBMT study.

Outcome after transplantation remains worse for patients with MDS than for those with de novo AML, mainly due to a higher transplant-related mortality and a higher relapse rate. Therefore, subsequent studies should focus on optimising pre-treatment schedules, conditioning regimens and post-transplant immune-modulation. Immunotherapy with donor lymphocyte infusions has been reported in cases of relapse after allogeneic stem cell transplantation.[92-94]

Application of RIC regimen approach is a logical consequence of these principles. RIC regimens allow allogeneic transplantation in recipients of older age or with co-morbidity, a frequent reality in the treatment of patients with MDS. In addition, the RIC approach is attractive since it allows optimal utilization of post-transplant immune-modulations with donor lymphocyte transfusions. However, the place of RIC regimens remains to be determined since the results of conventional, bone marrow ablative regimens have improved in recent years. Prospective, randomised studies are necessary to elucidate the contribution of RIC regimens to the treatment of MDS patients.

For patients lacking an HLA-identical sibling the choice is ambiguous. Although the reports on autologous stem cell transplantation are still limited, the disease-free survival after autologous transplantation seems comparable with disease-free survival after allogeneic stem cell transplantation with genotypically non-identical related donors and

voluntary unrelated donors. The high incidence of relapse in autologous transplantation is counterbalanced by the high TRM in alternative donor transplantation. A prerequisite for autologous transplantation is that patients enter complete remission before transplantation and that sufficient numbers of stem cells can be harvested. Autologous transplantation is a valid option for a patient who fulfils these criteria. For patients who fail to enter complete remission allogeneic stem cell transplantation with a genotypically non-identical related donors or a voluntary unrelated alternative donor may constitute an alternative treatment option.

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CHAPTER 2

Outcome of patients with myelodysplastic syndrome according to donor availability from time of HLA-typing: an EBMT registration study

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ABSTRACT

High-risk MDS patients are candidates for several treatment strategies, including matched family donor stem cell transplantation (SCT), alternative donor SCT, autologous SCT, high-dose chemotherapy and/or supportive care. The purpose of the present analysis was to assess prospectively the value of different treatment strategies. In all, 11 European centres have registered 248 patients, who were untreated at time of HLA-typing. A matched family donor was identified in 52% of patients. The 3-year survival rates were 46% and 43% for patients with and without a donor. Seventy-eight percent of patients with a donor received the intended allogeneic stem cell transplantation (SCT). In patients without a donor a lower percentage received the intended treatment; 46% underwent the intended alternative donor SCT, 50% autologous SCT, 67% high-dose chemotherapy and 97% supportive care. In multivariate analysis age, chromosomal abnormalities and RA(RS) FAB subtype appeared prognostic for survival, while intended treatment was not prognostic for survival. On intention-to-treat basis the estimated 3-year survival was 48% for immediate allogeneic SCT, 34% for allogeneic SCT after remission-induction chemotherapy, 37% for alternative donor SCT, 36% for autologous SCT, and 35% for patients intended for chemotherapy only. This analysis confirms that alternative donor SCT, autologous SCT and high-dose chemotherapy may provide an alternative therapy for patients lacking a matched family donor.

INTRODUCTION

Myelodysplastic syndromes (MDS) form a heterogeneous group of clonal stem cell disorders. In 1982 the FAB classification proposed five subgroups based on the percentage of blast cells in blood and bone marrow, the percentage of ringed sideroblasts and monocytes: RA (Refractory anemia), RARS (Refractory anemia with ringed sideroblasts), RAEB (Refractory anemia with excess of blasts), RAEBt (Refractory anemia with excess of blasts in transformation) and CMML (Chronic myelomonocytic leukemia).[1] In 1997 the World Health Organization (WHO) proposed a re-classification of MDS.[2] One of the major changes between the WHO and FAB classification is the distinction between single lineage versus multilineage dysplasia (RA(RS) versus RCMD (Refractory cytopenias with multilineage dysplasia). Furthermore, the WHO classification lowered the threshold value to 20% blasts in the bone marrow to define AML instead of 30% in the FAB classification. As a consequence RAEBt has been eliminated from the WHO classification. Another important difference is the removal of CMML from MDS to a myeloproliferative-myelodysplastic overlap category.

The natural course of MDS is variable. RA and RARS are defined as less advanced MDS. These patients have a low risk of developing acute myeloid leukemia and their median survival is over 30 months.[3] Most patients die due to bone marrow failure or due to iron overload as a result of repeated blood transfusions. Advanced MDS is defined as RAEB, RAEBt and CMML. Median survival of patients presenting with RAEB and RAEBt is generally shorter than 12 months.[4] However, the prognosis of patients within the different FAB categories varies and RA(RS) patients with severe cytopenias and poor prognostic cytogenetic features have a poor outcome despite a low blast percentage in the bone marrow. Therefore, multiple scoring systems have been proposed to predict the natural history of an individual patient. At present, the most widely accepted scoring system is the IPSS (International Prognostic Scoring System).[5] The IPSS analysed data of 816 patients with de novo MDS, who received supportive care. Four categories are distinguished based on the percentage of blasts in the bone marrow, the number of cytopenias and the presence of cytogenetic abnormalities (Low, Intermediate-1, Intermediate-2 and High risk).

For elderly patients supportive care is the mainstay of treatment. Also, growth factors, hypomethylating agents and anti-apoptosis approaches are investigated currently, but these strategies do not intend to cure MDS patients.[6-8] The primary curative option for

myelodysplastic syndromes is allogeneic stem cell transplantation (SCT). This treatment is only available for younger MDS patients (aged less than 50-60 years) with an HLA-identical sibling donor. Disease-free survival ranges from 29-41%, relapse rate from 28-52% and non-relapse mortality from 39-50%.[9-11] For patients lacking an HLA-identical donor intensive chemotherapy regimens with or without autologous stem cell transplantation may be an alternative approach.[12-17] After autologous transplantation in first complete remission the 2-year survival, disease-free survival, and relapse rates were 39%, 34%, and 64%, respectively.[13]

However, the superior results after allogeneic stem cell transplantation may be due to selection of patients fit enough to undergo SCT and exclusion of patients with an early relapse. The value of SCT compared to intensive chemotherapy only or chemotherapy followed by autologous stem cell transplantation has never been defined. Randomisation, the classical approach to test the value of different treatment strategies is not feasible. An alternative approach is registration at a fixed point in time; the time of HLA-typing of patient and siblings. In 1992 the CLWP (Chronic Leukemia Working Party) of the EBMT (European Group for Blood and Marrow Transplantation) asked centres to participate in a prospective registration study. The principal aim was to make an assessment of the value of SCT compared to other therapeutic modalities. A second question was whether patients with more than 5% blasts in the bone marrow benefit from remission-induction therapy prior to transplantation.

PATIENTS AND METHODS

Between April 1992 and October 1995 88 patients have been registered prospectively in the study at time of HLA family typing or at time of referral to a transplant centre. Information was collected on age, sex, FAB classification, cytogenetics, date of primary diagnosis, date of HLA-typing and disease status at time of HLA-typing. The physicians were asked to give the intention-to-treat depending on the outcome of the donor search at time of registration. In case of an available HLA-identical sibling donor the possibilities were immediate SCT (without preceding chemotherapy), SCT after chemotherapy or SCT at progression of disease. In case no donor was available, the options were search for an alternative donor, intensive chemotherapy only, chemotherapy followed by autologous stem cell transplantation or supportive care. The registration forms were collected centrally before outcome was known. Data about results of HLA-typing, disease stage at

typing, applied treatment, current disease status, survival status and causes of death were collected between 1996 and 1998. Six patients were excluded from the analysis for the following reasons: no HLA-typing performed (N=1), and no diagnosis of MDS (N=5). In 13 patients no follow-up data could be collected. Consequently, 69 out of 88 patients were prospectively included.

Since the number of registered patients was not sufficient for statistical analyses, the HLA-typing laboratories were asked to provide the investigators a list of all MDS patients, who had HLA family typing in their centre after 1992. So, retrospectively another 227 patients have been registered (23 of these patients were typed between 1985 and 1991). The physicians were asked to give the intention-to-treat according to the policy of the centre depending on the availability of a donor. Data of these patients were collected between 2000 and 2002. In all, 11 European centres have registered 296 patients.

Definitions

The classification of MDS was performed according to the criteria of the French-American-British (FAB) working group. AML that developed after pre-existing MDS was defined as secondary AML (sAML).

Statistical analysis

The duration of survival was calculated from the date of HLA-typing until death, whatever the cause. Actuarial curves were calculated according to the Kaplan-Meier technique. The differences between curves were tested statistically using the two-tailed log-rank test (Breslow). For ordered variables, the log-rank test for linear trend was used. The prognostic value of covariables was studied by Cox's regression.

RESULTS

In all, data on 296 patients have been collected. Out of 296 patients, 248 patients were untreated at time of HLA typing. Seventeen patients were typed in first CR, 22 patients with refractory disease and 9 patients were typed in more advanced disease. Since our purpose was to avoid selection as much as possible, we focussed on the 248 patients who underwent HLA-typing before administration of any treatment. Patients with an HLA-identical donor, a syngeneic donor and a phenotypical identical family donor were classified in the matched family donor group (N=130), all other patients in the group without a matched family donor (N=118). Patients were treated according to local protocols. Patients with and without a matched family donor did not differ regarding age, sex, sub-classification at HLA typing and cytogenetics. Clinical characteristics are given in table 1.

Table 1. Characteristics of patients according to donor availability (N=248).

	All patients N=248 (%)	Matched family donor N=130 (%)	No matched family donor N=118 (%)	P-value[a]
Age at HLA-typing (yr.)				
< 20	36 (15)	15 (12)	21 (18)	0.08
20-40	105 (42)	51 (39)	54 (46)	
> 40	106 (43)	64 (49)	42 (36)	
Male	130 (52)	66 (51)	64 (54)	0.59
Female	118 (48)	64 (49)	54 (46)	
Sub-classification at HLA typing				
RA(RS)	78 (31)	45 (35)	33 (28)	0.23
RAEB	72 (29)	37 (28)	35 (30)	
RAEBt	64 (26)	36 (28)	28 (24)	
CMML	17 (7)	4 (3)	13 (11)	
sAML	16 (7)	8 (6)	8 (7)	
Unclassified	1		1	
Prospective study	64 (26)	36 (28)	28 (24)	0.48
Retrospective	184 (74)	94 (72)	90 (76)	
Cytogenetics				
Normal	104 (42)	53 (41)	51 (43)	0.93
Abnormal	88 (35)	47 (36)	41 (35)	

Not done/failed/unknown	56 (23)	30 (23)	26 (22)	
Sub-classification at SCT				
RA(RS)	36 (15)	31 (24)	5 (4)	< 0.0001
RAEB	28 (11)	20 (15)	8 (7)	
RAEBt	38 (15)	25 (19)	13 (11)	
CMML	9 (4)	3 (2)	6 (5)	
sAML	34 (14)	22 (18)	12 (10)	
No transplantation	103 (42)	29 (22)	74 (63)	
Applied treatment				
Chemotherapy only	42 (17)	13 (10)	29 (25)	< 0.0001
Autologous SCT	13 (5)		13 (11)	
Allogeneic SCT	132 (53)	101 (78)	31 (26)	
Supportive care	61 (25)	16 (12)	45 (38)	
Allogeneic transplantation				
Matched family donor	101 (77)	101		< 0.0001
Mismatched family donor	12 (9)		12	
Unrelated donor	19 (14)		19	
Stage at transplantation				
Direct transplantation	69 (28)	54 (42)	15 (13)	< 0.0001
CR-1	56 (22)	39 (30)	17 (14)	
Refractory disease	12 (5)	4 (3)	8 (7)	
More advanced disease	8 (3)	4 (3)	4 (3)	
No transplantation	103 (42)	29 (22)	74 (63)	
Alive	109 (44)	55 (42)	54 (46)	0.58
Dead	139 (56)	75 (58)	64 (54)	

[a]: Comparison matched family donor versus no matched family donor

Intended therapy and actually applied therapy

Patients with a matched family donor (N=130)

Immediate SCT without prior remission-induction chemotherapy was performed in 42 out of 47 patients (89%) intended for this treatment option according to the physician. SCT after chemotherapy was performed in 45 out of 58 patients (78%) and 14 out of 25 patients (56%) underwent allogeneic transplantation at progression of the disease (Table 2). In all, 101 of 130 patients (78%) with a matched family donor received the intended allogeneic transplantation. Progression of disease between HLA-typing and allogeneic

transplantation was reported in 20 patients. In 29 patients no allogeneic transplantation was performed: 9 RA(RS) patients, 12 RAEB patients, 7 RAEBt patients and 1 sAML patient. Overall, in the matched family donor group 101 patients underwent allogeneic transplantation, 13 patients received chemotherapy only and 16 patients received supportive care.

Patients without a matched family donor (N=118)

Fifty patients without a matched family donor were intended for alternative donor transplantation (mismatched family transplantation or matched unrelated transplantation) and 23 patients (46%) received this treatment. Autologous transplantation after chemotherapy was intended for 20 patients and 10 of these patients (50%) were treated with ABMT. Sixty-seven percent (8/12 patients) intended for chemotherapy only actually received chemotherapy. Supportive care was administered to almost all patients intended for this approach (97%). Another six patients, for whom the intention-to-treat was unknown, underwent alternative donor transplantation.

Overall, in the group without a matched family donor 31 patients underwent alternative donor allogeneic transplantation, 29 patients received chemotherapy only, 13 patients received chemotherapy followed by autologous transplantation and 45 patients received supportive care only (Table 2). Progression of disease between HLA-typing and alternative donor transplantation was reported in 9 patients.

Table 2. Intention-to-treat at time of HLA family typing and applied treatment.

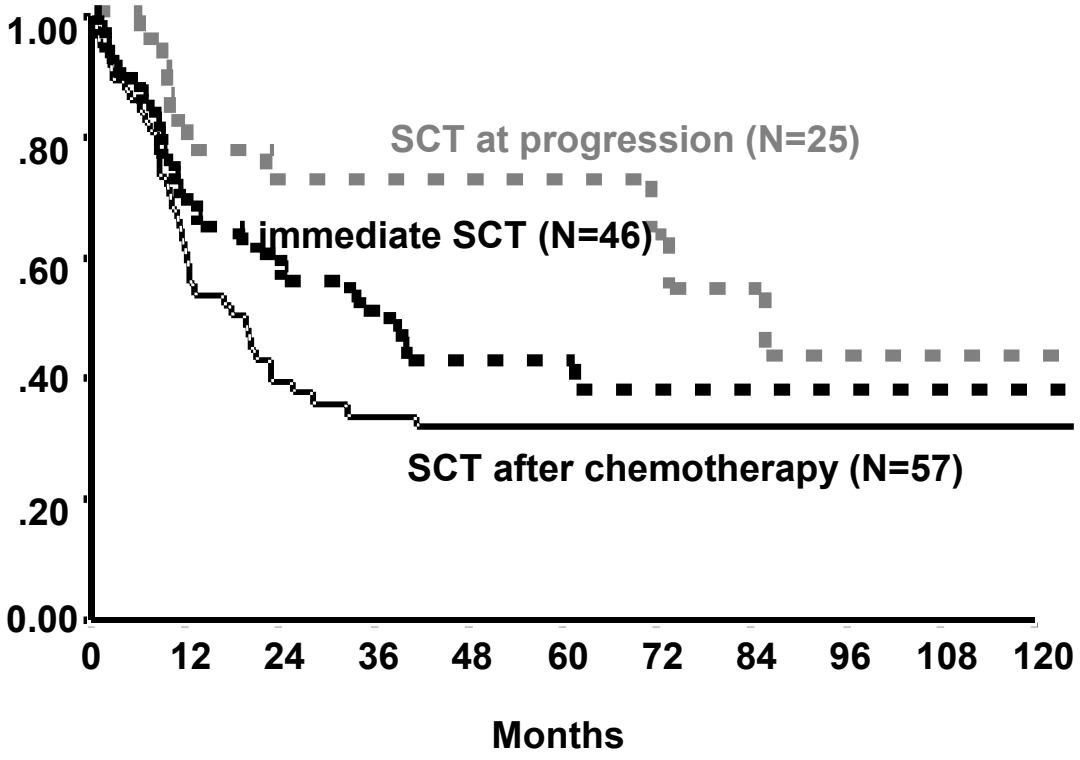
	Intention-to-treat	Applied treatment
Matched family donor (N=130)		
Immediate SCT	47	42 SCT (89%)
		5 Supportive care
SCT at progression	25	14 SCT (56%)
		11 Supportive care
SCT after chemotherapy	58	45 SCT after chemotherapy (78%)
		13 Chemotherapy only
No matched family donor (N=118)		
Search alternative donor	50	23 Alternative donor SCT (46%)
		1 Autologous SCT
		12 Chemotherapy only
		14 Supportive care
Chemotherapy only	12	8 Chemotherapy only (67%)
		1 Alternative donor SCT
		2 Autologous SCT
		1 Supportive care
Autologous SCT	20	10 Autologous SCT (50%)
		1 Alternative donor SCT
		8 Chemotherapy only
		1 Supportive care
Supportive care	30	29 Supportive care (97%)
		1 Chemotherapy only
Missing	6	6 Alternative donor SCT

Outcome of patients according to intended treatment

Median survival from HLA-typing of all 248 patients was 33 months. Median survival from HLA-typing of the patients with a matched family donor was 28 months versus 35 months for the patients without a matched family donor. The estimated 3-year survival rates were 46% for patients with a matched family donor compared to 43% for patients without a matched family donor (p=0.98) (Table 3). To investigate the influence of alternative donor transplantation in patients without a matched family donor, we censored at time of alternative donor transplantation. By doing this, median survival of the patients without a matched family donor became 45 months, with an estimated 3-year survival of 52%.

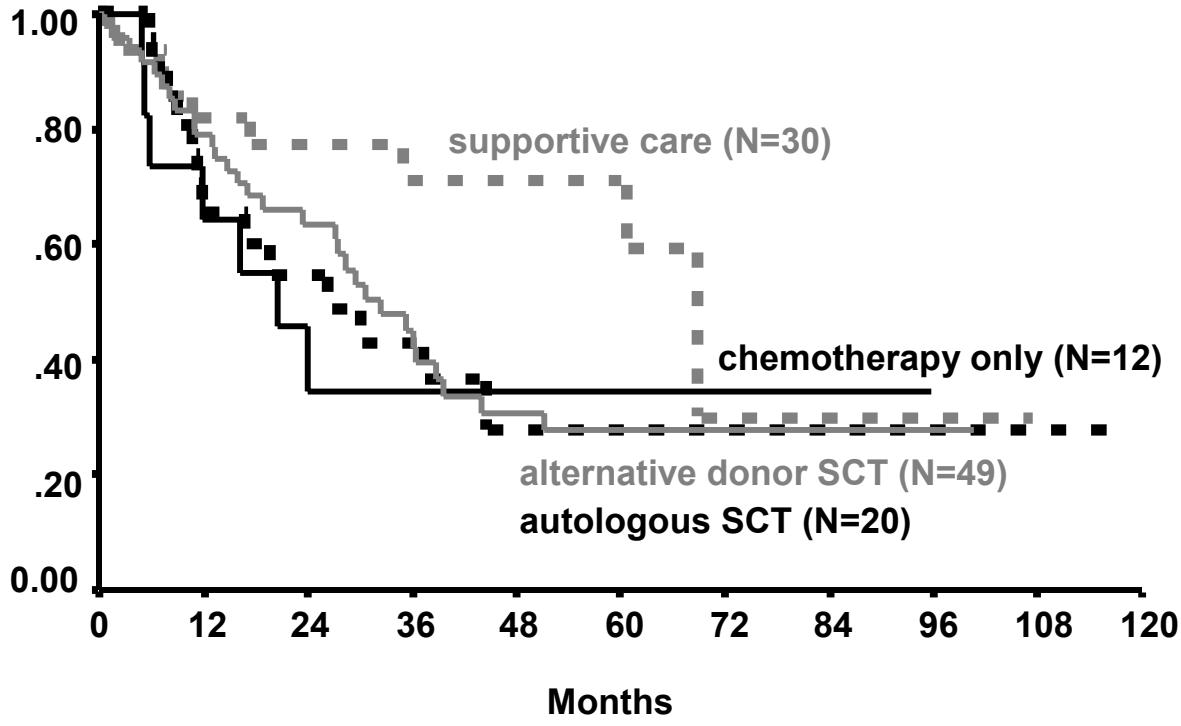
In the group with a matched family donor, median survival of the patients intended for immediate BMT was 39 months, 20 months for patients intended for BMT after remission-induction chemotherapy and 86 months for patients intended for BMT at progression of disease (p=0.25). The estimated 3-year survival rates were 48%, 34%, and 72%, respectively (Figure 1A).

Figure 1A. Overall survival from HLA-typing in patients with a matched family donor according to intended treatment**.**



In the group of patients without a matched family donor median survival was 32 months for the patients intended for alternative donor transplantation, 20 months for patients intended for chemotherapy only, 27 months for patients intended for autologous transplantation and 69 months for patients intended for supportive care only (p=0.11). The estimated 3-year survival rates were 37%, 35%, 36% and 71%, respectively (Figure 1B).

Figure 1B. Overall survival from HLA-typing in patients without a matched family donor according to intended treatment.



Outcome of patients according to applied treatment

In the matched family donor group, median survival according to applied treatment was 39 months after allogeneic transplantation, 11 months after chemotherapy only and not reached after supportive care. The estimated 3-year survival rates were 49%, 0% and 57% (Figure 2A). In the group without a matched family donor, median survival after alternative donor transplantation was 27 months, 12 months after chemotherapy only, not reached after autologous transplantation and 69 months after supportive care. The estimated 3-year survival rates were 34%, 9%, 67%, and 68%, respectively (Table 3) (Figure 2B). Clearly, the patients receiving supportive care form a subgroup of MDS patients. Although HLA-typing was initiated in these patients, there was no need yet for starting intensive antileukaemic treatment.

Table 3. Survival from HLA-typing according to matched family donor availability, intended treatment and applied treatment (3 patients data lacking).

	Number	Median survival (months) (95% CI)	3-year survival (%) (s.e.)	P-value
Donor availability				
Matched family donor	128	28 (13-44)	46 (4.6)	0.98
No matched family donor	117	35 (27-43)	43 (5.2)	
Intention-to-treat (donor)				
Immediate SCT	46	39 (21-56)	48 (7.6)	0.25
SCT at progression	25	86 (66-106)	72 (9.8)	
SCT after chemotherapy	57	20 (11-29)	34 (6.4)	
Intention-to-treat (no donor)[a]				
Search alternative donor	49	32 (23-42)	37 (7.7)	0.11
Chemotherapy only	12	20 (9-32)	35 (15.1)	
Autologous SCT	20	27 (10-44)	36 (11.4)	
Supportive care	30	69 (57-81)	71 (9.8)	
Applied treatment (donor)				
Matched family donor SCT	99	39 (7-70)	49 (5.1)	0.45
Chemotherapy only	13	11 (0-26)	0	
Supportive care	16	Not reached	57 (13.5)	
Applied treatment (no donor)				
Alternative donor SCT	30	27 (5-49)	34 (9.7)	0.11
Chemotherapy only	29	12 (10-14)	9 (5.8)	
Autologous SCT	13	Not reached	67 (13.8)	
Supportive care	45	69	68 (8.4)	

[a]: 6 patients with an alternative donor (matched unrelated donor) no intention-to-treat without a donor was given

Figure 2A. Overall survival from HLA-typing in patients with a matched family donor according to applied treatment.

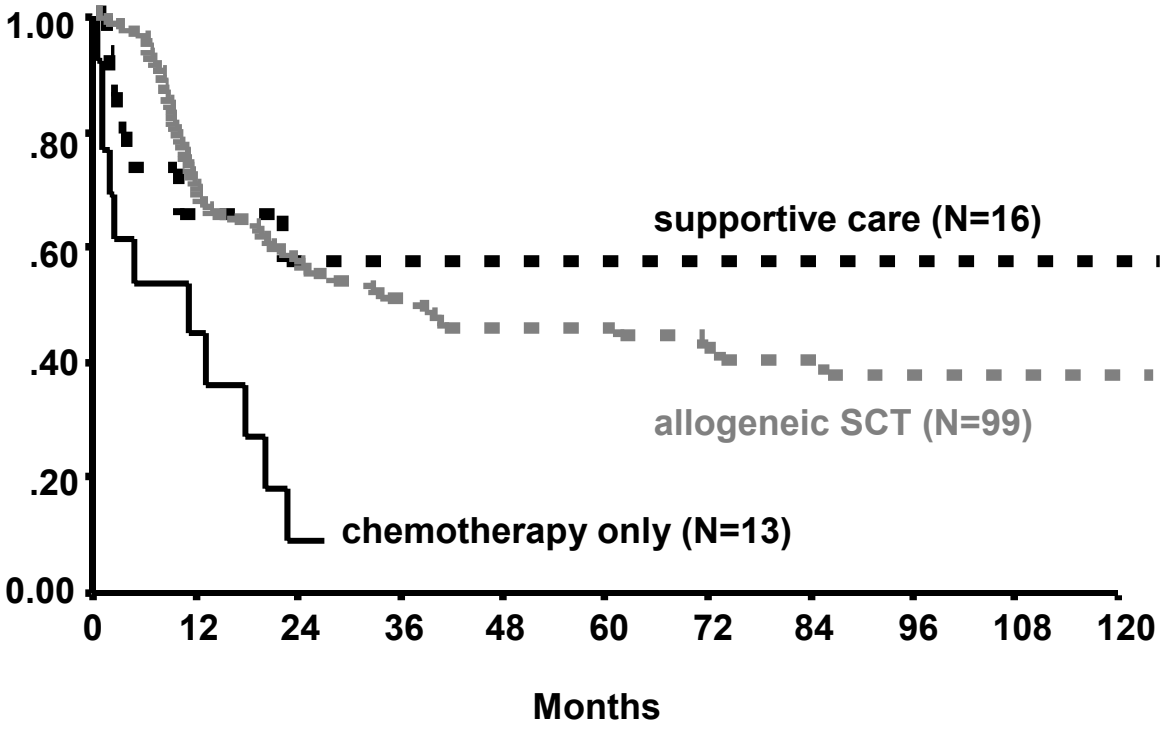
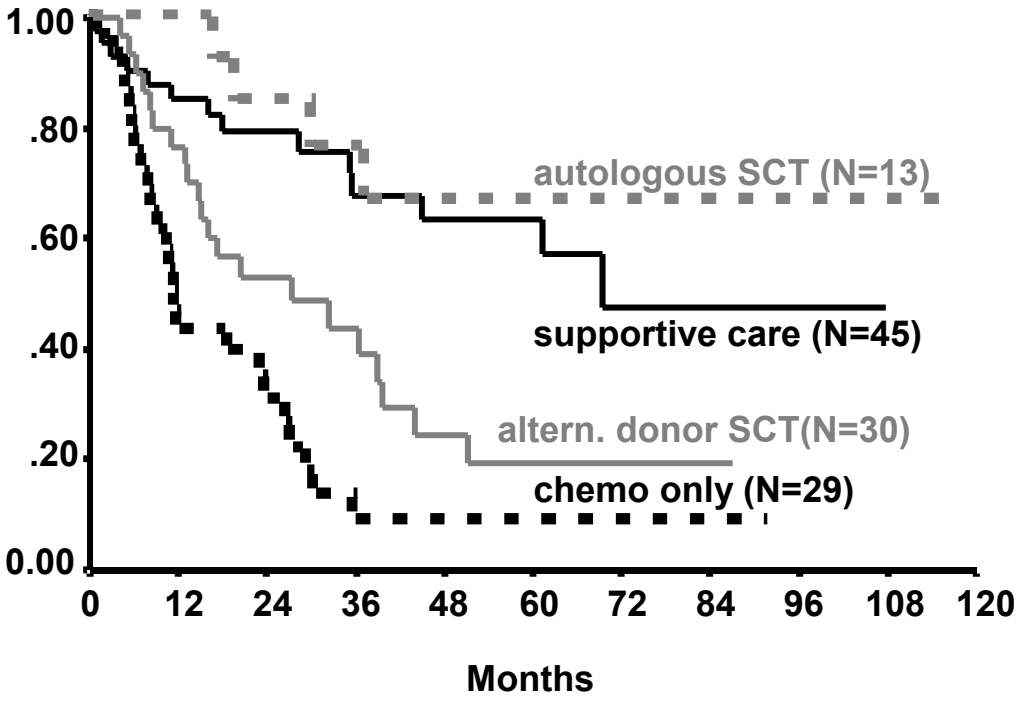


Figure 2B. Overall survival from HLA-typing in patients without a matched family donor according to applied treatment.



Multivariate analyses

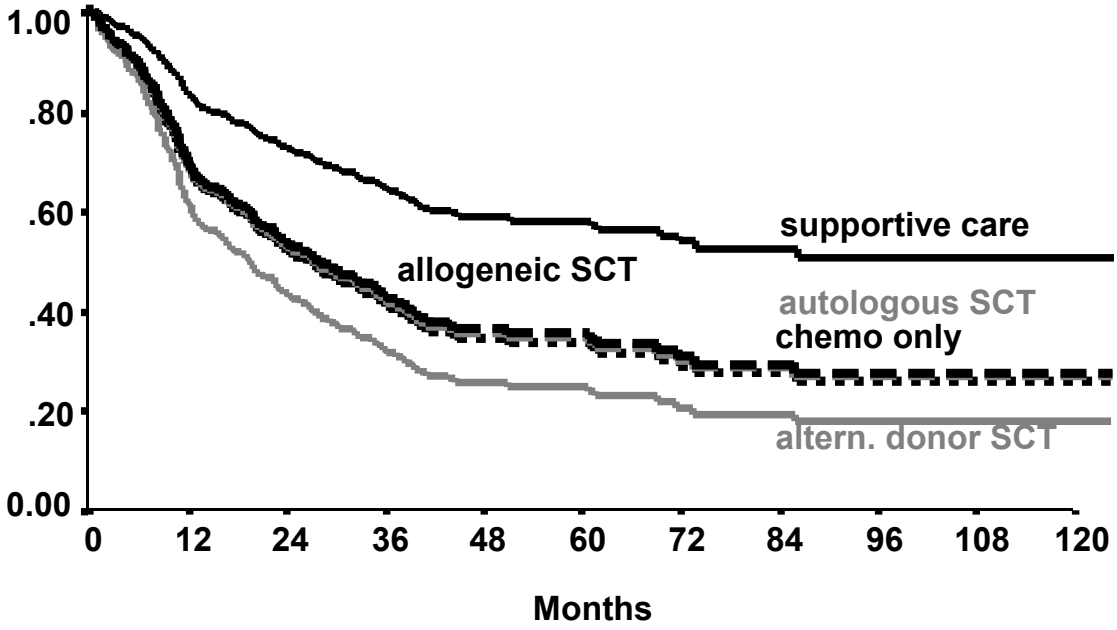
To evaluate whether the similar outcome of patients with and without a matched family donor was a true finding or due to differences in the patients groups a multivariate analysis was performed. The following factors were considered in the model: age, FAB classification at HLA-typing (RA(RS) versus other FAB subtypes), cytogenetic abnormalities, and intended treatment (allogeneic SCT, alternative donor SCT, autologous SCT, chemotherapy only and supportive care). The results of the multivariate Cox's proportional hazards model for survival are shown in table 4. Age, as a continuous variable, appeared to be most predictive for survival with a HR of 1.02 (95% Confidence Interval (CI) 1.01-1.04) ($p<0.0001$). A diagnosis of RA(RS) at time of HLA-typing and cytogenetic abnormalities were prognostic for survival as well. Survival of patients intended for allogeneic SCT was not better than for patients intended for other treatment strategies (Figure 3).

Table 4. Results of Cox's proportional hazards model for overall survival.

	Hazard ratio[a]	95% CI	P-value
Age	1.02	1.01-1.04	< 0.0001
Chromosomal abnormalities			0.03
Normal	1.00		
Abnormal	1.28	0.85-1.93	
Not done/unknown/failed	1.86	1.19-2.92	
Intended treatment			0.21
Allogeneic SCT	1.00		
Alternative donor SCT	1.35	0.86-2.12	
Autologous SCT	1.02	0.56-1.86	
Chemotherapy only	1.06	0.48-2.34	
Supportive care	0.53	0.26-1.06	
RA(RS)	0.58	0.38-0.88	0.01

[a]: A value >1 indicates that the outcome is worse in that category in comparison with the baseline.

Figure 3. Overall survival from HLA-typing in all patients according to intended treatment.



In addition, we considered the influence of the different treatment strategies on survival of patients with and without a matched family donor (Table 5). In the subgroup of patients with a matched family donor age and chromosomal abnormalities were predictive for survival. The intended treatment (direct transplantation, chemotherapy followed by transplantation or transplantation at progression of disease) was not predictive for survival in patients with a matched family donor. Survival of patients intended for transplantation after chemotherapy was not different from survival of patients intended for immediate allogeneic transplantation without preceding chemotherapy. A diagnosis of RA(RS) had no significant impact on survival.

Table 5. Results of Cox's proportional hazards model for overall survival in patients with and without a matched family donor.

	Matched family donor			No matched family donor		
	Hazard Ratio[a]	95% CI	P-value	Hazard Ratio[a]	95% CI	P-value
Age	1.02	1.00-1.04	0.02	1.03	1.01-1.05	0.003
Chromosomal abnormalities			0.05			0.08
Normal	1.00			1.00		
Abnormal	0.97	0.54-1.72		1.98	1.07-3.66	
Not done/unknown/failed	1.92	1.04-3.52		1.79	0.88-3.64	
Sex	1.02	0.63-1.66	0.93	0.69	0.40-1.19	0.18
Intended treatment (donor)			0.43			
Direct transplantation (SCT)	1.00					
SCT at progression	0.61	0.28-1.34				
SCT after chemotherapy	1.02	0.56-1.86				
Intended treatment (no donor)						0.09
Alternative donor SCT				1.00		
Autologous SCT				0.69	0.34-1.40	
Chemotherapy only				0.83	0.35-1.96	
Supportive care				0.36	0.16-0.80	
RA(RS)	0.74	0.40-1.39	0.35	0.44	0.21-0.95	0.04

[a]: A value >1 indicates that the outcome is worse in that category in comparison with the baseline.

In the subgroup of patients without a matched family donor age and FAB subtype appeared prognostic for survival. In the overall group chromosomal abnormalities appeared not prognostic, although the subgroup of patients with an abnormal karyotype showed a worse survival with a HR of 1.98 (95% C.I. 1.07-3.66) (p=0.03) compared to patients with a normal karyotype. The intended treatment (alternative donor transplantation, chemotherapy only, chemotherapy followed by autologous transplantation, supportive care) was not prognostic for survival.

DISCUSSION

This study was initiated to assess the role of allogeneic stem cell transplantation (SCT) compared to alternative treatment approaches like chemotherapy only, chemotherapy followed by autologous stem cell transplantation, alternative donor transplantation and supportive care only. The question whether allogeneic SCT is a superior treatment option compared to other treatment modalities is difficult to answer. Most studies on allogeneic SCT report patients, who actually received an allogeneic transplantation, thereby neglecting patients, who do not reach the transplantation step, due to toxicity or early relapse. To avoid selection bias as much as possible, we performed this analysis in previously untreated MDS patients selected at time of HLA-typing of patient and siblings. This time was chosen since HLA-typing is only undertaken when the patient is considered to be suitable for allogeneic stem cell transplantation (SCT). In a random population sample about one third of patients are expected to have an HLA-identical sibling donor. In the present analysis about 50% of patients had a donor. This illustrates that pre-selection has occurred to a certain extent. A possible explanation is that transplant centres have reported the majority of patients and patients without siblings are less likely to be referred to a transplant unit.

Our principal finding is that on intention-to-treat basis survival from HLA-typing is not different for patients with and without a matched family donor. In patients with a matched family donor allogeneic SCT is a feasible option. Overall 78% of patients in this group underwent allogeneic transplantation. In this analysis clinicians considered alternative donor transplantation the best alternative for patients without a matched family donor. Fifty patients (42%) were intended for alternative donor SCT and about half of the patients (46%) received this treatment. Clinicians were less likely to proceed to autologous SCT in MDS; this was the intended treatment in only 17% (20 out of 118) of

patients. Since attaining complete clinical remission is a prerequisite for autologous SCT, this treatment option was feasible in 50% of patients. Chemotherapy as only treatment was intended in a minority of patients (10%). In a quarter of patients without a matched family donor, no further intensive treatment was intended.

These data clearly illustrate that selection occurs when different treatment strategies are analysed in a retrospective study. The majority of patients with a matched family donor received the intended treatment, so selection is limited at this stage in the procedure. However, alternative donor SCT was feasible in only 46% of patients, due to limited availability of alternative donors and the duration of the donor search procedure. The dropout frequency of patients intended for autologous stem cell transplantation was 50%. In a recent European study 61% of patients in complete remission after remission-induction chemotherapy proceeded to autologous stem cell transplantation.[14] A similar percentage (62%) was reported in a French study.[17] Although a larger percentage of patients with a matched family donor underwent the intended treatment compared to the patients without a matched family donor, our present analysis fails to demonstrate a survival advantage of patients with a matched family donor over patients without a matched family donor.

The estimated survival rate at 3 years after matched family donor transplantation of 49% is in accordance with the literature. The EBMT registry data reported 41% survival at 3 years in patients with an HLA-identical donor.[18] In a large series from Seattle disease-free survival at 5 years was 38%.[19]

Alternative donor SCT resulted in a 3-year survival rate of 34% in the present analysis. In the EBMT experience survival was 26% after matched unrelated donor transplantation and 31% after non-identical family donor transplantation.[18] The National Marrow Donor Program reported a 2-year survival rate of 30% after unrelated donor SCT.[20]

In this analysis 3-year survival rate after autologous SCT was 67%. In an EBMT study 4-year survival rate from CR was 33% for patients intended for autologous SCT [14] similar to an earlier EBMT report [18] and a French report.[17]

The value of continued chemotherapy and chemotherapy followed by autologous SCT in the treatment of high-risk MDS patients is under investigation in the recently closed CRIANT study (EORTC 06961).[21] In the present analysis 3-year survival rate of patients who received chemotherapy only was 9%. An earlier analysis compared outcome of patients treated at the M.D. Anderson Cancer Center, receiving chemotherapy only, with outcome of patients treated by the EORTC, who received chemotherapy followed by

transplantation. Overall survival at 4 years was 18% for patients receiving chemotherapy only.[22]

Myelodysplastic syndrome differs from AML through the clinical behaviour in some subgroups of MDS, which may have a more indolent course compared to AML. The majority of patients with a protracted course belong to the RA(RS) FAB types. However, some of these RA(RS) patients have profound cytopenias and/or cytogenetic abnormalities, justifying a donor search. The present analysis included RA(RS) patients, who were on clinical grounds potential candidates for allogeneic SCT. Nowadays, the IPSS is a valuable instrument to predict the prognosis of an individual patient. However, when this analysis was designed the IPSS was not yet available and therefore data on cytopenias were not collected for the purpose of this analysis. To overcome this difficulty, we performed a multivariate analysis including the following variables: age, cytogenetic abnormalities, intended treatment and diagnosis of RA(RS) versus other FAB types. We adjusted for the RA(RS) FAB type, since earlier analyses showed that only a blast percentage less than 5% predicted for a better outcome after allogeneic SCT, but no differences were found for a blast percentage over 5%.[11,18] Our analysis confirmed the importance of age and cytogenetic abnormalities on survival. Intended treatment was not prognostic for survival. Outcome of patients with RA(RS) was significantly better compared with other FAB types with a hazard ratio of 0.58 (95% CI 0.38-0.88).

Multivariate analysis in the subgroup of patients with a matched family donor demonstrated the importance of age on survival. Cytogenetic abnormalities appeared prognostic in the entire group, but there was no significant difference in survival for patients with and without an abnormal karyotype. Presumably, the impact of cytogenetic abnormalities is less pronounced due to the graft-versus-MDS effect in the donor group. Intended treatment appeared not prognostic for survival in multivariate analysis.

In patients with a donor intended for allogeneic stem cell transplantation the use of chemotherapy prior to SCT to lower disease burden is still controversial. An important argument against the use of chemotherapy before SCT is the risk of developing life-threatening infections and bleeding complications due to prolonged periods of hypoplasia. In this analysis 78% of patients receiving chemotherapy before SCT reach the transplantation step, compared to 89% of patients who undergo SCT without preceding chemotherapy. Obviously, the FAB type was different for patients intended for allogeneic SCT with or without preceding chemotherapy. The subgroup of 58 patients intended for SCT after chemotherapy consisted of 2 RA(RS) patients, while the subgroup of 47

patients intended for SCT without preceding chemotherapy consisted of 28 RA(RS) patients at time of HLA-typing. To correct for this imbalance we adjusted for the RA(RS) FAB type in multivariate analysis. By doing this, no difference in survival was detected after SCT with or without preceding chemotherapy. This suggests that patients do not benefit from remisson-induction chemotherapy prior to transplantation.

Nevertheless, the definitive answer to this important question can only be given by a prospective study and is currently under investigation in an EBMT trial, randomising MDS patients with less than 20% blasts cells in the bone marrow between immediate SCT and delayed SCT after chemotherapy. In patients with a matched family donor a diagnosis of RA(RS) was not significantly associated with a better survival. This cannot be explained by progression to a more aggressive disease at time of transplantation. The most likely explanation is that the survival advantage after allogeneic SCT is counterbalanced by the treatment-related mortality in these patients. In the present analysis patients with a matched family donor, who do not receive allogeneic stem cell transplantation have a good prognosis. Obviously clinicians are able to identify patients with a more indolent course in whom a wait-and-see policy is justified.

In patients without a matched family donor younger age and a diagnosis of RA(RS) were prognostic for survival. The subgroup of patients with an abnormal karyotype showed a worse survival with a hazard ratio of 1.98. On intention-to treat basis outcome was not different after alternative donor SCT, autologous SCT, chemotherapy only or supportive care, although patients intended for supportive care showed a better survival compared to patients intended for alternative donor SCT with a hazard ratio of 0.36. In this analysis survival after autologous SCT appeared superior when compared to alternative donor SCT, but these patients are highly selected.

The issue of selection, when different treatment strategies in MDS are assessed, is not frequently addressed in the literature. We performed an intention-to-treat analysis in a large European study of high-risk MDS and secondary AML patients, who underwent chemotherapy followed by allogeneic or autologous stem cell transplantation.[23] Patients with an HLA-identical donor were scheduled for allogeneic SCT, patients without a donor for autologous transplantation. This study, confirming our present finding, did not demonstrate a survival advantage for patients with a donor with 4-year survival rates of 33% and 39% respectively for patients with and without a donor.

In 1993 Ljungman et al. performed a similar analysis to determine the optimal post-remission therapy for patients with AML.[24] Eighty-five percent of patients with a donor

received an allograft, while 32% of patients received the intended autologous SCT. In contrast to our analysis, Ljungman et al. demonstrated a survival advantage for patients with an HLA-identical donor over patients without a donor with survival rates at 3 years of 44% and 21% respectively (p=0.02). In the AML-8A trial of the EORTC and GIMEMA patients with a donor showed a better DFS compared to patients without a donor, but no significant differences in overall survival could be detected. In this AML study patients without a donor were randomised between autologous stem cell transplantation and continued chemotherapy.[25] Subsequently the framework of the EORTC/GIMEMA AML-10 was used to investigate the value of allogeneic and autologous stem cell transplantation in patients younger than 46 years in complete remission after remission-induction and consolidation chemotherapy.[26] The 4-year DFS rate of the donor group was superior to that of the no donor group: 52% versus 42% (p=0.04), but survival from CR was comparable, due to a rather high treatment-related mortality (TRM).

In conclusion: this prospective analysis failed to demonstrate a survival advantage of MDS patients with a matched family donor over patients without a matched family donor. In contrast to AML, MDS is a more heterogeneous disease. Therefore, different treatment options like alternative donor transplantation, autologous stem cell transplantation, or high-dose chemotherapy should be considered in patients without a donor, preferentially based on a refined risk profile. This risk profile might be based on cytogenetic abnormalities, number of cytopenias and duration of antecedent disease (antecedent hematologic disorder).

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CHAPTER 3

Chemotherapy only compared to chemotherapy followed by transplantation in high-risk myelodysplastic syndrome and secondary acute myeloid leukemia; two parallel studies adjusted for various prognostic factors

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ABSTRACT

Comparisons of the effectiveness of chemotherapy and transplantation in AML in first complete remission (CR) have focused almost exclusively on patients with de novo disease. Here we used Cox modelling to compare these strategies in patients with MDS and sAML treated by the Leukemia Group of the EORTC or at the M.D. Anderson Cancer Center. All patients were aged 15-60. The 184 EORTC patients received conventional dose ara-C + idarubicin + etoposide for remission induction, and after one consolidation course, were scheduled to receive an allograft, or an autograft if a sibling donor was unavailable. The 215 MDA patients received various high-dose ara-C containing induction regimens, and in CR, continued to receive these regimens at reduced dose for 6-12 months. CR rates were 54% EORTC and 63% MDA (p=0.09). Sixty-five of the 100 EORTC patients who entered CR received a transplant in first CR. Disease-free survival in patients achieving CR was superior in the EORTC cohort, the 4-years DFS rates were 28.9% (s.e. = 4.8%) EORTC vs. 17.3% (s.e. = 3.7%) MDA (p=0.017). Survival from CR was not significantly different in the EORTC and MDA groups, as was survival from start of treatment. After accounting for prognostic factors the conclusions were unchanged. Despite various problems with the analysis discussed below, the data suggest that neither transplantation nor chemotherapy, as currently practised, can be unequivocally recommended for these patients in first CR and that questions as to the superior modality may be less important than the need to improve results with both.

INTRODUCTION

It is established that the prognosis of some patients presenting with myelodysplastic syndromes (MDS) resembles that of patients with AML. Such patients include those classified as having “intermediate-2” or “high” risk MDS by the International Prognostic Scoring System (IPSS).[1] These patients typically have RAEB or RAEB-t, or more rarely CMMoL or RA but with particularly severe cytopenias. These observations have led to the use of AML-type therapy in younger patients meeting these criteria.[2-4]

It is similarly well-known, however, that outcome of AML-type therapy in such patients is poor, and, in particular, is worse than that seen in patients with de novo AML. The poor results in turn raise the question of the value of transplantation in first CR in patients with MDS. Although there have been frequent comparisons between continued chemotherapy and transplantation in this setting in patients with de novo AML, such comparisons are lacking in patients with MDS.[5-7] Rather the literature is dominated by reports of one approach or the other, usually as conducted by a single centre or a single consortium of centres.[8-15]

The purpose of this paper is to formally compare continued chemotherapy and transplantation in first CR in patients under age 60 years with high-risk MDS or secondary AML (sAML), recalling that the response to AML-type therapy in the latter is more reminiscent of that seen in MDS than in de novo AML. Patients were treated at the M.D. Anderson Cancer Center (MDA) or by the Leukemia Group of the European Organisation for Research and Treatment of Cancer (EORTC) in co-operation with SAKK, GIMEMA and EBMT (EORTC study 06921).[16] All patients received AML-type therapy in order to achieve a CR. Subsequently, after an intensive consolidation course, patients treated by the EORTC received an allogeneic transplant, or lacking an HLA-matched sibling donor, an autologous transplant. In contrast, patients treated at M.D. Anderson continued to receive AML-type therapy but without a transplant. Below we report the results of analyses designed to determine, after accounting for important covariates such as age and cytogenetics, which strategy produced superior outcomes in the combined group of 399 patients (184 EORTC, 215 MDA).

PATIENTS AND METHODS

Between November 1992 and March 1997 184 evaluable patients from 35 European centres were entered in the EORTC 06921 study. Two hundred and fifteen comparable patients were treated between January 1990 and December 1997 at MDA. One hundred and thirty-eight of the EORTC patients (75%) had MDS, and 46 secondary AML. One hundred and thirty-one (61%) of the MDA patients had MDS and 84 sAML. AML and the various subtypes of MDS were defined using FAB criteria.[17,18] Patients with AML M3 were excluded. The MDA reported 23 patients with more than 30% blasts in the peripheral blood and less than 30% bone marrow blasts. These patients were classified as peripheral acute leukaemia.[19]

Selection criteria were those used in the EORTC 06921 study. Patients were included if they were aged 15-60 years, had a WHO / Zubrod performance status $\leq$ 2 and had untreated (1) RAEBt, (2) RAEB with more than 10% blasts cells in the bone marrow, (3) other forms of MDS with multiple chromosomal abnormalities and/or profound cytopenias (neutrophil count < 0.5 x 10^9/l and/or platelet count < 20 x 10^9/l), or (4) CMMoL with > 5% blasts cells in the bone marrow or > 16 x 10^9/l neutrophils or > 2.6 x 10^9/l monocytes in the blood. Since MDA used protocols not calling for AML-type therapy to treat CMMoL, MDA patients with CMMoL were not included in the study group. The outcome of CMMoL patients in the EORTC study was not different from that of the RAEBt patients and therefore these patients were not excluded from the analysis. Patients with secondary AML (sAML), i.e. AML supervening after overt MDS or after an antecedent hematological disorder (AHD) of more than 6 months duration or after prior chemotherapy and/or radiotherapy for another, presumably cured, disease were included. Criteria for an AHD included any of the following: hemoglobin < 12 g/dl, platelet count < 150 x 10^9/l, neutrophil count < 1.5 x 10^9/l or white blood count (WBC) > 20 x 10^9/l. Many patients in whom a local physician first documented such abnormalities did not have bone marrow examined until referred to the treating centre (EORTC or MDA). Therefore, an AHD was said to be present when the blood count abnormality was first documented regardless of whether a marrow was done simultaneously. Karyotyping was done using standard techniques and criteria.[20] A normal karyotype, minus Y, inv(16) or t(8;21) were considered to convey a better prognosis, abnormalities involving chromosomes 5 and/or 7 a worse prognosis and other abnormalities an intermediate prognosis.

Treatment in EORTC 06921 (Table 1)

Remission-induction in the 06921 study consisted of conventional dose ara-C, idarubicin and etoposide (ICE, Table 1). In case of a partial response a second remission-induction course was given. Patients in CR received one consolidation course consisting of ara-C combined with mitoxantrone (NOVIA, Table 1). HLA family typing was initiated at the onset of remission-induction therapy, with the intention of allografting patients in first CR after the course of NOVIA if they had a compatible sibling donor. All patients without a donor were scheduled for autologous bone marrow transplantation or peripheral blood stem cell transplantation. In the initial phase of the study autologous bone marrow cells were used. Since the hematological recovery after transplantation was very prolonged, the protocol was adapted and bone marrow stem cells were replaced by peripheral blood stem cells mobilized with filgrastim during the recovery phase of the consolidation course. One of two conditioning regimens for allogeneic BMT and autologous stem cell transplantation was used: cyclophosphamide 60 mg/kg/day on 2 consecutive days and total body Irradiation (TBI) 12 Gy in four to six fractions over 2 or 3 days. The alternative regimen was busulfan 4 mg/kg/day on 4 consecutive days in combination with cyclophosphamide 60 mg/kg/day on 2 days.

Prophylaxis for GVHD following allogeneic BMT consisted of cyclosporin A alone or in combination with methotrexate.

The minimally required number of nucleated cells was 2 x 10^8/kg or 2 x 10^4 CFU-GM/kg for autologous bone marrow transplantation and 10 x 10^4 CFU-GM/kg or 2 x 10^6 $CD34^+$ cells/kg for peripheral blood stem cell transplantation. All transplants were unpurged.

MDA Treatments (Table 1)

All remission-induction regimens used at the MD Anderson contained high dose ara-C alone (N=5 patients) or combined with (1) anthracycline (N=146: daunorubicin 15, idarubicin 131), (2) fludarabine (N=135) with (N=92) or without (N=43) idarubicin, or (3) topotecan (N=21). Growth factors were used in 136 patients during and after chemotherapy (GM-CSF: 15, G-CSF: 121). Once in CR patients received post-remission therapy of similar type but at a lower dose intensity every 5-6 weeks for 6-12 months.

Table 1. Treatment schedules (N = number of patients).

EORTC		
	ICE (184)	idarubicin 10 mg/m^2/d iv days 1, 3, 5, ara-C 100 mg/m^2/d iv days 1-10 cont. infusion, etoposide 100 mg/m^2/d iv days 1-5
	NOVIA	ara-C 2 x 500 mg/m^2/d iv days 1-6, mitoxantrone 12 mg/m^2/d iv days 4-6
MDA		
	IA (39)	idarubicin 12 mg/m^2/d iv days 1, 2, 3, ara-C 1.5 g/m^2/d iv days 1-4 cont. infusion
	FA (43)	fludarabine 30 mg/m^2/d iv days 1-5, ara-C 2 g/m^2/d iv days 1-5
	FAI (92)	+ idarubicin 12 mg/m^2/d iv days 2, 3, 4
	TA (21)	topotecan 1.25 mg/m^2/d iv days 1-5, ara-C 1 g/m^2/d iv days 1-5
	DA (15)	daunorubicin 50 mg/m^2/d iv days 1-3, ara-C 1.5 g/m^2/d iv days 1-4 cont. infusion
	A (5)	ara-C 1.5 g/m^2/d iv days 1-4 cont. infusion

Definitions

CR was defined conventionally. Response in patients not achieving CR was called either "resistant" or "early death". Disease was considered resistant if the post-day 28 marrow showed > 5% blasts in a marrow that was $\geq$ 20% cellular. We did not distinguish between failure to ever meet these criteria and regrowth of disease after meeting them prior to achievement of CR. Disease was also considered resistant if the marrow remained hypoplastic for more than 42 days from the start of treatment, because of the likelihood that had CR been achieved it would have been very transient.[21] Early death was said to have occurred if death occurred before day 28 or between days 28 and 42 in patients in whom the marrow between these dates was < 20% cellular with < 5% blasts.

Statistical analysis

The duration of survival was calculated from the date of start of treatment until death, whatever the cause. For patients who achieved CR after induction, the disease-free survival was calculated from the date of first CR until the date of first relapse or until death in CR. The duration of survival of remitters corresponds to the time from first CR to the date of death. The actuarial curves were computed using the Kaplan-Meier technique.[22] The Cox Proportional Hazards Model and the Wald test have been used to determine the prognostic importance of several factors regarding the time to event outcomes (DFS, survival from CR, overall survival) and to obtain estimates of the hazard

ratios and the corresponding 95% confidence intervals (CI).[22] All analyses were performed according to the intent-to-treat principle.

A total of 325 events are required to detect a 10% difference (20% versus 30%) in terms of DFS at 4 years between the two studies (alpha=5%, beta=20%). This corresponds to a hazard ratio of 0.75. A lower number of events (i.e. deaths) and a smaller difference in terms of survival from CR, provides a smaller statistical power for the statistical comparison between the outcome of the studies.

The linear logistic model has been used to assess the prognostic importance of several factors, including the study (EORTC or MDA), for reaching CR after induction courses.[23] The Wald test has been used to obtain the p-value and assess the 95% confidence interval of the odds ratio. The distribution of patient characteristics in the two studies has been compared using the usual chi-square test.

RESULTS

Patients

Patient characteristics are shown in Table 2. MDA patients were older and more likely to have a poor performance status and sAML, while EORTC patients were more likely to have MDS. Sixteen CMMoL patients were included in the EORTC study. The outcome of these patients was similar to the outcome of RAEBt patients, with 4-year survival rates of 29% for CMMoL and 32% for RAEBt respectively. Excluding CMMoL patients from the analysis would emphasise the imbalance between the percentage RAEBt patients in the MDA (71%) and EORTC (43%) study. Abnormalities of chromosomes 5 and/or 7 denoting particularly poor prognoses were more common at MDA. The hemoglobin level and platelet count at the start of therapy were lower in MDA patients, while the white blood count (WBC) was higher. The median follow-up for EORTC patients was 3.6 years and for MDA patients 3.0 years.

Table 2. Patient characteristics.

		EORTC (N)	%	MDA (N)	%	P
Cytogenetics	Good	70	38	77	36	<0.001
	Intermediate	42	23	50	23	
	Bad	39	21	79	37	
	ND/IM	33	18	9	4	
Age (years)	< 35	38	21	39	18	0.038
	35-45	40	22	47	22	
	46-55	72	39	64	30	
	> 55	34	18	65	30	
PS	0 or 1	164	89	162	76	<0.001
	2	19	11	53	24	
Prior therapy	No	144	79	135	63	<0.001
	Yes	38	21	80	37	
AHD (months)	< 6	130	71	135	67	0.22
	≥ 6	54	29	75	32	
Disease	MDS	138	75	131	61	0.003
	sAML	46	25	84	39	
MDS FAB	RA	7	5	-	-	0.01[a]
	RARS	1	1	-	-	
	RAEB	54	39	38	29	
	RAEBt	60	43	93	71	
	CMMoL	16	12	-	-	
BM blasts (%)	< 5	9	5	9	4	0.296
	5-10	22	12	37	17	
	11-20	58	32	55	26	
	21-30	46	25	52	24	
	> 30	45	24	61	28	
Hb (g/dl)	< 10	136	74	185	86	0.004
	≥ 10	48	26	30	14	
WBC (x 10^9/l)	< 1	8	4	16	7	0.019
	1-2.9	76	41	60	28	
	3-9.9	59	32	71	33	
	≥ 10	41	22	68	32	
Platelets (x 10^9/l)	< 50	83	45	134	62	0.003
	50-99	58	32	45	21	
	≥ 100	43	23	36	17	

Cytogenetics: Good: NN, -Y, inv(16), t(8,21); Bad: -5, 5q-, -7, 7q- ; Intermediate: +8, 11q, other; ND/IM: not done/insufficient metaphases; AHD: antecedent hematologic disorder; prior therapy: earlier radiotherapy or chemotherapy for a (non-)malignant disease; PS: performance status.
[a]: Considering RA, RARS, RAEB versus RAEBt, CMMoL

Response Rates

CR rates were 54% (100/184) in the EORTC and 63% (135/215) at MDA (p=0.09). The estimated odds ratio was 0.71 (=(100/84)/(135/80)) with a 95% confidence interval (CI) of 0.47-1.05. Over 85% of the CRs occurred after the first course of treatment. The lower response rate in the EORTC reflected a higher rate of resistance (30% versus 17%), with rates of early death of 16% EORTC and 19% MDA.

Outcome after CR

Thirty-nine of the 100 EORTC patients who achieved a CR had a compatible sibling donor. Twenty-eight of these 39 received an allograft. Thirty-six out of 61 patients without a donor were autografted (19 autologous bone marrow transplantation and 17 peripheral blood stem cell transplantation). One additional patient underwent a matched unrelated donor transplantation in first CR after the consolidation course. Thirty-five patients were not transplanted in first CR. Two patients died due to toxicity of the consolidation course, 26 patients showed an early relapse and 7 patients went off-study due to toxicity or treatment refusal.

The outcome of patients with an HLA-identical donor (scheduled for allogeneic BMT) did not significantly differ from the outcome of patients without an HLA-identical donor (scheduled for autologous stem cell transplantation). The 4-year DFS rates in the group with or without an HLA-identical donor were 31% (s.e. = 7.9%) and 27% (s.e. = 6.1%), respectively. Therefore, for the purpose of this study, we did not discriminate between allogeneic and autologous transplantation and considered it as one strategy.

DFS from time of CR was longer for the EORTC patients as compared to MDA patients (p=0.017, Figure 1). The median DFS was 1.0 years (EORTC) versus 0.8 years (MDA), the 4-year DFS rate estimates were 28.9% (s.e. = 4.8%) versus 17.3% (s.e. = 3.7%) and the hazard ratio was 0.69 with a 95% confidence interval (CI) of 0.50-0.95. Among EORTC patients who achieved CR, 32% remained alive in first CR, 52% had disease recurrence and 16% died in first CR. The corresponding figures at MDA were 20%, 72% and 8%.

Figure 1. Disease-free survival of patients who achieved complete remission by study.

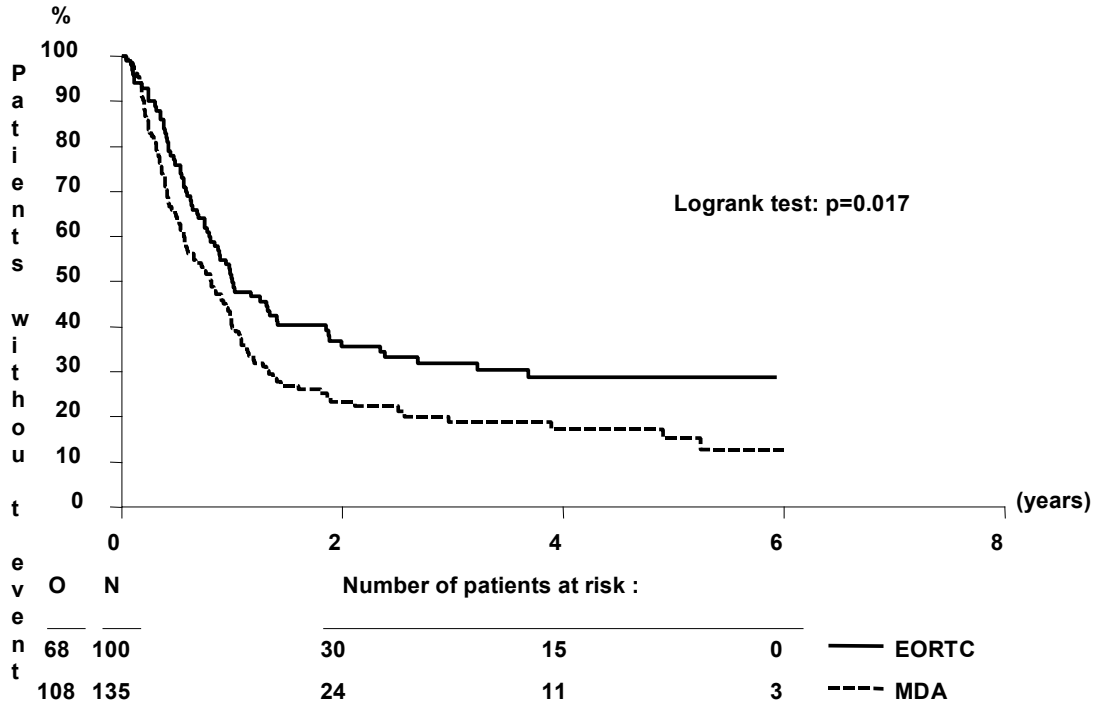
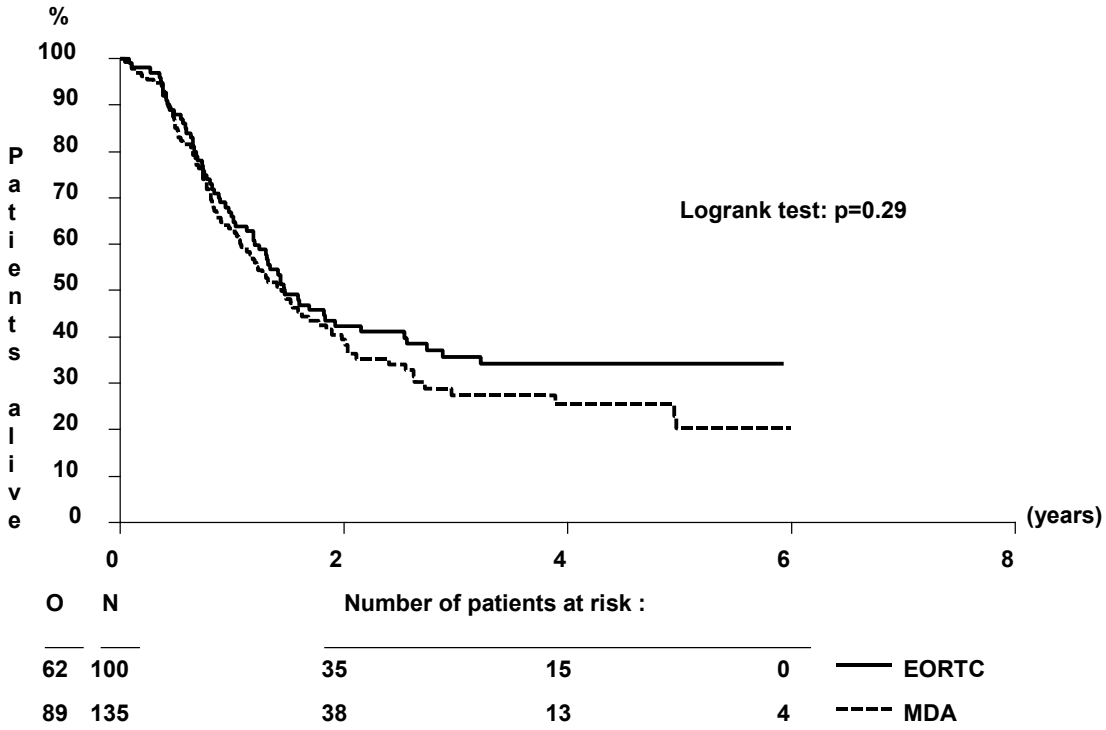


Figure 2. Survival of patients from complete remission by study.

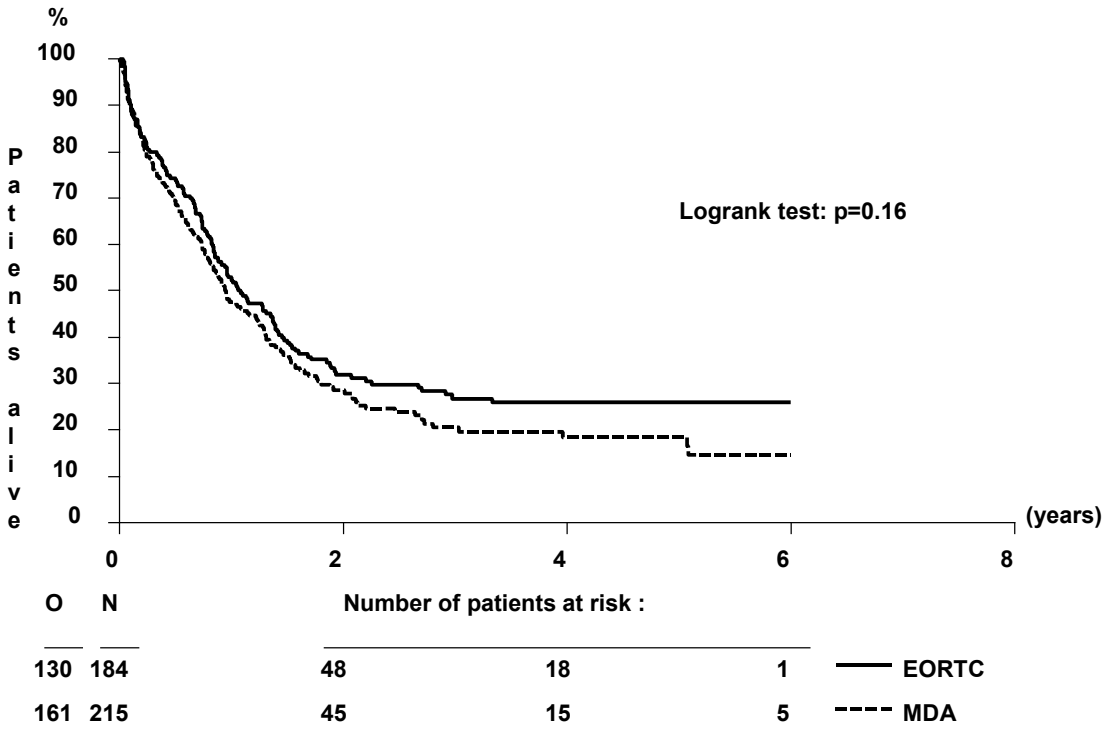


Survival

Survival from CR was not statistically different (p=0.29) between the EORTC and MDA patients (Figure 2). The median survival from CR was 1.5 versus 1.4 years, the 4-year survival from CR rate estimates were 34.4% (s.e. = 5.1%) versus 25.5% (s.e. = 4.6%), the estimated hazard ratio was 0.84 with a 95% CI of 0.61-1.16.

Survival from the start of treatment was also similar in EORTC and MDA (Figure 3). The median survival was 1.08 vs. 0.95 years, the 4-year survival estimates were 26.0% (s.e. = 3.5%) versus 18.4% (s.e. = 3.2%), the estimated hazard ratio was 0.85 with a 95% CI of 0.61-1.20.

Figure 3. Survival of patients from start of treatment by study.



Prognostic factors: univariate analyses

The following variables appeared to be prognostic factors for overall survival considering all 399 patients: cytogenetics (4 categories: good, intermediate, bad prognostic, not done/insufficient metaphases), age as a continuous variable, platelet count as a categorial variable (< 50, 50-99, $\geq$ 100 x 10^9/l), WBC as a continuous variable, hemoglobin as a categorial variable (Hb < 10 g/dl vs. $\geq$ 10 g/dl) and performance status (WHO / Zubrod 0, 1 versus 2).

Important prognostic factors for disease-free-survival were cytogenetics, hemoglobin and disease category (RA, RARS, RAEB vs. RAEBt, CMMoL vs. sAML).

Multivariate analyses

The question remained whether the different outcomes in the EORTC and MDA cohorts (higher CR rate at MDA versus superior DFS, although comparable survival, once in CR in the EORTC) reflected the different treatment regimens (ICE/NOVIA and then transplant in CR by the EORTC vs. higher doses of ara-C in induction, continued chemotherapy without transplant in CR at the MDA) or, rather differences in the patients treated (e.g. a greater frequency of -5/-7 at MDA). We addressed this question by examining which factors ("covariates") independently predicted the various outcomes (CR, DFS in CR, survival in CR, survival). We considered the following covariates: treatment site (EORTC or MDA), and the ones which appeared of prognostic importance in univariate analyses (cytogenetics, disease category, WBC, age, platelet count, hemoglobin and performance status).

A linear logistic regression model showed (Table 3) that treatment site (EORTC or MDA) remained important for achievement of CR.

Table 3. Results of linear logistic model for predicting the CR.

Variable[a]	Odds ratio Estimate	95% CI	P-value
Cytogenetic			
Good risk	1.89	1.22-2.94	0.004
Platelets			
50-99	2.14	1.27-3.57	0.004
$\geq$ 100	1.84	1.06-3.20	0.030
Study			
EORTC	0.60	0.40-0.92	0.019

[a]: Baseline category for cytogenetic risk group comprised all patients without good cytogenetic features, for platelets was < 50 x 10^9/l, for study was MDA

The Cox's model indicated (Table 4) that after accounting for relevant covariates, treatment in the EORTC was associated with longer DFS, while survival in CR and overall survival were not significantly influenced by treatment site.

Table 4. Results of Cox's proportional hazards model for several endpoints.

Variable[a]	DFS			Survival from CR			Survival		
	Hazard Ratio[b]	95% CI	P-value	Hazard Ratio[b]	95% CI	P-value	Hazard Ratio[b]	95% CI	P-value
Cytogenetic									
Bad risk	2.04	1.35-3.09	0.0008	2.40	1.54-3.73	0.0001	2.02	1.47-2.77	<0.0001
Good risk	0.46	0.31-0.69	0.0001	0.52	0.34-0.81	0.003	0.63	0.46-0.87	0.0049
ND/IM	0.69	0.37-1.29	0.24	0.69	0.35-1.38	0.30	1.00	0.64-1.58	0.98
WBC							1.01	1.00-1.02	0.0005
Age							1.02	1.01-1.03	0.0018
Platelets									
50-99							0.68	0.51-0.91	0.01
$\geq$ 100							0.87	0.64-1.19	0.39
Hb $\geq$ 10	0.58	0.39-0.85	0.005	0.64	0.42-0.98	0.04	0.68	0.50-0.93	0.02
Study									
EORTC	0.69	0.50-0.95	0.024	0.85	0.61-1.20	0.36	0.99	0.77-1.26	0.92

ND/IM, not done/insufficient metaphases

[a] : Baseline category for variable cytogenetic was intermediate risk, for platelets was < 50 x 10^9/l, for hemoglobin was < 10 g/dl, for study was MDA. White blood count (WBC x 10^9/l) and age (years) were considered as continuous variables

[b]: A value < 1 indicates that the outcome is better for that category in comparison with the baseline

DISCUSSION

The relative merits of chemotherapy versus transplantation once patients with AML achieve CR have been debated for years. The discussion has focussed primarily on patients with de novo AML given that patients with MDS or sAML have often been ineligible for AML trials. Recently however, the possibility of including such patients in protocols examining AML-type therapy has gained attention, and hence questions about the relative benefits of various treatments for such patients have arisen. These questions prompted this paper, which we believe is the first to address the comparative benefits of chemotherapy and transplantation in MDS and sAML, recalling that these disease entities are more closely linked to each other than to de novo AML.

In our study multivariate analyses revealed several independent prognostic factors for outcome. For disease-free-survival not only a treatment including transplantation, but also the absence of cytogenetic abnormalities and a hemoglobin level of at least 10 g/dl predicted for a better outcome. Since most institutions handle a cut-off value of 10 g/dl or less for a blood transfusion this value designates patients who are transfusion independent at diagnosis.

For overall survival cytogenetics was also the most important independent prognostic factor. In addition several other factors had prognostic value. Increasing age was negatively associated with survival. A normal white blood cell count and a platelet count between 50-100 x 10^9/l predicted independently for a better survival and patients with a hemoglobin of at least 10 g/dl at the start of therapy also showed a better survival. Recently, various scoring systems for the prognosis of MDS patients were developed.[1,24-29] Several authors stressed the importance of a normal WBC and hemoglobin of at least 10 g/dl.[24-26] Morel et al. included cytogenetics in their scoring system.[27,28] In 1997 Greenberg et al. used the data of previously reported studies to generate an international prognostic scoring system (IPSS).[1] They distinguished 4 risk groups based on cytogenetics, number of cytopenias and bone marrow blasts. However, the majority (75%) of patients in the IPSS study was older than 60 years and these patients have been treated with supportive care only or low intensity regimens.

Our principal findings are that a strategy offering allografting in CR, or autografting if a compatible donor was unavailable appeared to produce longer disease-free survival, but similar survival than chemotherapy alone. Survival from start of treatment considering all 399 patients was not significantly influenced by the two different treatment strategies.

These findings are thus reminiscent of those found when emphasis has been placed on patients with de novo AML.

Several points must be stressed. First and perhaps most important, the value of chemotherapy versus transplantation as post-remission treatment was raised neither prospectively nor in the context of a randomized clinical trial. The EORTC study included high-risk MDS patients only and for the present analysis successive MDA patients were retrospectively selected on the basis of the EORTC eligibility criteria. The EORTC cohort included eight RA(RS) patients with multiple chromosome abnormalities and/or profound cytopenias and 16 CMMoL patients with bad prognostic features. Since MDA used protocols not calling for AML-like therapy to treat CMMoL, MDA patients with CMMoL were not included in the study group. RA(RS) patients with bad prognostic features were neither treated according to these protocols in MDA. At the time of initiating the present analysis the new WHO classification was not yet issued.[30] This classification considers CMMoL rather as a myelodysplastic / myeloproliferative disease than a myelodysplastic syndrome. However, when we excluded the CMMoL patients from the EORTC cohort the overall results of the EORTC and the comparison with the MDA remained practically unchanged. The overall survival rate at 4 years of the EORTC cohort including the CMMoL patients was 26.0% compared to 25.9% by excluding them. The prognostic importance of the other factors did not change drastically. Excluding the CMMoL patients would further increase the imbalance of the WBC distribution. Similarly, the DFS rate at 4 years was 28.9% including the CMMoL patients compared to 28.8% by excluding them. Finally, the survival rate from CR was 34.4% including CMMoL patients and 34.7% by excluding them (data not shown). So our results remained unchanged, if we had excluded the CMMoL patients.

Secondly, although the multivariate regressions may have accounted for differences in the distribution of known covariates (e.g. age) between the MDA and EORTC cohorts, it is very difficult to ascertain whether these cohorts differed with regard to potentially important but unknown covariates. For example, it is impossible to ascertain whether the proportion of patients who were eligible for the studies described here but were not entered was similar in the EORTC and at MDA.

A third difficulty is that we consider “transplantation” as one strategy regardless of whether patients received an allograft or an autograft and we have also assumed that results were equivalent at all EORTC centres contributing data to this analysis. Similarly, we have assumed that the various MDA chemotherapy regimens were approximately identical. A

fourth difficulty is that the EORTC and MDA induction regimens differed, with the latter employing higher doses of ara-C. Several reports have noted that the therapy given during induction can influence outcome in CR.[31] For example, it can be argued that the higher CR rate produced by the MDA induction regimens, with these higher rates reflecting a lower "resistance" rate, would tend to make the MDA post-remission treatment strategy appear better a priori. It could also be contended, however, that because the MDA induction regimens produced CRs in patients who would not have achieved CR with the "ICE" regimen, the MDA post-remission strategy would appear inferior a priori given that the MDA patients were more likely to relapse perhaps due to factors that cannot currently be specified ("latent variables").

A final difficulty is that obviously we cannot speak to the strategy of transplantation at diagnosis rather than in CR. Several of these difficulties will be addressed in the ongoing prospective randomized European study (EORTC 06961) comparing high dose cytarabine with peripheral blood stem cell transplantation as post-consolidation treatment after a common remission-induction and consolidation course.

Pending results of this trial, it appears that our results lend support to either strategy. Supporters of a transplant strategy can claim that this strategy appears to unequivocally lengthen disease-free survival in CR. Supporters of a chemotherapy strategy can point to the absence of a major effect of transplantation on survival. Perhaps then the important question may not be which strategy is superior, but rather whether either can be made to produce better results.

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CHAPTER 4

The presence of an HLA-identical sibling donor has no impact on outcome of patients with high-risk MDS or secondary AML (sAML) treated with intensive chemotherapy followed by transplantation: results of a prospective study of the EORTC, EBMT, SAKK and GIMEMA Leukemia Groups (EORTC study 06921)

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ABSTRACT

This report used the framework of a large European study to investigate the outcome of patients with and without an HLA-identical sibling donor on an intention-to-treat basis. After a common remission-induction and consolidation course, patients with an HLA-identical sibling donor were scheduled for allogeneic transplantation and patients lacking a donor for autologous transplantation. In all, 159 patients alive at 8 weeks from start of treatment were included in the present analysis. In total, 52 patients had a donor, 65 patients did not have a donor and in 42 patients the availability of a donor was not assessed. Out of 52 patients, 36 (69%) with a donor underwent allogeneic transplantation (28 in CR1). Out of 65 patients, 33 (49%) received an autograft (27 in CR1). The actuarial survival rates at 4 years were 33.3% (s.e. = 6.7%) for patients with a donor and 39.0% (s.e. = 6.5%) for patients without a donor (p=0.18). Event-free survival rates were 23.1% (s.e. = 6.2%) and 21.5% (s.e. = 5.3%), respectively (p=0.66). Correction for alternative donor transplants did not substantially alter the survival of the group without a donor. Also, the survival in the various cytogenetic risk groups was not significantly different when comparing the donor versus the no-donor group. This analysis shows that patients with high-risk myelodysplastic syndrome and secondary acute myeloid leukemia may benefit from both allogeneic and autologous transplantation. We were unable to demonstrate a survival advantage for patients with a donor compared to patients without a donor.

INTRODUCTION

The myelodysplastic syndromes (MDS) form a heterogeneous group of diseases characterised by a hypercellular bone marrow and peripheral cytopenias, due to ineffective hematopoiesis.

The natural history of MDS is variable and depends on the stage of the disease.[1,2] Numerous classification systems have been used to predict outcome of MDS patients. In 1997, the International Prognostic Scoring System (IPSS) was developed based on the number of bone marrow blasts, number of cytopenias and the presence of cytogenetic abnormalities.[3]

In elderly patients, supportive care is the mainstay of therapy. For young patients with high-risk MDS, allogeneic bone marrow transplantation (BMT) is a curative option. Unfortunately, an HLA-identical sibling is only available in one-third of patients. Disease-free survival (DFS) after allogeneic BMT, ranges between 35% and 45%.[4-10] Young patients (less than 40 years) [11] and patients with a low marrow blast count (less than 5%) [9,12] have a better prognosis. The reported transplant results are likely to be influenced by selection of patients in a good clinical condition and excluding patients with an early relapse.

For young patients (less than 60 years) with high-risk MDS who lack an HLA-identical donor, intensive chemotherapy results in complete remission (CR) rates of 15-65%.[13-17] The median remission duration is usually short because of a high incidence of early relapses. Therefore, the role of autologous stem cell transplantation (SCT) after remission-induction and consolidation chemotherapy has been investigated.[18-20] The EBMT registry reported 79 patients with MDS, secondary acute myeloid leukemia (sAML) or therapy-related AML (tAML) who received an autograft in first CR after chemotherapy. The 2-year survival, DFS and relapse rate were 39%, 34% and 64%, respectively.[19]

Until now there have been no reports comparing allogeneic transplantation and autologous transplantation. The optimal approach to evaluate the superiority of allogeneic BMT to autologous SCT is to compare these treatments in a randomised trial. For practical reasons this is not feasible.

The Leukemia Groups of the EORTC, EBMT, GIMEMA and SAKK conducted a prospective multi-centre trial for bad prognostic MDS and AML secondary to MDS (sAML) in patients less than 60 years. The overall results of this study have been reported recently.[21] After a common remission-induction and consolidation course, patients with an

HLA-identical sibling donor were scheduled for allogeneic BMT and patients without a donor for autologous SCT. Since all patients with an HLA-identical sibling donor were scheduled for allografting, this approach mimics a kind of randomisation by genetic chance. We decided to analyse the data of the above-mentioned study on an intention-to-treat basis. For the present analysis 159 patients who were alive at 8 weeks from start of treatment were included. The main focus of this analysis was to address the question as to which subgroup of patients without a donor would achieve sustained DFS without allogeneic SCT.

PATIENTS AND METHODS

Patient's selection criteria

Patients were included if they were aged 16-60 years and had untreated (1) RAEBt, (2) RAEB with more than 10% blasts cells in the bone marrow, (3) other forms of MDS with multiple chromosomal abnormalities, and/or profound cytopenias defined as neutrophil count <0.5 x 10^9/l and/or platelet count <20 x 10^9/l, (4) CMMol with > 5% blasts cells in the bone marrow or with a neutrophil count >16 x 10^9/l or a monocyte count > 2.6 x 10^9/l in the blood, and (5) secondary AML supervening after overt MDS of more than 6 months duration. Patients with AML M3 were excluded.

Exclusion criteria were the following: patients aged less than 16 years or more than 60 years, patients already treated for MDS or AML by intensive chemotherapy and/or radiotherapy, treatment with biological response modifiers and/or low dose cytarabine within 2 months prior to entry, WHO performance status 3 or 4, no informed consent, or life expectancy less than 3 months.

For the present analysis, only patients alive at 8 weeks from the start of treatment were selected since these patients were candidates for transplantation and the availability of an HLA-identical sibling donor should be known by this time. The impact of a donor is supposed to influence the outcome only from 8 weeks after start of treatment if the patient is treated according to the protocol.

Prognostic factors

Cytogenetic analysis was to be performed in all patients at the start of treatment using standard techniques and criteria.[22] Patients were subdivided into different prognostic subgroups based on cytogenetics, number of cytopenias and percentage of bone marrow

blasts according to criteria of the IPSS [3] and according to the prognostic cytogenetic criteria as described by Keating et al.[23]

Design of study protocol

The remission-induction course (ICE) consisted of idarubicin 10 mg/m^2/day by intravenous push injection on days 1, 3, 5 combined with cytarabine 100 mg/m^2/day continuous intravenous infusion from days 1 to 10 and etoposide 100 mg/m^2/day 1h intravenous infusion from days 1 to 5. In case of a partial response, a second remission-induction course was scheduled.

Patients entering CR after one or two remission-induction courses received a consolidation course (NOVIA) consisting of cytarabine 500 mg/m^2 2h intravenous infusion every 12 hours from days 1 to 6 combined with mitoxantrone 12 mg/m^2/day 30 min intravenous infusion on days 4-6.

HLA typing of patient and family was initiated at the onset of induction therapy if patients were younger than 50 years (or younger than 55-60 years according to the policy of the centre). In case of an HLA-A, -B, -DR identical MLC nonreactive sibling, the patient was proposed for allografting after recovery from the consolidation course.

All patients without an HLA-identical sibling were scheduled for autologous SCT. In the initial phase of the study, autologous BMT was performed. Since hematological recovery was slow, the protocol was adapted and autologous BMT was replaced by autologous peripheral blood SCT mobilised with filgrastim (dose 300 μg/day s.c.) from day 20 after start of the consolidation course until completion of the stem cell aphereses.

Two conditioning regimens for allogeneic BMT and autologous SCT were recommended: cyclophosphamide 60 mg/kg/day on two consecutive days and total body irradiation 12 Gy in four to six fractions over 2 or 3 days. The alternative regimen was busulphan 4 mg/kg/day on four consecutive days in combination with cyclophosphamide 60 mg/kg/day on 2 days.

Prophylaxis of graft-versus-host disease (GVHD) following allogeneic BMT consisted of cyclosporin A alone or cyclosporin A in combination with methotrexate. T-cell depletion of the allografts may be performed according to the policy of the centres.

The minimally required number of nucleated cells was 2 x 10^8/kg or 2 x 10^4 CFU-GM/kg for autologous bone marrow transplantation and 10 x 10^4 CFU-GM/kg or 2 x 10^6 CD34$^+$ cells/kg for peripheral blood SCT. All transplants were unpurged.

Definitions

AML evolved from myelodysplasia was defined as sAML. AML after chemotherapy or radiotherapy for an earlier disease was defined as tAML.

CR was defined as absence of clinical manifestations of leukemia and less than 5% blasts cells in a normocellular marrow with normal morphology. The peripheral blood neutrophil count should be $\geq$ 1.5 x 10^9/l. and platelet count more than 100 x 10^9/l. Normalisation of cytogenetic abnormalities was not a prerequisite for CR.

Partial remission (PR) was characterised by normocellular bone marrow containing less than 25% blasts and 50% or more decrease of blast percentage from pre-therapeutic levels with normal peripheral blood count without circulating blasts.

Statistical analysis

All patients were registered prospectively at the EORTC Data Center in Brussels. The duration of survival was calculated from the date of start of treatment until death, by whatever cause. The DFS was the time from CR until relapse or death in CR. The event-free survival (EFS) was the time from CR until relapse or death in CR; patients who did not reach complete remission after the induction were considered events at time 0. The actuarial curves were computed using the Kaplan-Meier technique and the standard errors (s.e.) of the estimates were obtained via the Greenwood formula.[24] The estimates of the incidence of death in first CR and of death of other cause were obtained using the cumulative incidence method, where the risk of death in CR and death of other cause were considered as competing risks.[24] The same method has been used for estimating the cumulative incidence of relapse and of death in CR in patients who reached CR. The Cox Proportional Hazards Model has been used to determine the prognostic importance of several factors regarding survival and to obtain estimates of the hazard ratio (HR) and the corresponding 95% confidence interval (CI).[24] All analyses were performed according to the intent-to-treat principle.

The relationship between donor availability variable and patient characteristics or outcome has been tested for significance using the usual chi-square test. For ordered variables, like WBC or response to induction, the chi-square test for linear trend has been used.

RESULTS

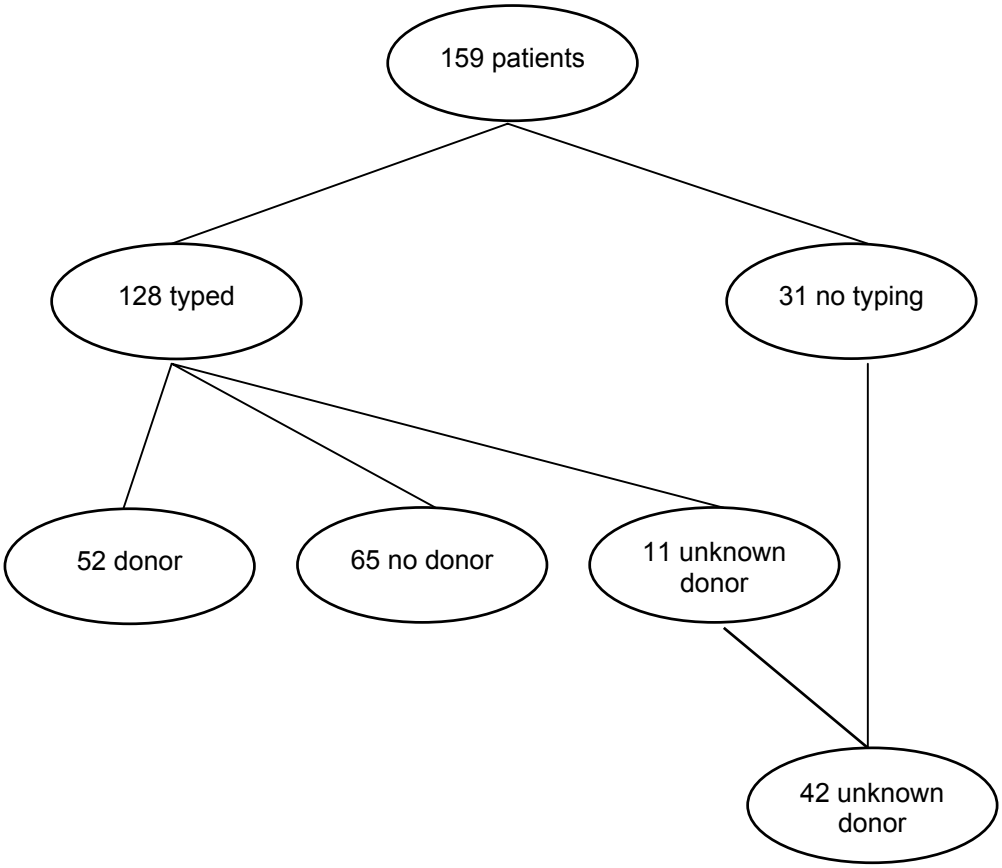
Overall results

A total of 197 patients from 35 institutions were registered between December 1992 and April 1997. Data from 184 patients were evaluable. The median age was 47 years (range 16-60 years). Of the patients, 138 (75%) had MDS, and 46 secondary AML. A total of 38 patients developed MDS or AML after treatment with chemotherapy or radiotherapy for an earlier disease (tMDS/tAML). Out of 184 patients, 100 (54%) reached complete remission after one or two courses of chemotherapy. In all, 29 patients (16%) died during remission-induction chemotherapy. The median survival of all patients was 13 months, and the actuarial survival rate at 4 years was 26% (s.e. = 3.5%). The median actuarial follow-up for all patients was 3.6 years. Of 29 patients, 25 died before day 56 after start of treatment. The present analysis represents all 159 patients who were alive at 8 weeks from start of treatment.

Donor availability

Out of 159 patients, 122 had at least one living sibling; 11 patients had no sibling. The availability of a sibling was not known for 26 patients. HLA-typing was performed in 128 out of 159 patients (81%). Of the 128 patients typed, 52 had an HLA-identical sibling and 65 patients did not. In 11 additional patients, typing of the patient was performed, but family typing was not performed. Nine of these 11 patients were aged over 50 years. In 31 of 159 patients no typing was performed. Reasons for not typing were no sibling available (N=3), too old (N=15), hypoplastic death (N=2), insufficient response (N=6), toxicity (N=2), patient refusal (N=2), unknown (N=1). Overall in 42 patients the availability of a donor was unknown (Figure 1).

Figure 1. Donor availability of 159 patients alive more than 8 weeks from start of treatment.



The patient characteristics according to the availability of a donor are given in Table 1. The median age of the patients with and without a donor was 43 years. Patients were subdivided in the cytogenetic risk groups as proposed by Greenberg et al.[3] Of the patients, 52% with a donor and 49% without a donor showed intermediate and poor prognostic cytogenetic features. Cytogenetic risk group was unknown in 15% of patients with a donor and 12% of patients without a donor. The majority of MDS patients with a donor (76%) and without a donor (75%) belonged to the intermediate-2 and high-risk group of the IPSS.

Table 1. Patient characteristics according to donor availability.

	Donor N=52	No donor N=65	
Variable	N (%)	N (%)	P-value
Disease			
MDS	38 (73.1)	53 (81.5)	0.38
sAML	14 (26.9)	12 (18.5)	
Age at start (yr.)			
< 50	40 (76.9)	50 (76.9)	0.83
≥ 50	12 (23.1)	15 (23.1)	
FAB			
RA(RS)	2 (3.8)	4 (6.2)	0.73
RAEB	16 (30.8)	19 (29.2)	
RAEBt	16 (30.8)	26 (40.0)	
CMMoL	4 (7.7)	4 (6.2)	
sAML	14 (26.9)	12 (18.5)	
WBC (x 10^9/l)			
< 3	23 (44.2)	27 (41.5)	0.75
3-10	18 (34.6)	23 (35.4)	
≥ 10	11 (21.2)	15 (23.1)	
Cytogenetics IPSS[a]			
Good	17 (32.7)	25 (38.5)	0.81
Intermediate	15 (28.8)	15 (23.1)	
Poor	12 (23.1)	17 (26.2)	
ND/IM	8 (15.4)	8 (12.3)	
Cytogenetics Keating[b]			
Good	4 (7.7)	2 (3.1)	0.60
NN, -Y	16 (30.8)	25 (38.5)	
Other	11 (21.2)	14 (21.5)	
Poor	13 (25.0)	16 (24.6)	
ND/IM	8 (15.4)	8 (12.3)	
IPSS (MDS only)			
Low	0 (0.0)	1 (1.9)	0.78
Intermediate-1	4 (10.5)	5 (9.4)	
Intermediate-2	11 (28.9)	20 (37.7)	
High	18 (47.4)	20 (37.7)	
Unknown	5 (13.2)	7 (13.2)	

[a]: Good: NN or -Y, 5q-, 20q- only; poor: chromosome 7 abnormalities, complex (≥ 3) abnormalities; intermediate: other abnormalities; ND/IM: not done/insufficient metaphases

[b]: Good: t(8;21), inv(16); poor: -5, 5q-, -7, 7q-, 11q, complex (> 3); other: other abnormalities

Patients with an unknown donor

In 42 patients, the availability of a donor was unknown. The median age of these patients was 55 years. A total of 35 patients (83%) were aged over 50 years. The availability of a sibling donor was not explored, since it was the intention to treat these patients without allogeneic SCT. Only seven patients aged less than 50 years were not typed for the following reasons: no sibling available (N=2), typing refused (N=1), early death (day 58) (N=1), toxicity (N=1) and unknown (N=2). The CR rate in the unknown donor group was only 45%, reflecting the older age of this group. Nine patients (21%) underwent autologous transplantation in first CR, none of the patients received an allograft from an alternative donor. The survival rate at 4 years was 10%.

Outcome of patients according to donor availability

Out of the 52 patients, 39 (75%) with a donor and 42 out of 65 (65%) without a donor attained CR after one or two remission-induction courses (p=0.31). Of the 52 patients with a donor five (10%) reached a partial response, five (10%) showed resistance, two (4%) showed persistent hypoplasia and one (2%) died in hypoplasia. Ultimately, out of 39 patients with a donor, who achieved CR, 13 patients remained alive and free of disease, 16 patients relapsed and 10 patients died in CR (Table 2). Of the 13 patients not attaining complete remission after remission-induction therapy according to the protocol, 10 patients have died and three patients are still alive in CR after salvage allogeneic transplantation (Table 3).

Of the 65 patients without a donor 10 (15%) reached a partial response, eight (12%) showed resistance, two (3%) had persistent hypoplasia and 3 (5%) died in hypoplasia. Of the 42 patients in CR without a donor, 15 patients remained alive and free of disease, 26 relapsed and one died in complete remission (Table 2). Of these patients, 10, who did not achieve CR after remission-induction therapy according to the protocol, are still alive with seven of these patients in CR after salvage treatment (Table 4).

Table 2. Treatment results according to donor availability.

Variable	Donor N=52 N (%)	No donor[a] N=65 N (%)	P-value
Response induction			
CR	39 (75.0)	42 (64.6)	0.31
PR	5 (9.6)	10 (15.4)	
Resistance	5 (9.6)	8 (12.3)	
Persistent hypoplasia	2 (3.8)	2 (3.1)	
Death in hypoplasia	1 (1.9)	3 (4.6)	
Stage at transplantation			
No CR	7 (13.5)	10 (15.4)	0.65
CCR	28 (53.8)	28 (43.1)	
After relapse	1 (1.9)	3 (4.6)	
No transplantation	16 (30.8)	24 (36.9)	
Event-free-survival			
CCR	13 (25.0)	15 (23.1)	0.01
Relapse	16 (30.8)	26 (40.0)	
Death in CR	10 (19.2)	1 (1.5)	
No CR	13 (25.0)	23 (35.4)	
Survival			
Alive	18 (34.6)	28 (43.1)	0.18
Dead	34 (65.4)	37 (56.9)	

CR: complete remission; PR: partial remission; CCR: continuous complete remission

[a]: Nine patients in the no donor group received an allograft from an alternative donor: six not in CR, two after relapse and one in CCR.

Actually administered treatment

Out of 39 complete remitters, 28 (72%) with an HLA-identical donor received an allograft in first CR according to the protocol. One patient was transplanted after relapse and seven patients received an allograft as salvage therapy. Overall 36 patients (69%) with an HLA-identical sibling donor underwent allogeneic transplantation. In all, 16 patients with an HLA-identical donor did not reach the transplantation step. Reasons for not performing BMT were treatment failure (N=12), toxicity (N=3) and treatment refusal (N=1). Two of the non-transplanted patients are still alive; one patient has relapsed and one patient is in continuous complete remission (Table 3).

Of 42 complete remitters without an HLA-identical donor, 27 were autografted in first CR according to the protocol (64%) and five patients in more advanced disease stages: one patient after relapse and four patients not in CR after remission-induction chemotherapy according to the protocol. These five patients underwent rescue chemotherapy with stem cell mobilisation followed by SCT. Overall, 32 of 65 patients (49%) without a donor underwent autologous transplantation. In all, 33 patients received no autologous transplantation for the following reasons: treatment failure (N=21), toxicity (N=11) and protocol violation (N=1). Nine of these patients received an allograft from an alternative donor (one in first CR, two after relapse and six in partial response or resistance); 12 patients, who did not receive an autologous transplantation, are still alive (including six of nine patients after allografting with an alternative donor) (Table 4).

Time to event analysis according to donor availability

The actuarial survival rate at four years of the 52 patients with a donor was 33.3% (s.e. = 6.7%) versus 39.0% (s.e. = 6.5%) for the 65 patients without a donor (p=0.18) (Figure 2A). The estimated HR for survival for the comparison donor versus no donor was 1.37 and the 95% confidence interval was 0.86-2.19. The EFS rates at 4 years were 23.1% (s.e. = 6.2%) for the donor group and 21.5% (s.e. = 5.3%) for the no donor group (p=0.66) (Figure 2B).

Figure 2A. Survival from start of treatment according to donor availability.

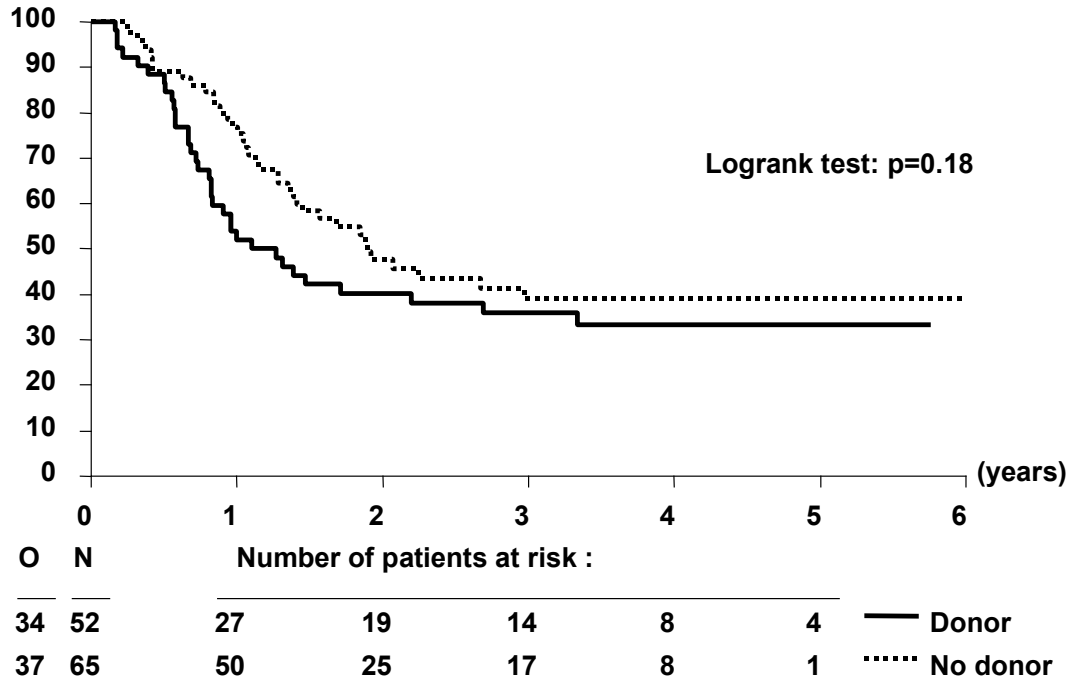
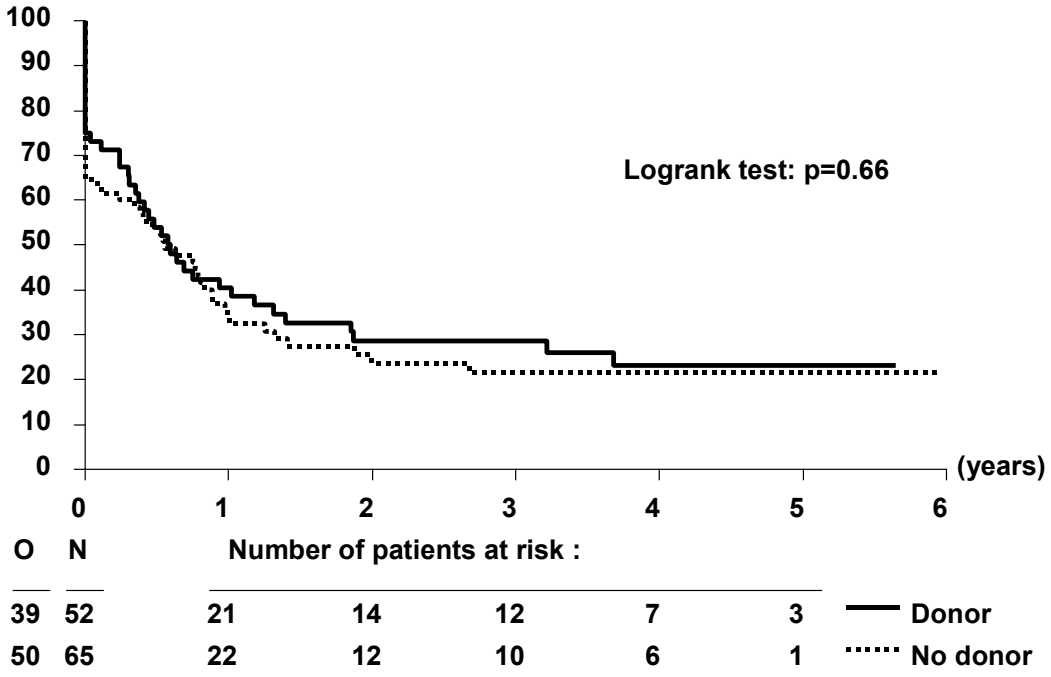


Figure 2B. Event-free survival from evaluation of remission-induction treatment according to donor availability.



The 4-year cumulative incidences of death in first CR were 19.9% and 1.5% in the two groups, respectively (Figure 3A). In total, 10 patients in the donor group died due to toxicity (N=2), infection (N=5), GVHD (N=2) and hemorrhage (N=1). One patient without a donor died of toxicity after autologous transplantation. The respective incidences of death due to other causes (progression of MDS/AML or related to transplantation not performed in first CR) were 46.8% and 59.5% (Figure 3B).

In the 81 patients who reached CR after remission-induction chemotherapy (39 patients in the donor group, 42 patients in the group without a donor), the 4-year DFS rate was 30.8% (s.e. = 7.9%) in the donor group and 33.3% (s.e. = 7.7%) in the no donor group. The cumulative incidences of relapse at 4 years from CR were 42.6% and 64.3%, respectively, and of death in first CR were 26.5% and 2.4%, respectively.

Figure 3A. Cumulative incidence of death in first CR according to donor availability.

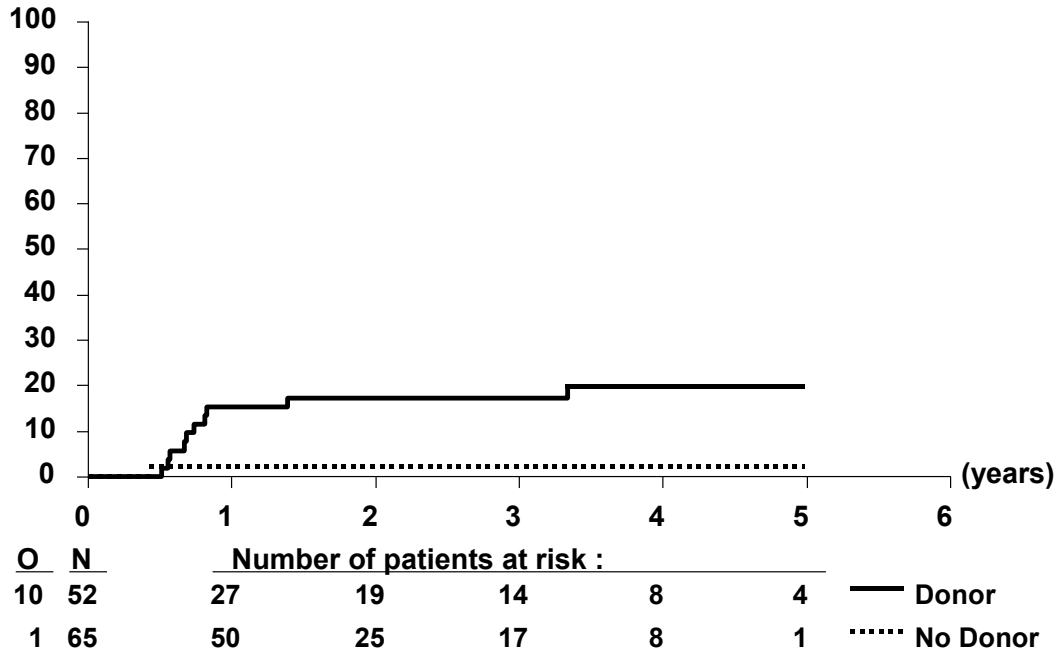
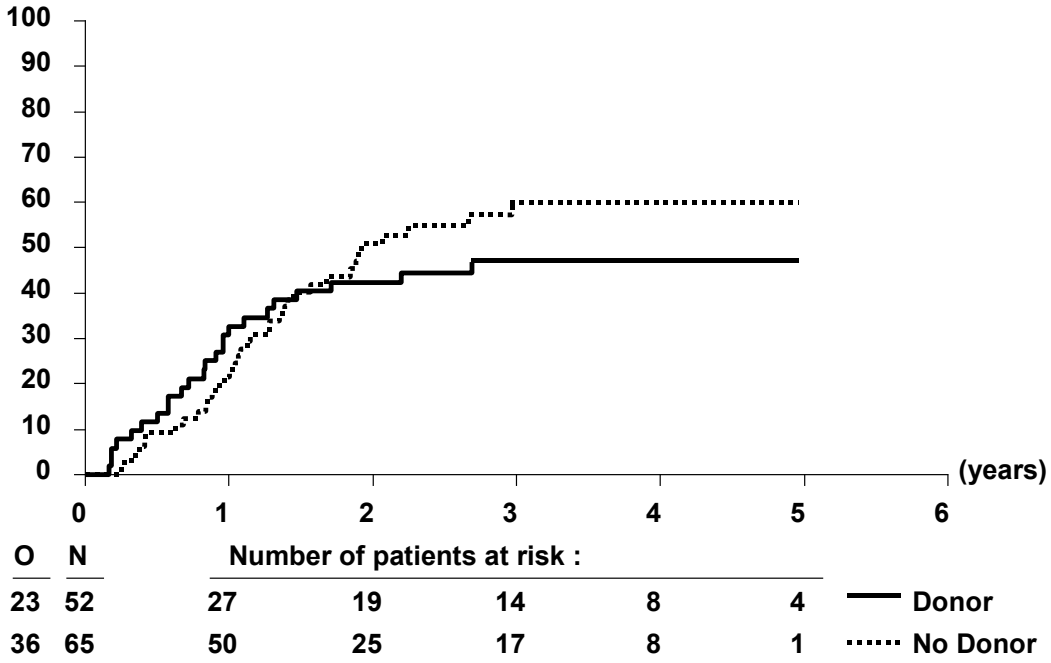


Figure 3B. Cumulative incidence of death after no CR or after relapse.



To investigate the influence of the alternative donor transplantation in the patients without an HLA-identical sibling, we censored the survival at the time of alternative donor transplantation. The 4-year survival rate estimate for the no donor group was 37.1% (s.e. = 6.9%) if patients were censored at time of alternative donor transplantation compared to 39.0% without correction.

Since the upper age limit for allogeneic bone marrow transplantation was restricted to patients younger than 50 years in many centres we repeated the analysis for patients aged less than 50 years (40 patients with a donor, 50 patients without a donor). Outcome according to donor availability was not different for patients under 50 years. The 4-year survival rates were 33.6% (s.e. = 7.7%) for patients with a donor and 47.4% (s.e. = 7.4%) for patients without a donor.

Influence of cytogenetic abnormalities on survival

In the combined group of 117 patients (52 with a donor, 65 without a donor) cytogenetic analysis was successfully performed in 101 patients. Cytogenetic features were highly predictive for overall survival. Patients with good and intermediate cytogenetic risk scores according to IPSS had a 4-year actuarial survival rate of 51% (s.e. = 8.7%) and 38% (s.e. = 9.2%), respectively, whereas in patients with poor prognostic cytogenetic features the 4-year actuarial survival rate was only 10% (s.e. = 5.7%). In patients with an unknown or failed cytogenetic examination the 4-year survival rate was 44% (s.e. = 12.4%) ($p< 0.0001$). In the subgroup with poor cytogenetic features (29 patients), we were unable to demonstrate a difference in survival for patients with or without a donor (Figure 4A). In the combined group of patients with good, intermediate and unknown cytogenetic features (40 patients with a donor and 48 patients without a donor) survival according to donor availability was likewise comparable (Figure 4B).

Figure 4A. Survival according to donor availability in patients with poor prognostic cytogenetic features.

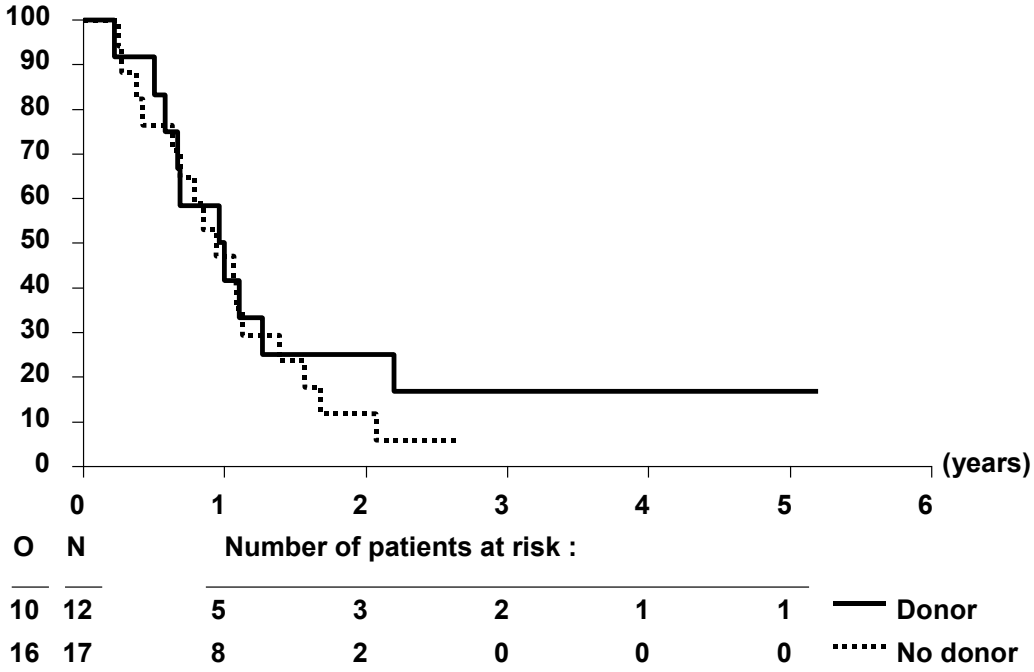
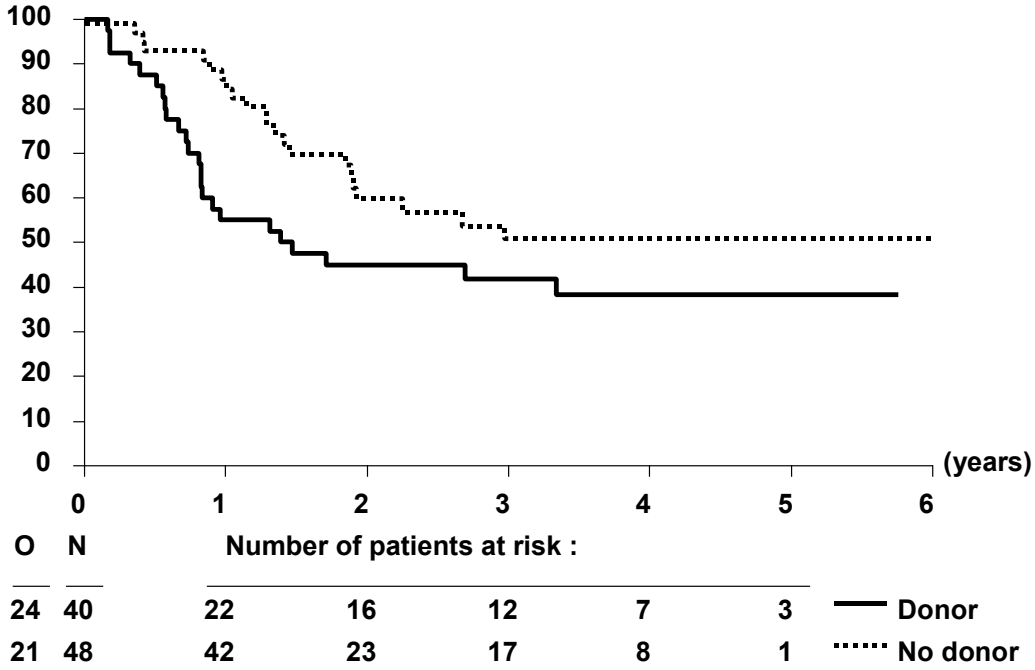


Figure 4B. Survival according to donor availability in patients with good, intermediate and unknown cytogenetic features.



Characteristics of long-term survivors according to donor availability

In all, 18 patients with an HLA-identical sibling donor are alive at the end of follow-up. A total of 16 patients survived in CR (Table 3). Patient number 2 did not receive any post-consolidation therapy, the remaining patients have received an allograft either according to the protocol (12 patients) or as salvage treatment (three patients). Eight of 16 patients presented with good-risk cytogenetic abnormalities, five with intermediate-risk cytogenetic abnormalities and two patients with poor prognostic cytogenetic features. Cytogenetic analysis had failed in one patient.

Two other patients are still alive after a relapse: one intermediate-risk patient, who showed a relapse after allogeneic transplantation and one poor-risk patient, who had relapsed before transplantation.

A total of 28 patients without an HLA-identical sibling donor are alive at the end of follow-up. In total, 20 patients survived in CR (Table 4). Four patients (patients number 6, 10, 11, 14) did not receive any post-consolidation treatment, 10 patients received an autograft according to the protocol and six patients received an allogeneic SCT from an unrelated donor. Of 20 patients, 11 showed good-risk cytogenetic abnormalities, three intermediate cytogenetic abnormalities and one patient poor-risk cytogenetic

abnormalities. In five patients cytogenetic analysis failed. Eight patients are alive without CR. Three patients not in CR after remission-induction chemotherapy underwent rescue chemotherapy followed by autografting and failed to reach CR, three patients relapsed after autologous transplantation and two patients received no autograft because of persistent hypoplasia. Four of these eight patients had good-risk cytogenetic abnormalities, two intermediate-risk and in two patients cytogenetic analysis failed.

Multivariate Cox's proportional hazards model for the duration of survival

The results of the multivariate Cox's proportional hazards model for survival are shown in Table 5. Cytogenetic risk categories according to IPSS appeared to be the most important prognostic variable for the duration of survival. The estimated HR for the poor-risk cytogenetic subgroup compared to the good-risk cytogenetic subgroup was 3.88 with a 95% CI of 2.09-7.20 ($p<0.0001$). The estimated HR of older versus younger patients was 1.65 with a 95% CI of 0.97-2.83 ($p=0.07$), and of the donor versus no donor it was 1.30 with a 95% CI of 0.81-2.09 ($p=0.28$). As age seemed not to have a constant influence on the outcome, we have applied a Cox model stratified for cytogenetic risk group and age to assess the relative prognostic importance of donor availability: the estimated HR was 1.17, with a 95% CI of 0.71-1.90 ($p=0.54$).

Table 5. Results of Cox's proportional hazards model for overall survival.

Variable	Hazard Ratio	95% CI	P-value
Cytogenetic risk group			
Good risk	1.00		
Intermediate risk	1.50	0.78-2.90	0.22
Poor risk	3.88	2.09-7.20	<0.0001
ND/IM	1.93	0.85-4.36	0.11
Age (yr.)			
< 50	1.00		
≥ 50	1.65	0.97-2.83	0.07
Donor			
No	1.00		
Yes	1.30	0.81-2.09	0.28

CI = Confidence Interval, ND/IM = not done/insufficient metaphases

Table 3. Characteristics of patients with an HLA-identical sibling donor alive at the end of study (N=18).

Patient	Age (yr.)	FAB	Cytogenetics	Response after RI[a]	Response after cons[b]	Stage at Tx[c]	Status	Follow-up (days)
1.	43	RAEB*	Good	CR	CR	CCR	CCR	1838
2.	47	RAEB	Poor	CR	CR	No Tx	CCR	1900
3.	46	sAML	Good	CR	CR	CCR	CCR	2103
4.	54	RAEBt	Intermediate	CR	CR	CCR	CCR	1955
5.	46	RAEBt	Good	CR	CR	CCR	CCR	1538
6.	36	RAEBt	Intermediate	CR (2)	CR	CCR	CCR	1516
7.	47	sAML	Unknown	CR	CR	CCR	CCR	1655
8.	30	RAEB*	Good	CR	CR	CCR	CCR	920
9.	52	sAML	Intermediate	CR	CR	CCR	CCR	1412
10.	57	CMMoL	Good	CR	CR	CCR	CCR	1321
11.	36	RAEBt	Good	CR	CR	CCR	CCR	1246
12.	28	CMMoL	Good	CR	CR	CCR	CCR	987
13.	30	sAML	Intermediate	CR	CR	CCR	CCR	683
14.	16	RAEBt	Good	PR (2)	No cons	PR[1]	CR	1614
15.	46	sAML	Poor	PR (2)	No cons	PR[2]	CR	1281
16.	46	RAEB*	Intermediate	CR	CR	CCR	Relapse	1392
17.	27	RAEBt	Intermediate	Hypoplasia (2)	No cons	No CR[3]	CR	1044
18.	52	RAEB*	Poor	CR	No cons	No Tx	Relapse	573

RAEB*: RAEB with $\geq$ 10% blasts in the bone marrow

[a]: Remission-Induction course; (2): after 2 remission-induction courses; [b]: Consolidation course; [c]: Allogeneic transplantation

[1]: Allogeneic BMT in PR, hereafter CR; [2]: Allogeneic BMT in PR, hereafter CR; [3]: Allogeneic BMT in hypoplastic phase, hereafter CR

Table 4. Characteristics of patients without an HLA-identical sibling donor alive at the end of study (N=28).

Patient	Age (yr.)	FAB	Cytogenetics	Response after RI[a]	Response after cons[b]	Stage at Tx[c]	Tx	Status	Follow-up (days)
1.	29	sAML	Good	CR	CR	CCR	ABMT	CCR	2210
2.	47	RAEBt	Good	CR	CR	CCR	APSCT	CCR	1699
3.	33	RAEBt	Intermediate	CR	CR	CCR	APSCT	CCR	1694
4.	36	RAEBt	Good	CR	CR	CCR	ABMT	CCR	1420
5.	38	RAEBt	Good	CR	CR	CCR	ABMT	CCR	1606
6.	53	RAEBt	Good	CR	CR	No Tx		CCR	1591
7.	44	sAML	Unknown	CR	CR	CCR	ABMT	CCR	1294
8.	26	RAEBt	Unknown	CR	CR	CCR	ABMT	CCR	1649
9.	39	RAEBt	Unknown	CR	CR	CCR	APSCT	CCR	1414
10.	44	sAML	Good	CR	CR	No Tx		CCR	1159
11.	48	sAML	Unknown	CR	CR	No Tx		CCR	762
12.	43	RAEB*	Intermediate	CR	CR	CCR	APSCT	CCR	832
13.	24	sAML	Good	CR	CR	CCR	APSCT	CCR	602
14.	27	RAEBt	Good	CR	CR	No Tx		CCR	576
15.	23	RAEB*	Good	CR	CR	CCR	Allo	CCR	487
16.	47	RAEBt	Intermediate	Resistance	Rescue[1]	CR	Allo	CR	1357
17.	33	RAEBt	Unknown	PR	Rescue[2]	No CR	APSCT	CR	1314
18.	37	RAEBt	Unknown	PR (2)	No cons	No CR	Allo	CR	1656
19.	47	RAEBt	Unknown	CR	CR	CCR	APSCT	Relapse	1226
20.	24	sAML	Poor	PR (2)	No cons	No CR	Allo	CR	967
21.	39	RAEB*	Good	CR	CR	CCR	APSCT	Relapse	1505
22.	42	CMMoL	Good	PR	Rescue[3]	CR	ABMT	Relapse	1214

23.	23	RA	Intermediate	Hypoplasia	No cons	No Tx		No CR	1301
24.	24	RAEBt	Good	Resistance	Rescue	No CR[4]	Allo	CR	735
25.	43	CMMoL	Intermediate	Hypoplasia	No cons	No Tx		No CR	680
26.	50	RAEB*	Good	Resistance	Rescue[5]	CR	APSCT	CR	585
27.	16	RAEB	Good	PR	PR	No CR[6]	Allo	CR	718
28.	52	RAEBt	Good	CR	CR	CCR	APSCT	Relapse	534

RAEB*: RAEB with ≥ 10% blasts in the bone marrow; ABMT: autologous bone marrow transplantation; APSCT: autologous peripheral blood stem cell transplantation; Allo: allogeneic bone marrow transplantation unrelated donor

[a]: Remission-Induction course; (2): after 2 remission-induction courses; [b]: Consolidation course; [c]: Transplantation;

[1]: Rescue chemotherapy with cytarabine and amsacrine, hereafter CR

[2]: Rescue chemotherapy with idarubicin and high dose cytarabine (IDIA), hereafter partial response (less than 5% blasts in bone marrow)

[3]: Rescue chemotherapy with idarubicin and high dose cytarabine (IDIA), hereafter ABMT in CR, subsequently relapse after ABMT

[4]: CR after salvage chemotherapy with cytarabine and mitoxantrone, hereafter progression to AML

[5]: Rescue chemotherapy with high dose cytarabine, hereafter CR

[6]: Consolidation course after PR (protocol violation), CR after transplantation

DISCUSSION

This analysis was performed to assess the role of allogeneic and autologous SCT in the treatment of patients with high-risk MDS and sAML. Reports in the literature suggest the superiority of allogeneic transplantation with DFS varying from 35-45%.[4-10,12,25] However, all these studies have reported observational data. Selection of patients fit enough to go through allogeneic SCT may introduce a selection bias.

The optimal way to avoid selection bias is to conduct prospective randomised trials in patients with an HLA-identical sibling donor. Since most clinicians consider it unethical to exclude the option of an allogeneic BMT from young patients with a donor, this approach might not be feasible. An alternative way to assess the value of allogeneic BMT without bias is to compare the outcome of patients with and without a donor on an intention-to-treat basis, regardless of therapy actually received.[26] We used the framework of a large European multi-centre study (EORTC 06921) to compare the results of allogeneic and autologous SCT. The original paper about this prospective study demonstrated feasibility of both treatment arms with common remission-induction and consolidation treatment followed by allogeneic SCT if a sibling donor was available and autologous SCT otherwise.[21] Such a prospective study comparing autologous and allogeneic SCT as post-consolidation therapy is hampered by the following phenomenon: patients may not receive the scheduled therapy because of early relapse or treatment-related toxicity. In the original paper an intention-to-treat analysis was performed in patients, who reached CR comparing outcome of patients with and without a donor. This resolves some of these biases but induces others. First, patients who did not enter CR were excluded from the analysis. Secondly, all patients without a known donor were categorised in the no donor group regardless of whether HLA-typing of patient and family was performed. Therefore, no firm conclusions could be drawn about the comparison between the two arms of the study. The present analysis is restricted to patients, alive at 8 weeks from the start of treatment, in whom HLA-typing was performed, irrespective of achievement of CR. Such an analysis at a fixed point of time minimises selection. Moreover, this policy includes the profit of salvage therapy for patients not in CR after remission-induction chemotherapy, since rescue therapy might be a curative option for patients with persistent disease. Our principal finding is that the overall survival at 4 years did not differ between the patients with and without an HLA-identical donor.

The reported survival rate of 33.3% for patients with a donor is in accordance with the literature.[7,12,27,28] Of complete remitters, 72% received the intended allograft in first CR and 69% of all patients with a donor actually received an allograft.

The experience with autologous transplantation in high-risk MDS and sAML patients is limited.[18-20,28] The EBMT reported a 3-year survival of 38% for patients transplanted in first CR.[28] The French study was the first reported prospective study on autologous stem cell transplantation in 83 patients with MDS and sAML.[20] In 24/39 (62%) of the patients, who achieved CR, transplantation was performed. The median overall survival from transplantation was 33 months. In the present analysis, the overall survival rate at 4 years was 39.0% for the patients without a donor. The percentage of complete remitters who reached the transplantation step was 64% and overall 49% of patients without a donor underwent autologous transplantation. A significantly higher number of patients received the intended allogeneic transplantation compared to autologous transplantation ($p<0.05$), similar to observations in AML patients.[29,30] The requirement to obtain a CR, in order to harvest normal stem cells, is the main cause of this difference. Nine patients without an HLA-identical donor received an allogeneic transplantation from an alternative donor. This might have contributed to the relatively good overall survival of the patients without an HLA-identical donor. However, by censoring the survival at the time of alternative donor transplantation, the 4-year survival estimate in the no-donor group was 37% compared to 39% without censoring.

Several reports studied the same issue in primary AML.[31,32] In order to answer the question as to whether allogeneic transplantation was superior or not compared to autologous transplantation or chemotherapy as post-remission therapy, the Leukemia Party of the European Group for Blood and Marrow Transplantation registered patients from the time of HLA-typing on an intention-to-treat basis.[29] Of 26 patients with a donor, 22 (85%) were allografted. In contrast, only 15 out of 47 patients (32%) intended for ABMT underwent ABMT. In this study the 3-year survival was significantly better for patients with a donor ($p=0.02$).[29] Within the framework of the EORTC-GIMEMA AML 8A study a similar analysis was performed. Patients with an HLA-identical donor were scheduled for allogeneic BMT and patients without a donor were randomised between ABMT and chemotherapy.[30] The AML 8A analysis showed an 8% difference in survival rate at the median follow-up of 6 years, the survival being 48% for patients with a donor compared to 40% for patients without a donor. This difference was not significant. The DFS for patients in CR with a donor was significantly longer than for those without (46%

versus 33%; p=0.01), owing to a lower relapse rate in the group with a donor (42% versus 63%; p<0.001).

In the present analysis the upper age limit for allogeneic transplantation was variable and depended on the policy of the different transplant centres. In most European centres, patients less than 50 years are candidates for allogeneic BMT. Several studies reported a decreased survival in patients over 40 years, mainly due to an increased transplant-related mortality.[7,10,28] In the present analysis, 12 patients in the donor group and 15 patients in the group without a donor (23%) were aged over 50 years. Five of these patients received an allograft and three patients were autografted. If we confined the analysis to patients less than 50 years, the difference in overall survival between patients with and without a donor remained non-significant.

Compared to the original paper, a second distinction is that the present analysis discriminates between patients with a donor, patients without a donor and patients with an unknown donor. The latter group comprises mainly patients in whom the availability of a donor was not explored, since there was no intention to treat these patients with allogeneic SCT. In the unknown donor group, 83% of patients were aged over 50 years. Apparently, age was the major reason for not performing HLA typing in patient and family. Nine out of 42 patients received autologous SCT and the overall survival rate at four years was 10%. If we had included this group of patients in the group without a donor, then the results of the donor group would have been superior to the reference group. This emphasises the importance of prospective studies analysed on an intention-to-treat basis.

Cytogenetic abnormalities are highly prognostic in MDS and sAML. Patients were classified according to the cytogenetic risk groups of the IPSS.[3] Patients with good and intermediate prognostic risk showed a survival rate at 4 years of 51% and 38% respectively. The 4-year survival rate of patients with bad prognostic cytogenetic features was only 10%. One could hypothesise that patients with poor prognostic cytogenetic features do better with allogeneic transplantation and patients with better prognostic cytogenetic features benefit by autologous transplantation. Therefore, we compared survival according to donor availability in the group with poor prognostic cytogenetic features and in the combined group with good, intermediate and unknown cytogenetic features. Outcome of patients with and without a donor was comparable, independent of the cytogenetic risk category. Only three patients with poor-risk cytogenetic features survived in CR: one patient with a histocompatible sibling who has not been allografted,

one patient who received an allograft after a partial response and one patient after salvage allogeneic SCT with an unrelated donor.

Overall, the results of this analysis show that patients with high-risk MDS and sAML may benefit from intensive treatment strategies including allogeneic or autologous SCT. We were unable to demonstrate a survival advantage for patients with an HLA-identical donor over patients without a donor. The successful outcome of patients without a donor cannot be explained by salvage BMT with alternative donors. This analysis demonstrates that patients with an HLA-identical donor have a lower relapse risk compared to patients without a donor. Unfortunately, this advantage is neutralised by a substantial higher treatment-related mortality. Median follow-up was 3.6 years. We cannot disprove that after a longer follow-up, a higher percentage of patients without a donor might relapse, and that outcome of patients without a donor might become different. Despite small numbers at risk in both groups, only two patients without a donor and one patient with a donor relapsed after 2 years of follow-up.

At present, most clinicians consider allogeneic SCT as the treatment of choice for younger patients with a donor. Nevertheless, 14 of 65 patients without a donor remained in first remission without allogeneic SCT. This outcome proves that long-term DFS is feasible without allogeneic SCT in a substantial proportion of patients with chemotherapy followed by autologous SCT. For patients lacking a donor, this treatment option must be considered as a reasonable alternative. Further development of accurate prognostic classification systems, incorporating response to chemotherapy, is needed to gear to a risk-adapted strategy for an individual patient.

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CHAPTER 5

The impact of intensive antileukemic treatment strategies on prognosis of MDS patients aged less than 61 years according to IPSS risk groups

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ABSTRACT

The present study applies the International Prognostic Scoring System (IPSS) to 306 consecutive MDS patients diagnosed between August 1977 and September 2000 at the University Medical Centre Nijmegen. The aim was to investigate whether the IPSS could be used as a prognostic tool in MDS patients aged less than 61 years who were treated with acute myeloid leukemia (AML)-like chemotherapy with or without transplantation, and whether the scoring system discriminated between the subgroups of patients, who benefit from intensive treatment strategies. The patients were retrospectively assigned to the IPSS risk categories and compared with the IPSS workshop patients. Eighty-three of 159 patients aged < 61 years, classified as intermediate-1, intermediate-2 and high risk according to the IPSS, received intensive treatment consisting of chemotherapy only (N=30), chemotherapy followed by either autologous stem cell transplantation (N=7) or allogeneic stem cell transplantation (N=46). After intensive treatment, the median survival was 2.6 years for the intermediate-1 risk group (N=33), 3.4 years for the intermediate-2 risk group (N=27) and 0.9 years for the high-risk group (N=23). We conclude that the IPSS is an improved scoring system for patients receiving supportive care. Nevertheless, the scoring system does not seem to be the best method for predicting outcome after intensive antileukemic treatment. In particular, intermediate-2 risk patients may benefit from intensive treatment.

INTRODUCTION

The myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by peripheral blood cytopenias in the presence of hypercellular bone marrow with features of ineffective hematopoiesis. Since 1982, MDS have been classified according to French-American-British (FAB) criteria, based on the number of blasts in bone marrow and peripheral blood and the percentage of ringed sideroblasts in the bone marrow and monocytes in the blood.[1] Five subgroups have been defined: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEBt) and chronic myelomonocytic leukemia (CMML). Although this classification has shown its usefulness in predicting the outcome of patients, considerable variation still exists within the different subgroups regarding clinical features and survival. Numerous scoring systems have been proposed to predict the prognosis of individual patients.[2,3] In 1997, an international workshop combined the data of seven previously reported studies [2-8] to generate an International Prognostic Scoring System (IPSS).[9] The IPSS determined four risk groups for survival and acute myeloid leukemia (AML) evolution (low risk, intermediate-1 risk, intermediate-2 risk and high risk), based on karyotype, number of blasts in the bone marrow and number of cytopenias (Table 1). Age was an additional prognostic factor for survival, but not for AML evolution. The IPSS seemed to be an improved classification system for predicting the natural history in MDS.[10] However, the IPSS was based on data of patients treated with transfusions, biologic response modifiers and low-dose oral chemotherapy. Patients treated with intensive chemotherapy and/or stem cell transplantation and patients with therapy-related MDS were excluded from this analysis.

The present study is a retrospective analysis of 306 untreated MDS patients who have been seen in the Nijmegen University Hospital, many of whom subsequently received intensive antileukemic treatment consisting of AML-like chemotherapy with or without autologous stem cell transplantation, allogeneic transplantation with or without preceding chemotherapy. Classified according to the IPSS criteria, the outcome of our patients was compared with that of the IPSS workshop patients.

The principle aim was to investigate whether the IPSS predicts outcome of patients aged less than 61 years treated with intensive therapy, and whether the scoring system

discriminates between subgroups of patients, who may benefit from these intensive treatment strategies.

Table 1. The International Prognostic Scoring System (IPSS).

	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	5	5-10	-	11-20	21-30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0/1	2/3			

Scores for risk groups are as follows: Low: 0; Intermediate-1: 0.5-1.0; Intermediate-2: 1.5-2.0; and High: $\geq$ 2.5

[a]: Good: normal, -Y, del(5q), del(20q); Poor: complex ($\geq$ 3) abnormalities, chromosome 7 abnormalities; Intermediate: other abnormalities

[b]: Hemoglobin < 6.2 mmol/l, neutrophil count < 1.8 x 10^9/l, platelet count < 100 X 10^9/l

PATIENTS AND METHODS

Patients

Between August 1977 and September 2000, 380 newly diagnosed MDS patients have been referred to the University Medical Centre Nijmegen. This group consisted of patients referred by their family practitioners or physicians from general hospitals in south-east Netherlands. We reviewed the data of all MDS patients. In 74 patients (19%), sufficient data were not available, mainly due to lack of cytogenetic data and these patients were excluded from the present analysis. In 302 out of the remaining 306 patients the karyotype was known. Four patients with unknown karyotype belonged to the high-risk group of the IPSS based on the number of blasts in the bone marrow (21-30%) and the number of cytopenias (2/3). Therefore, these patients were not withdrawn from the analysis. In all, 306 patients were retrospectively assigned to the various IPSS risk categories.

Treatment

All patients received supportive care. The majority of elderly patients (aged 60 years or over) received supportive care without intensive treatment. Only nine elderly patients (7%) were treated with intensive chemotherapy followed by autologous stem cell transplantation in one patient.

Generally, the accepted age limit for allogeneic stem cell transplantation varies between 50 and 60 years. In Nijmegen, patients aged < 61 years are eligible for allogeneic stem cell transplantation, in the absence of other medical contraindications. Low-risk IPSS patients were not candidates for intensive antileukemic treatment, in view of their relatively good prognosis. In contrast, patients aged < 61 years, belonging to the intermediate-1, intermediate-2 and high-risk categories of the IPSS could be considered as candidates for intensive treatment strategies including allogeneic stem cell transplantation. We divided the patients into two groups diagnosed before and after 1 January 1992. Before 1992, the decision to start intensive treatment was individually based. In those years, 13 patients with a human leukocyte antigen-identical donor underwent allogeneic stem cell transplantation: five patients with RA received a transplant without preceding chemotherapy, and eight RAEB/RAEBt patients underwent AML-like chemotherapy followed by an allogeneic transplantation. Six additional patients received chemotherapy but no transplantation at the time of progression of their disease. In January 1992, the department changed the treatment policy and, from 1992 onwards, all high-risk MDS patients were offered intensive antileukemic treatment, if they met the eligibility criteria of successive European Organization for the Research and Treatment of Cancer (EORTC) protocols. Patients were candidates for intensive treatment if they were aged 16-60 years and had untreated (i) RAEBt, (ii) RAEB with > 10% blasts cells in the bone marrow, (iii) other forms of MDS with multiple chromosomal abnormalities and/or profound cytopenias defined as: neutrophil count < 0.5 x 10^9/l and/or platelet count < 20 x 10^9/l, or (iv) CMML with > 5% blasts cells in the bone marrow or with a neutrophil count > 16 x 10^9/l or a monocyte count > 2.6 x 10^9/l in the blood.

After 1992, 64 patients were offered intensive antileukemic treatment. Twenty-two patients diagnosed after 1992 did not receive intensive treatment for the following reasons: treatment refused (N=3), psychiatric disorder (N=1), language barrier and platelet refractoriness (N=1), concomitant disease (N=2), death before start of treatment due to infection (N=2), cardiomyopathy (N=1), not eligible for the protocol (N=4), doctor's decision (N=5), unknown (N=3).

Statistical analysis

Chi-square tests were used to compare differences between groups. Kaplan-Meier survival analyses were used to estimate median survival time and to plot survival curves. To compare survival times in different strata, the log-rank test was used.[11]

The prognostic effect of IPSS, age, diagnosis period, treatment, bone marrow blasts, cytopenias and cytogenetics on survival time was analysed in multivariate analyses using proportional hazards models. In this multivariate analysis we also evaluated the interaction between IPSS and age (< 61 years versus > 60 years). A p-value < 0.05 was considered statistically significant.

RESULTS

The Nijmegen patients were younger than the IPSS workshop patients, with a median age of 58 years versus 69 years (Table 2). Eighteen per cent of patients developed MDS after prior treatment with chemotherapy or radiotherapy for a non-related disease (therapy-related MDS). The Nijmegen patients presented with more cytopenias and more severe cytopenias resulting in median hemoglobin level, neutrophil and platelet counts of 9.2 g/dl, 1.4 x 10^9/l and 75 x 10^9/l respectively. The corresponding blood counts for the IPSS workshop patients were 9.7 g/dl, 2.0 x 10^9/l and 132 x 10^9/l. Median survival was 5.1 years in the low-risk group, 2.4 years for the intermediate-1 risk group, 1.2 years for the intermediate-2 risk group and 0.8 year for the high-risk group ($p<0.0001$) (Figure 1). Median survival in the low risk and intermediate-2 risk group was comparable in the Nijmegen and the IPSS workshop patients. However, the median survival in the intermediate-1 risk group was lower in the Nijmegen patients, and median survival in the high-risk group was better for the Nijmegen patients (Table 3).

Intensive antileukemic therapy with or without stem cell transplantation was administered to patients younger than 61 years. Therefore, the outcome of patients aged < 61 years was compared with the same age category of the IPSS workshop patients. The differences in median survival between the Nijmegen patients and the IPSS workshop patients in the younger patient groups were similar to the differences found in the overall groups (Table 3).

Table 2. Characteristics of all Nijmegen MDS patients compared to IPSS workshop patients and of Nijmegen patients aged less than 61 years at diagnosis (low-risk excluded), according to applied treatment.

			Nijmegen < 61 years		
Variable	Nijmegen N (%)	IPSS workshop N (%)	No intensive treatment N (%)	Intensive treatment N (%)	P-value[a]
Number of patients	306 (100)	816 (100)	76 (100)	83 (100)	
Gender					
Male	198 (65)	491 (60)	43 (57)	54 (65)	0.27
Female	108 (35)	325 (40)	33 (43)	29 (35)	
Age (years)					
≤ 60	176 (58)	205 (25)	53[b]	45[b]	<0.001
> 60	130 (42)	611 (75)			
MDS					
Primary	250 (82)	816 (100)	56 (74)	72 (87)	0.04
Therapy-related	56 (18)	0	20 (26)	11 (13)	
FAB					
RA	94 (31)	294 (36)	29 (38)	18 (23)	<0.001
RARS	37 (12)	125 (15)	8 (11)	5 (6)	
RAEB	96 (31)	208 (26)	26 (34)	24 (29)	
RAEBt	64 (21)	61 (8)	9 (12)	34 (41)	
CMML	11 (4)	126 (15)	4 (5)	2 (2)	
Unknown	4 (1)				
BM blasts					
<5%	136 (44)	483 (59)	37 (49)	22 (27)	0.03
5-10%	81 (27)	183 (22)	20 (26)	26 (31)	
11-20%	60 (20)	114 (14)	13 (17)	24 (29)	
21-30%	29 (10)	36 (5)	6 (8)	11 (13)	
Cytopenias					
0/1	114 (37)	474 (58)	27 (36)	24 (29)	0.37
2/3	192 (63)	342 (42)	49 (64)	59 (71)	
Cytogenetic subgroup					
Good	139 (46)	570 (70)	22 (29)	36 (44)	0.15
Intermediate	83 (27)	112 (14)	26 (34)	22 (26)	
Poor	80 (26)	134 (16)	28 (37)	24 (29)	
Unknown	4 (1)			1 (1)	

IPSS					
Low	37 (12)	267 (33)			
Intermediate-1	124 (41)	314 (38)	38 (50)	33 (40)	0.17
Intermediate-2	88 (29)	176 (22)	26 (34)	27 (33)	
High	57 (19)	59 (7)	12 (16)	23 (28)	
Intensive treatment					
Yes	93 (30)	0	0	83 (100)	
No	213 (70)	816 (100)	76 (100)	0	
Diagnosis					
Before 1992	163 (47)	816 (100)	54 (71)	19 (23)	<0.001
After 1992	143 (53)	0	22 (29)	64 (77)	

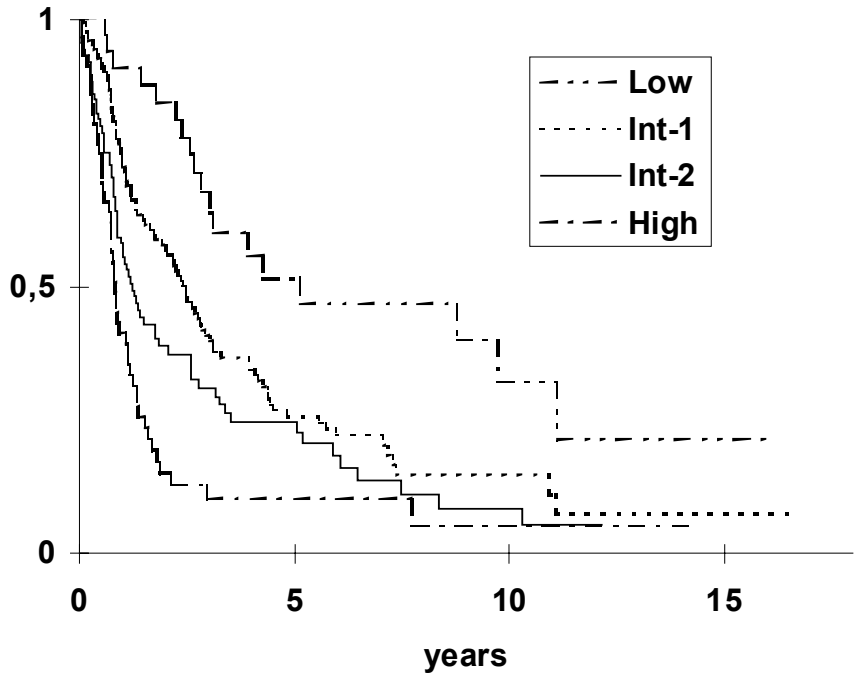
[a]: P-value for the comparison between intensive treatment and no intensive treatment in the Nijmegen patients

[b]: Median age (years)

Table 3. Survival of Nijmegen patients and IPSS workshop patients per IPSS risk group in all patients and in patients aged less than 61 years.

	Nijmegen		Greenberg		Nijmegen		Greenberg	
IPSS	all (N=306) N (%)	Median survival (years)	all (N=816) N (%)	Median survival (years)	< 61 yr. (N=176) N (%)	Median survival (years)	< 61 yr. (N=205) N (%)	Median survival (years)
Low	37 (12)	5.1	267 (33)	5.7	17 (10)	11.1	60 (29)	11.8
Int-1	124 (41)	2.4	314 (39)	3.5	71 (40)	2.5	87 (42)	5.2
Int-2	88 (29)	1.2	176 (22)	1.2	53 (30)	1.4	49 (24)	1.8
High	57 (19)	0.8	59 (7)	0.4	35 (20)	0.9	9 (4)	0.3

Figure 1. Survival from diagnosis in all patients according to IPSS risk group (N=306).



Effect of intensive treatment in patients aged less than 61 years

There were 176 patients who were aged < 61 years. Patients with intermediate-1, intermediate-2 and high-risk IPSS scores could be considered as candidates for intensive antileukemic treatment. Seventeen patients belonged to the low-risk group of the IPSS. Of the remaining 159 patients, classified as IPSS intermediate-1, intermediate-2 and high-risk categories, 83 patients (52%) received intensive treatment and 76 patients (48%) did not. Thirty patients received chemotherapy only, 7 patients underwent chemotherapy followed by autologous transplantation and, in 46 patients, allogeneic stem cell transplantation was performed (21 patients with RA(RS) without preceding chemotherapy). Four patients received a transplant from a voluntary unrelated donor (VUD).

Intensive chemotherapy in patients < 61 years consisted of cytarabine only (N=3), cytarabine plus anthracycline (N=7), cytarabine plus amsacrine plus etoposide (N=2), cytarabine plus anthracycline plus vincristine (N=3) or cytarabine plus anthracycline plus etoposide (N=47).

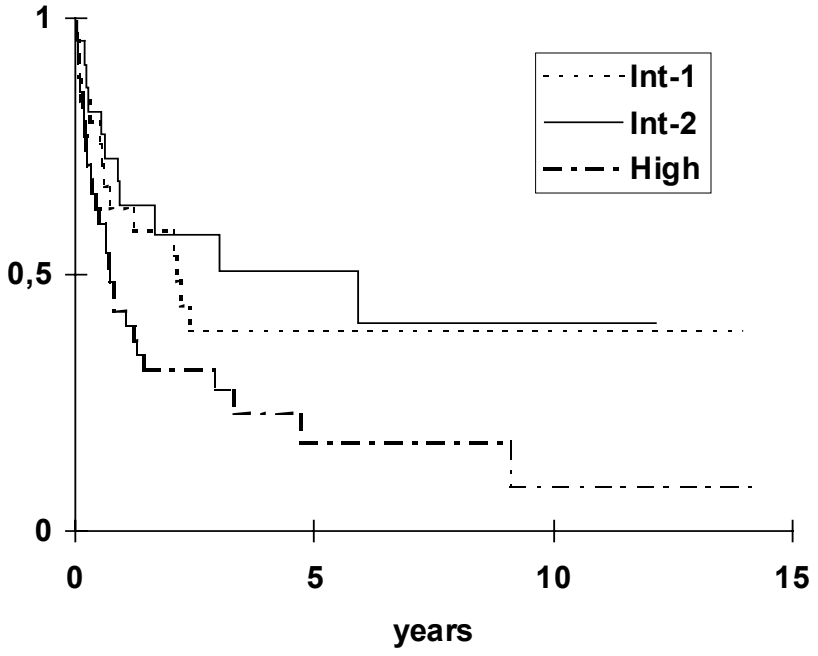
Seventy-six patients did not receive intensive treatment. Patient characteristics for both groups are shown in Table 2. Median age of the patients who received intensive treatment was 45 years versus 53 years for patients who received supportive care only.

The estimated 4-year survival of the 83 patients who underwent intensive treatment was 36.3% versus 23.0% for the 76 patients, who received supportive care only (p=0.02).
In the intensive treatment group, median survival from diagnosis was 2.6 years for the intermediate-1 risk group, 3.4 years for the intermediate-2 risk group and 0.9 years for the high-risk group. The estimated 4-year survival rates were 46%, 40% and 19% respectively (Table 4). In the intermediate-1 risk group, six patients received chemotherapy only, three patients received chemotherapy followed by autologous transplantation, and 24 patients underwent allogeneic stem cell transplantation. In the intermediate-2 risk group, 12 patients received chemotherapy only, three patients received chemotherapy followed by autologous transplantation, and 12 patients underwent allogeneic stem cell transplantation. These numbers were 12, 1 and 10, respectively in the high-risk group. The median time between diagnosis and start of treatment was 0.2 years (range 0-5.7 years). At the start of treatment, 15 patients had progressed to a higher IPSS risk category than at initial diagnosis. Hence, at the start of intensive treatment, 25 patients were classified in the intermediate-1 risk group, 23 patients in the intermediate-2 risk group and 35 patients in the high-risk group. Survival from start of treatment for the different IPSS risk categories at start of intensive treatment is shown in Figure 2. The survival from diagnosis in patients, who received no intensive treatment, is shown in Table 4.
An additional analysis was performed, which excluded the secondary MDS patients, as these patients were not included in the IPSS workshop. Median survival according to IPSS risk groups of both intensively treated patients (N=72) and not-intensively treated patients (N=56) was not different, if the analysis was restricted to primary MDS patients (data not shown).

Table 4. Survival of patients aged less than 61 years according to IPSS risk group at diagnosis (low- risk excluded) for patients with and without intensive treatment (N=159).

IPSS	No intensive treatment (N=76)	Median survival (years)	4-year survival (%)	Intensive treatment (N=83)	Median survival (years)	4-year survival (%)
Intermediate-1	38	2.2	37	33	2.6	46
Intermediate-2	26	0.8	11	27	3.4	40
High	12	0.7	0	23	0.9	19

Figure 2. Survival from start of treatment in patients aged less than 61 years after intensive antileukemic therapy according to IPSS risk group at start of intensive treatment (N=83).



Effect of allogeneic stem cell transplantation in patients aged < 61 years

Forty-six patients underwent allogeneic stem cell transplantation. Median survival of these 46 patients was 5.7 years compared to 0.9 years for the 37 patients who received chemotherapy with or without autologous stem cell transplantation (p=0.0005). Of the 46 patients receiving an allogeneic transplantation, 24 belonged to the intermediate-1 risk group, 12 to the intermediate-2 risk group and 10 to the high-risk group. Median survival after allogeneic stem cell transplantation was 5.7 years for the intermediate-1 risk group, 10.3 years for the intermediate-2 risk group and 1.1 years for the high-risk group

(p=0.28). The estimated 4-year survival rates were 50% for the intermediate-1 risk group, 67% for the intermediate-2 risk group and 30% for the high-risk group.

Effect of the year of diagnosis on treatment in patients aged < 61 years

A total of 159 patients were assigned to the intermediate-1, intermediate-2 and high-risk groups of the IPSS. Eighty-three patients who were younger than 61 years received intensive treatment. Nineteen patients diagnosed before 1992 received intensive treatment and 64 patients thereafter. The median survival was 1.4 years versus 1.8 years respectively (p=0.5).

Seventy-six patients received supportive care only. The median survival of 54 patients diagnosed before 1992 was 1.2 years versus 2.2 years for the 22 patients diagnosed after 1992 (p=0.7).

Influence of cytogenetic abnormalities

In 302 out of 306 patients the karyotype was known. A total of 139 patients (46%) showed good prognostic cytogenetic features according to IPSS (normal cytogenetics, 5q-, 20q- or -Y). Poor prognostic features (three or more abnormalities, chromosome 7 abnormalities) were observed in 80 patients (26%) and intermediate prognostic features (any other cytogenetic abnormality) in 83 patients (27%). Median survival of patients with a good karyotype was 2.8 years, with a poor karyotype 0.8 years and with an intermediate karyotype 2.0 years ($p < 0.0001$).

According to the Keating classification [12] as used for AML, no patients had favourable cytogenetic abnormalities [inv(16), t(8,21) or t(15,17)]. Intermediate prognostic cytogenetic abnormalities (normal, -Y) occurred in 149 patients (49%), and unfavourable prognostic cytogenetic abnormalities (chromosome 5 or 7 abnormalities, 11q, other abnormalities) were found in 153 patients (61%). The median survival for the intermediate prognostic group according to this classification was 2.7 years versus 1.2 years for the unfavourable prognostic group.

Multivariate analyses

Since the IPSS was designed to predict the survival of patients treated with supportive care or low-intensity regimens, we analysed the prognostic effect of the different IPSS categories and age on survival in 213 patients who received supportive care only. The results of the multivariate Cox's proportional hazards model are shown in Table 5. The classification into the four IPSS categories appeared to be highly prognostic for the duration of survival. The estimated hazard ratio for the high-risk group compared to the intermediate-1 risk group was 2.84 [95% confidence interval (CI), 1.80-4.49; p<0.0001]. The estimated hazard ratio of older versus younger patients was 1.01 (95% CI 0.99-1.02; p=0.18).

Table 5. Results of Cox's proportional hazards model for overall survival in patients who received no intensive treatment (N=213).

Variable	Hazard Ratio[a]	95% CI	P-value
IPSS risk group			
Low	0.40	0.23-0.69	0.0009
Intermediate-1	1.00		
Intermediate-2	1.65	1.14-2.40	0.008
High	2.84	1.80-4.49	< 0.0001
Age (years)			
< 60	1.00		
≥ 60	1.01	0.99-1.02	0.18

CI, Confidence Interval

[a]: A value >1 indicates that the outcome is worse for that category in comparison with the baseline

Secondly, the impact of intensive treatment was tested in 159 younger patients, belonging to the intermediate-1, intermediate-2 and high-risk categories of the IPSS. The results are shown in Table 6. The IPSS risk groups appeared to be of significant prognostic value. The comparison between patients who received intensive treatment and those who received supportive care only yielded a hazard ratio of 0.65 (95% CI of 0.45-0.94). This indicates that the rate of death was 35% lower in patients receiving intensive antileukemic treatment (p=0.02).

Table 6. Results of Cox's proportional hazards model for survival of intermediate-1, intermediate-2 and high-risk patients aged less than 61 years (N=159).

Variable	Hazard Ratio[a]	95% CI	P-value
IPSS risk group			
Intermediate-1	1.00		
Intermediate-2	1.46	0.96-2.23	0.08
High	2.22	1.38-3.58	0.001
Intensive treatment			
Yes	0.65	0.45-0.94	0.02
No	1.00		
Diagnosis			
Before 1992	1.17	0.80-1.70	0.41
After 1992	1.00		

CI, Confidence Interval

[a]: A value >1 indicates that the outcome is worse for that category in comparison with the baseline

Ultimately, we analysed the prognostic effect of the IPSS in 83 intensively treated patients aged < 61 years (excluding the low-risk group). The estimated hazard ratio for the high-risk group compared with the intermediate-1 risk group was 1.81 (95% CI 0.16-21.16; p=0.63). The estimated hazard ratio for the intermediate-2 risk group compared with the intermediate-1 risk group was 0.83 (95% CI 0.22-3.13; p=0.78). The percentage of bone marrow blasts cells was not predictive for survival. There was a trend for better survival in patients with fewer cytopenias and without poor prognostic cytogenetic features, although this did not reach statistical significance. Outcome after allogeneic stem cell transplantation was significantly better than after chemotherapy with or without autologous stem cell transplantation (p=0.006).

DISCUSSION

Since 1982, the FAB classification has been used to classify MDS patients and to predict outcome in terms of survival and risk of AML development. The FAB classification is based solely on morphological criteria. It has been increasingly acknowledged that biological and molecular variables are important for diagnosing and stratifying MDS patients.

The development of the International Prognostic Scoring System (IPSS) in 1997, based on cytogenetic criteria, number of blasts in the bone marrow and number of cytopenias, was a major step forward towards a risk-adapted treatment strategy for an individual patient. We applied the IPSS to 306 MDS patients from a single university centre. The Nijmegen patients formed a rather heterogeneous group compared with the IPSS workshop patients (i.e. different age distribution, including secondary MDS patients and patients receiving intensive treatment). To investigate the effectiveness of the IPSS in a large group of unselected patients, we applied the IPSS to all Nijmegen patients. Despite the different nature of the Nijmegen patients, the IPSS stratified our patients effectively into the four different categories. The number of reports applying the IPSS is still limited.[10,13-16] An overview of the reported results is given in Table 7. The patients from the M.D. Anderson Cancer Center [13] were younger, had more often RAEBt, two or three cytopenias and prognostically poor cytogenetic abnormalities. A shorter survival for each of the IPSS risk categories was found. In the Leuven analysis [10] patients were diagnosed during a different period. This analysis included only patients who underwent bone marrow biopsy. Out of 184 patients, 30 (16%) received high-dose chemotherapy. Outcome of low and high-risk patients was better (6.5 and 0.7 years) and outcome of intermediate-1 risk patients (2.6 years) was worse compared to the IPSS workshop patients. The median age of the patients in the Korean study was 53 years.[14] This study included patients treated with low-dose cytarabine, androgen and all-*trans* retinoic acid. Jaiyesimi et al. applied the IPSS to 74 patients diagnosed between 1990 and 1997.[15] Compared with the workshop patients, their patients were older and presented with more cytopenias. The median survival for the intermediate-1 (3.4 years) and high-risk (0.5 years) group was comparable, but an improved survival for the intermediate-2 risk group (4.1 years) was found. However, patient numbers in the low risk, intermediate-2 risk and high-risk groups were small.

The observed differences in median survival within the four risk categories raises several questions. Do the IPSS workshop patients represent patients diagnosed nowadays? Does the selection of patients play a role in the reported results? The IPSS workshop obtained clinical data of 816 primary MDS patients from seven previously reported studies. Together, these studies included over 1600 patients between 1970 and 1992. In about 50% of reported patients, insufficient data were available, and hence selection may have occurred. Compared with the IPSS workshop patients, the Nijmegen patients presented with more adverse prognostic features. As Nijmegen is a referral centre for MDS patients in the south-eastern part of The Netherlands, this may in part explain the observed differences. As in the series of Estey et al. [13], median blood counts in Nijmegen patients were lower than in the IPSS workshop patients. The workshop authors [17] confirmed a shorter survival in patients with more profound cytopenias.

Another point to consider is whether the natural history of MDS has changed over time, and whether supportive care has improved in recent years. All IPSS workshop patients were diagnosed before 1992. In the Nijmegen patients, a trend towards better survival was observed for both intensively treated and not-intensively treated patients diagnosed after 1992. However, this was not statistically significant.

In the Nijmegen cohort, 213 out of 306 patients received supportive care only. In these patients, the IPSS was highly predictive for survival. Multivariate analysis showed a sevenfold risk of death for the IPSS high-risk patients compared with the low risk patients. The key question is whether the IPSS could also predict the outcome of MDS patients aged < 61 years treated with intensive therapies, including stem cell transplantation. Therefore, we evaluated survival in 83 intensively treated patients. In this study the median survival of intermediate-2 risk patients was better than that of intermediate-1 risk patients. This suggests that patients belonging to the intermediate-2 risk group, in particular, benefited from intensive treatment strategies. In multivariate analysis, the different IPSS risk groups were not predictive for survival. Hence, this analysis does not support the value of the IPSS to predict survival after intensive antileukemic treatment.

Median survival after intensive antileukemic treatment was significantly better than median survival after supportive care only. Opponents of intensive treatment in MDS often argue that the reported results are biased by selection of patients with a relatively good prognosis. The present analysis establishes that survival of non-intensively treated patients did not deteriorate with the course of time. This supports the fact that we did not select patients with a relatively good prognosis for intensive treatment. Nevertheless, this

analysis was not designed to compare the outcome of intensively treated patients with that of patients who received supportive care only. An important pitfall of observational studies is that selection bias can never be ruled out completely.

Another point to consider is whether the applied treatment was effective. Treatment included chemotherapy only, chemotherapy followed by autologous transplantation and allogeneic transplantation with or without preceding chemotherapy. We demonstrated that chemotherapy only and chemotherapy followed by autologous stem cell transplantation were less effective than allogeneic stem cell transplantation. One can argue that the imbalance of the different treatments in the various IPSS risk groups may have influenced the outcome. However, in the more homogeneous group of 46 patients who underwent allogeneic stem cell transplantation, the conclusions remained unchanged.

Finally, it is still unclear which patients benefit most from intensive treatment strategies. The present study suggests that survival in the intermediate-2 risk group improved after intensive therapy. The estimated 4-year survival rate in the intermediate-2 risk group was 40% for patients treated intensive therapy versus 11% for patients receiving supportive care only. Survival in the high-risk group of the IPSS was rather disappointing. After intensive antileukemic therapy, the 4-year survival rate of the high-risk patients was 19%, whereas none of the patients receiving supportive care only achieved prolonged survival. The literature contains only a few reports on the value of the IPSS in intensively treated patients. Appelbaum et al. [18] applied the IPSS to 251 patients who underwent allogeneic bone marrow transplantation. They concluded that the IPSS was useful to predict relapse and disease-free survival after allogeneic transplantation. The reported 5-year disease-free survival rates were 60% for low-risk and intermediate-1 risk patients, 36% for intermediate-2 risk patients and 28% for high-risk patients. In our subanalysis of 46 patients who received allogeneic stem cell transplantation, the estimated 4-year survival rates were 50% for the intermediate-1 risk patients, 67% for the intermediate-2 risk patients and 30% for the high-risk patients.

Cytogenetic abnormalities occur in about 50% of MDS patients.[3,19-21] Two large studies demonstrated that karyotype has independent prognostic value.[3,8] Estey et al. [22] reported that cytogenetic risk groups were highly predictive for outcome after intensive chemotherapy. A study from Vancouver [23] showed that IPSS cytogenetic risk groups have impact on survival after allogeneic bone marrow transplantation. The Spanish group [24] confirmed the prognostic value of the IPSS in 640 patients. Their main criticism was

that the intermediate cytogenetic prognostic risk group is a receptacle of single- and double-chromosome abnormalities and that some single abnormalities might well prove to be of good or poor prognosis when a larger number of cases are analysed.

Although the Nijmegen patients showed worse prognostic features at diagnosis than the IPSS workshop patients, we conclude that the IPSS is an effective scoring system for MDS patients treated with supportive care only. However, the scoring system did not seem to be the best method for predicting outcome after intensive antileukemic treatment. In particular, the intermediate-2 risk patients seemed to benefit from intensive antileukemic treatment. Use of the IPSS is recommended for planning treatment for an individual patient. A scoring system based on the number of cytopenias and cytogenetic risk group might predict outcome after intensive therapy better than a scoring system that includes the percentage of bone marrow blasts.

Table 7. Application of the International Prognostic Scoring System in the literature regarding clinical outcome of MDS patients.

	IPSS	Estey	Maes	Lee	Jaiyesimi	Sperr	Nijmegen
Number of patients	816	219	184	91	79	102	306
Median age	69	65	64	53	74	71	58
Time period	'70-'92	< '91	'80-'97	'89-'97	'90-'97	'89-'99	'77-'00
Median survival (yr.) (%)[a]							
Low	5.7 (33)	2.1 (13)	6.5 (22)	3.8 (4)	NR (15)	7.5 (23)	5.1 (12)
Intermediate-1	3.5 (38)	1.2 (41)	2.6 (46)	3.6 (47)	3.4 (49)	1.7 (41)	2.4 (41)
Intermediate-2	1.2 (22)	0.7 (30)	1.3 (25)	0.8 (24)	4.1 (19)	1.9 (20)	1.2 (29)
High	0.4 (7)	0.4 (16)	0.7 (7)	0.7 (24)	0.5 (16)	1.0 (17)	0.8 (19)

NR, not reached

[a]: Percentage of patients in the different IPSS risk groups

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CHAPTER 6

Identification of prognostic clinical and biologic factors for outcome of patients with high-risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) treated with intensive antileukemic therapy

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ABSTRACT

High-risk MDS patients have a less favorable outcome after intensive treatment compared with AML. This may reflect disease-related factors or a higher frequency of patient-related factors. The purpose of this analysis was to identify clinical and biologic factors for outcome of MDS and AML patients. 981 patients (< 65 yr.) received identical remission-induction and consolidation treatment in two European studies (EORTC AML-10 and CRIANT). Estimated 5-year survival was comparable (34% (AML-10) vs. 27% (CRIANT)) but DFS was better in the AML-10 study (40% vs. 28%). In multivariate analysis cytogenetics, white blood count, age, and study protocol were prognostic for survival in all patients. However, some variables appeared prognostic in only one of the studies. AML-10: performance status, FAB M2/M4 and cytogenetics inv(16)/t(8;21), CRIANT: number of cytopenias and duration of Antecedent Hematologic Disorder. A prognostic score was developed for both studies. The scores distinguish 3 groups with a 5-year survival of 54%, 38%, and 19% (AML-10) vs. 69%, 37%, and 5% (CRIANT). According to the scores 30% of AML-10 and 43% of CRIANT patients have a survival less than 20%. Our finding that prognostic factors differ in MDS and AML patients supports the hypothesis that MDS and AML are intrinsically different disorders.

INTRODUCTION

In the early eighties the French-American-British (FAB) classification has been developed for the classification of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) based on the percentage of blast cells in the bone marrow and in the peripheral blood, as well as on the presence of Auer rods and monocytes.[1,2] Although dysplastic features form the hallmark of the myelodysplastic syndromes, dysplastic features are also observed in de novo AML.[3] The distinction between AML and MDS was based on an arbitrary cut-off of 30% bone marrow blasts. One of the major changes in the recently introduced WHO classification is lowering the blast percentage for the diagnosis of AML to 20%.[4]

The distinction between MDS and AML has important therapeutic consequences. Intensive chemotherapy regimens with or without stem cell transplantation (SCT) are widely used for de novo AML patients aged less than 60 years.[5-10] In about 75% of patients combination chemotherapy induces a complete remission with 30-40% long-term leukemia-free survivors. The use of AML-like therapy in patients with high-risk MDS has been accepted less widely. Remission-induction chemotherapy results in complete remission rates between 15-65%.[6,11-15] The median remission duration is usually short due to a high incidence of early relapses. The experience with autologous SCT in MDS is still limited.[16,17] Allogeneic SCT is a curative option for younger MDS patients with HLA-identical donors with reported disease-free survival of approximately 35-40%.[18,19] Recently, treatment of patients aged over 55 years resulted in a relapse-free survival of 47%.[20]

Important biologic differences between MDS and AML have been demonstrated.[21] The question is whether the reported poorer outcome of high-risk MDS patients compared to de novo AML patients reflects an intrinsic property of the stem cells involved (disease-related factors like cytogenetic abnormalities and molecular aberrations) and possibly of the microenvironment or reflects an increased incidence of poor prognostic patient-related factors (like advanced age and poor performance status) in MDS.[15]

In the present analysis we compared the treatment outcome of de novo AML patients with outcome of high-risk MDS and secondary AML (sAML) patients, after identical remission-induction and consolidation chemotherapy. Patients with de novo AML or sAML after MDS of less than 6 months were treated in the EORTC-GIMEMA AML-10 study (06931). Patients with high-risk MDS or secondary AML after MDS of at least 6 months were

treated in the CRIANT study (06961), a joint study of the EORTC, GIMEMA, EBMT, HOVON, SAKK and Nordic MDS Groups. The purpose of the present analysis was to identify prognostic factors for outcome of MDS and AML patients. A second question was whether disease-related factors differ between MDS and AML and whether poor prognostic factors occur more often in MDS.

PATIENTS AND METHODS

AML-10 study

Between November 1993 and December 1999 2157 patients were included in the AML-10 study. Patients aged 15-60 years with de novo AML or sAML supervening after documented MDS of less than 6 months duration were eligible, after informed consent was obtained. Patients with AML M3 were excluded. The objective of the AML-10 study was to compare the effect of three different intercalating agents (idarubicin, daunorubicin and mitoxantrone) in the remission-induction and consolidation regimens. For the present analysis we selected the 717 patients treated in the idarubicin arm. By doing this, we selected the patients from both studies (AML-10/CRIANT), who received identical remission-induction and consolidation chemotherapy. In the AML-10 study 25 patients appeared to be ineligible for the following reasons: other disease (N=11), age (N=1), performance status (N=1), concomitant disease (N=2), poor quality of the data (N=9), other (N=1). So, 692 patients from the AML-10 study were included in the present analysis.

CRIANT study

Between December 1996 and December 2001 324 patients were included in the CRIANT study. Patient aged between 16-60 years (or -65 years according to the policy of the centre), with a WHO performance status of 0-2, after informed consent was obtained, were included in the study if they had (a) untreated RAEBt or RAEB with more than 10% blasts in the bone marrow (b) sAML supervening after overt MDS of more than 6 months duration (c) CMML with more than 5% blasts in the bone marrow, more than 16 x 10^9/l neutrophils or more than 2.6 x 10^9/l monocytes in the blood (d) other forms of MDS with multiple chromosome abnormalities and/or profound cytopenias defined as neutrophil count less than 0.5 x 10^9/l and/or platelet count less than 20 x 10^9/l.

Since there is no consensus about the use of chemotherapy in RA(RS) patients, these patients (N=8) were excluded from the present analysis. The CMML patients (N=19) were excluded as well, since these patients are considered to have a myeloproliferative / myelodysplastic disorder according to the new WHO classification instead of a MDS. So, for the present analysis 297 patients presenting with RAEB, RAEBt and sAML were eligible. Eight patients were not evaluable for the following reasons: other disease (N=1), performance status (N=1), and poor quality of the data (N=6). Ultimately 289 patients from the CRIANT study were included.

Treatment

Remission-induction chemotherapy consisted of idarubicin 10 mg/m^2 iv. days 1, 3, 5, cytarabine 100 mg/m^2 continuous iv. days 1-10 and etoposide 100 mg/m^2 iv. days 1-5 (ICE). In the AML-10 study a single extra bolus of cytarabine 25 mg/m^2 was given on day 1, before starting the continuous infusion. In case of a partial remission (PR) a second identical remission-induction course was given. In case of a complete remission (CR) a consolidation course was given consisting of idarubicin 10 mg/m^2 iv. days 4-6 in combination with an intermediate dose of cytarabine 500 mg/m^2 twice daily iv. days 1-6 (IDIA).

HLA typing of patient and family was initiated at the onset of protocol treatment in all patients younger than 45-55 years (according to the policy of the centre) in the AML-10 study and in patients younger than 50-60 years in the CRIANT study. In case of an HLA-A, -B, -DR identical sibling and confirmed CR after the consolidation course, the patient was proposed for allografting.

In the AML-10 study patients lacking an HLA identical donor in continuous CR were eligible for autologous bone marrow transplantation (ABMT). In 1994, a second randomization was introduced comparing ABMT and autologous peripheral blood stem cell transplantation (APSCT).

In the CRIANT study patients lacking an HLA identical donor in continuous CR were randomized between a second consolidation course consisting of cytarabine 1 g/m^2 twice daily i.v. days 1-6 and APSCT.

The minimal required number for a successful harvest was 1 x 10^8/kg nucleated cells and 1 x 10^4/kg CFU-GM (ABMT) or 2 x 10^6 $CD34^+$ cells/kg (APSCT).

Definitions

Therapy-related MDS/AML (tMDS/tAML) was defined as MDS or AML supervening after chemotherapy or radiotherapy for an earlier (non)-malignant disease.

Secondary AML was defined as AML after documented MDS. In the CRIANT study patients with a history of at least 6 months were included, in the AML-10 study patients with AML after MDS less than 6 months were included.

The duration of Antecedent Hematologic Disorder (AHD) was defined as the time since initial diagnosis of MDS and the start of protocol treatment. For patients with sAML, AHD was defined as the time since diagnosis of MDS and the start of treatment for AML. For de novo AML, AHD was considered as the time between diagnosis of AML and the start of treatment.

Complete remission (CR) was defined as the absence of clinical signs of the disease with (near-) normal peripheral blood counts and a normocellular bone marrow containing less than 5% blast cells.

Partial remission (PR) was characterized by bone marrow containing less than 25% blasts and more than 50% decrease of blasts percentage from pre-therapeutic levels with (near-) normal blood counts and no circulating blasts.

CR lasting less than 4 weeks and PR lasting less than 8 weeks were classified as failures. Early death was defined as death within 10 days from start of treatment.

Statistical analysis

The overall duration of survival was calculated from start of induction until date of death (whatever the cause); patients still alive were censored at their last follow-up. For patients who reached CR the disease-free survival (DFS) was calculated from the date of CR until the date of first relapse or of death in first CR. The time to relapse and time to death in CR were calculated as the DFS; patients who died in CR and those who relapsed were respectively censored at that moment for these 2 analyses. By definition all patients who died in CR were considered as death from treatment related mortality (TRM).

Actuarial curves were calculated according to the Kaplan-Meier technique. The standard errors (SE) of the estimates were computed using the Greenwood formula.[22] The estimates of the incidence of relapse and of death in CR, and their corresponding standard errors, were obtained using the cumulative incidence method, where the risks of death in CR and of relapse were considered as competing risks.[22] The differences between actuarial curves were tested for statistical significance using the two-tailed log-

rank test [22], whereas for the cumulative incidences the Gray test has been used.[23] The Cox's proportional hazards model has been used to obtain the estimate and the 95% confidence interval (CI) of the hazard ratio (HR) of the instantaneous event rate in one group vs. the one in another group, as specified by a given variable, and the Wald test has been used to determine the prognostic significance.[22] The Cox model has also been used to determine the independent prognostic factors among those that appeared important in univariate analyses ($p<0.1$).

RESULTS

Patients

Median age of the 692 patients in the AML-10 study was 44 years versus 52 years for the 289 patients in the CRIANT study. In the AML-10 study 591 patients (85%) were aged less than 56 years compared to 203 patients (70%) in the CRIANT study. The median follow-up was 5.3 versus 3.5 years, respectively. The performance status was better in the CRIANT study: 93% of CRIANT patients had a WHO performance status of 0/1 versus 78% of AML-10 patients. The AML-10 study included 18 patients with performance status 3, whereas this was an exclusion criterion for the CRIANT study. In the AML-10 study 98% of patients did not have any AHD (Antecedent Hematologic Disorder). On the other hand 4% of patients in the CRIANT study did have an AHD with duration between 1 and 6 months and 14% an AHD with a duration of longer than 6 months. In the AML-10 study 659 patients (94%) presented with de novo AML, 16 patients (2%) with sAML and 17 patients (3%) with tAML. In the CRIANT study 197 patients (68%) were diagnosed as primary MDS, 21 patients (7%) as tMDS, 55 patients (19%) as sAML, 8 patients (3%) as tAML after MDS. In addition, 8 patients (3%) in the CRIANT study were diagnosed as de novo AML by the reviewer and 14 of 55 sAML patients had a history of MDS less than 6 months at reviewing. In order to be consistent with the intention-to-treat principle, these patients were not excluded from the analysis.

Cytogenetic data were unknown or failed in 45% and 14% of patients in the 2 studies. Poor prognostic cytogenetic data according to the IPSS (International Prognostic Scoring System) were less frequently found in AML-10 patients (11%) compared to CRIANT patients (28%). Since the IPSS is designed for MDS patients, the very good risk cytogenetic features for AML patients (inv(16), t(8;21)) are not separately recognized in this scoring system. The AML-10 study included 72 patients with inv(16) or t(8;21) and the CRIANT study 5 patients. For the purpose of this analysis these patients were included in the good risk group of the IPSS.

In the majority of patients review of the pathology has been performed (65% (AML-10) and 80% (CRIANT)), but information on dysplasia was reported infrequently. Patient characteristics of both studies are given in table 1.

Table 1. Characteristics of AML-10 and CRIANT patients.

Variable	AML-10	CRIANT
Number of patients	692	289
Median age (yr.) (range)	44 (15-60)	52 (16-65)
Sex (%)		
Male	364 (53)	163 (56)
Female	325 (47)	123 (43)
Unknown	3 (-)	3 (1)
Performance status (%)		
0-1	538 (78)	268 (93)
2	131 (22)	17 (6)
3	18 (3)	0 (-)
Unknown	5 (1)	4 (1)
History of toxic exposure (%)		
Yes	41 (6)	36 (13)
No	611 (88)	212 (73)
Unknown	40 (6)	41 (14)
AHD (%)		
No	676 (98)	226 (78)
1- 6 months	16 (2)	12 (4)
> 6 months		41 (14)
Unknown		10 (4)
Disease (%)		
De novo AML	659 (94)	8 (3)
De novo MDS		197 (68)
Secondary AML	16 (2)	55 (19)
Therapy-related AML	17 (3)	8 (3)
Therapy-related MDS		21 (7)
Median Hemoglobin (g/dl) (range)	8.8 (3.8-15.4)	8.1 (4.2-19.9)
Median WBC (x 10^9/l) (range)	16.6 (0.4-590)	3.4 (0.8-293)
Median PMN (x 10^9/l) (range)	1.4 (0-51.7)	1.0 (0-44.9)
Median Platelets (x 10^9/l) (range)	50 (4-998)	49 (3-648)
WBC (x 10^9/l) (%)		
< 25	402 (58)	261 (90)
25-100	201 (29)	23 (8)
$\geq$ 100	89 (13)	3 (1)
Unknown		2

Number of cytopenias (%)				
0/1	175 (25)		54 (19)	
2	310 (45)		111 (38)	
3	205 (30)		123 (43)	
Unknown	2 (-)		1 (-)	
Bone marrow blasts (%)				
< 5%	1 (-)		5 (2)	
5-10%			45 (16)	
11-20%			89 (31)	
21-30%	5 (1)		63 (22)	
≥ 30%	684 (99)		56 (19)	
Unknown	2 (-)		31 (11)	
FAB (%)				
AML / MDS	M0	27 (4)	RAEB < 10%	21 (7)
	M1	128 (19)	RAEB ≥ 10%	77 (27)
	M2	221 (32)	RAEBt	120 (42)
	M4	147 (21)	AML	71 (25)
	M5	131 (19)		
	M6	23 (3)		
	M7	5 (1)		
Unclassified		10 (1)		
Cytogenetics[a] (%)				
Good	72 (10)		5 (2)	
Normal, -Y	147 (21)		102 (35)	
Poor	163 (24)		143 (50)	
Unknown / failed	310 (45)		39 (14)	
Cytogenetics[b] (%)				
Good	213 (31)		111 (38)	
Intermediate	96 (14)		57 (38)	
Poor	73 (11)		82 (28)	
Unknown / failed	310 (45)		39 (14)	

[a]: Keating classification: Good: t(8;21) or inv(16); Poor: others

[b]: IPSS classification: Good: normal, -Y, 5q-, 20q-; Poor: chromosome 7 abnormalities, complex (≥ 3) abnormalities; Intermediate: other abnormalities. For the purpose of this analysis the very good risk AML patients with inv(16) and t(8;21) were included in the good risk group

Response to remission-induction chemotherapy

In the AML-10 study 472 patients (68%) achieved complete remission after one (440 patients) or two (32 patients) remission-induction courses. In the CRIANT study 169 patients (59%) entered CR after one (150 patients) or two (19 patients) courses. Ninety-four patients (14%) died during the first 10 days after start of treatment or in hypoplasia in the AML-10 study versus 28 patients (10%) in the CRIANT study. The remaining 126 patients and 92 patients showed a partial response (3% vs. 6%), failure (14% vs. 22%), extramedullary leukemic localization (0.3% vs. 0.7%), persistent hypoplasia (0.3 vs. 4%) or unknown response (AML-10: 0.7%) (Table 2).

Response to consolidation course

Four hundred forty-six out of 472 patients (94%) in CR after remission-induction treatment in the AML-10 study received the consolidation course compared to 157 out of 169 patients (93%) in the CRIANT study. In the AML-10 study CR was confirmed after recovery from the consolidation course in 438 patients (98%), 6 patients showed early relapse (1%) and in 2 patients the response was unknown. In the CRIANT study the complete remission percentage after the consolidation course was lower 70% (110 patients); among the remaining patients 20 (13%) had active disease, 25 patients (16%) showed persistent hypoplasia and in 2 patients (1%) the response was unknown. Median time to platelet recovery of > 20 x 10^9/l after the consolidation course was 26 days and 37 days for the 2 studies ($p < 0.0001$). Median time to PMN recovery of > 0.5 x 10^9/l was 26 versus 31 days, respectively ($p=0.0002$).

Donor availability and transplantation

In the AML-10 study 157 out of 472 patients in CR did have an HLA-identical sibling. One hundred-five patients (67%) underwent allogeneic SCT in first CR after the consolidation course according to the protocol and 9 patients received an autologous transplant in first CR. Of the 315 patients in CR after remission-induction chemotherapy without an HLA-identical donor 136 (43%) underwent autologous SCT according to the protocol and two patients received an allogeneic SCT from an alternative donor in first CR. In the CRIANT study 52 out of 169 patients in CR after remission-induction treatment did have an HLA-identical donor. Forty-two patients (81%) received an allogeneic SCT according to the protocol. In 117 patients in CR without a donor 59 patients (50%) were randomized between APSCT (N=30) and a second consolidation course (N=29). In all, 18 patients

underwent APSCT according to the protocol and 7 patients received an allogeneic transplant from an unrelated donor in first CR.

Table 2. Treatment results in AML-10 and CRIANT studies.

Variable	AML-10	CRIANT
Number of patients	692 (%)	289 (%)
Response remission-induction (RI)		
CR	472 (68)	169 (59)
PR	19 (3)	17 (6)
Resistance	97 (14)	63 (22)
Extra-medullary leukemic localization	2	2 (1)
Persistent hypoplasia	3	10 (4)
Death in hypoplasia	71 (10)	27 (9)
Early death (< 10 days)	23 (3)	1 (-)
Unknown	5 (1)	
Platelet recovery[a] > 20 x 10^9/l		
Median days	26	37
PMN recovery[a] > 0.5 x 10^9/l		
Median days	26	31
Stage at transplantation (SCT)		
In first CR	252 (36)	67 (23)
Allogeneic SCT	107	49
Autologous SCT	145	18
After first CR	24 (4)	15 (5)
Unknown stage	4 (1)	
After no CR[b]	29 (4)	23 (8)
No transplantation	383 (55)	184 (64)
Disease-free survival		
CCR	196 (42)	55 (33)
Relapse	218 (46)	97 (57)
Death in CR	58 (12)	17 (10)
Survival		
Alive	248 (36)	95 (33)
Dead	444 (64)	194 (67)

[a]: After the start of consolidation course

[b]: Salvage treatment (off protocol)

Outcome of patients

Median survival was 1.5 years in the AML-10 study compared to 1.3 years in the CRIANT study. The estimated 5-year survival rates were 34% (s.e = 1.9%) versus 27% (s.e. = 3.2%) (p=0.26) (Figure 1). The estimated 5-year DFS rate was higher in the AML-10 study (40%, s.e = 2.3%) compared to the CRIANT study (28%, s.e. = 4.0%) (p=0.02) (Figure 2). The 5-year cumulative incidences of relapse were 48% (s.e. = 2.4%) and 62% (s.e. = 4.3%) (p=0.004). The 5-year incidences of death in CR were 13% (s.e. = 1.6%) and 11% (s.e. = 2.4%) (p=0.47).

Figure 1. Overall survival in AML-10 and CRIANT study.

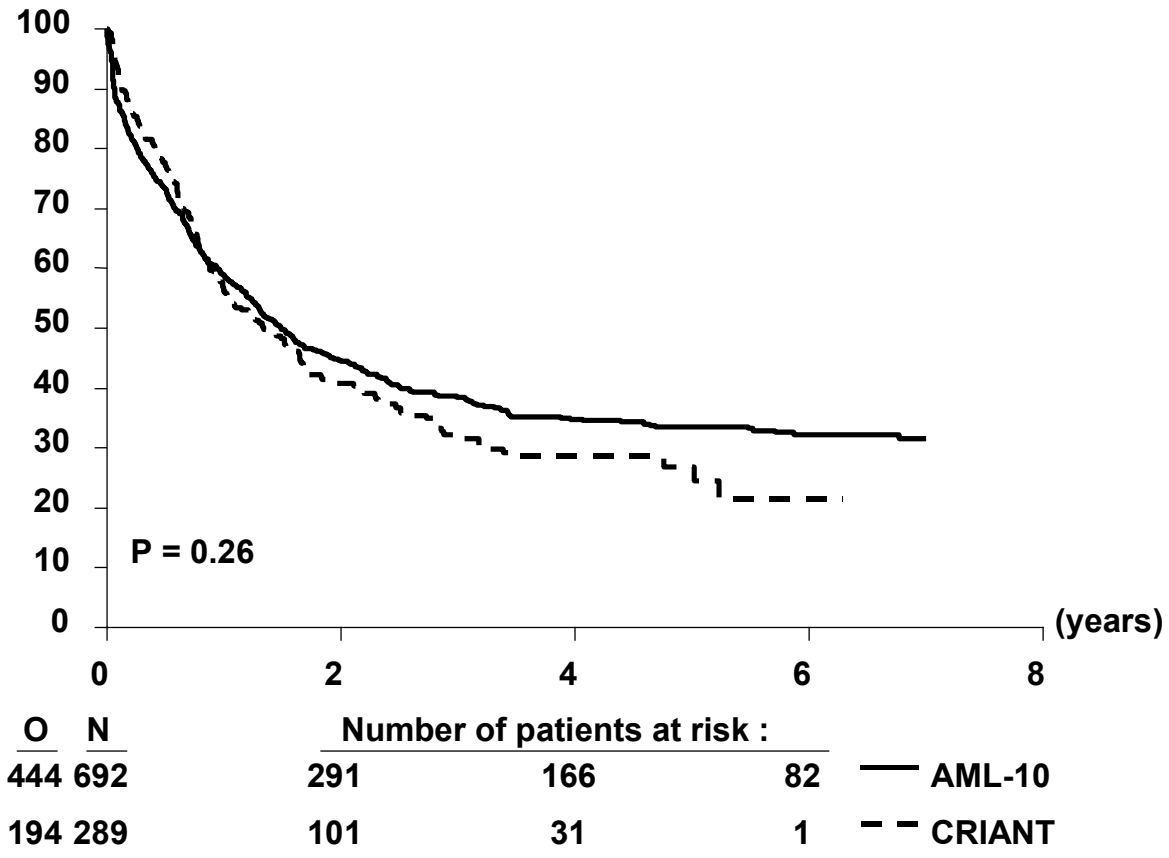
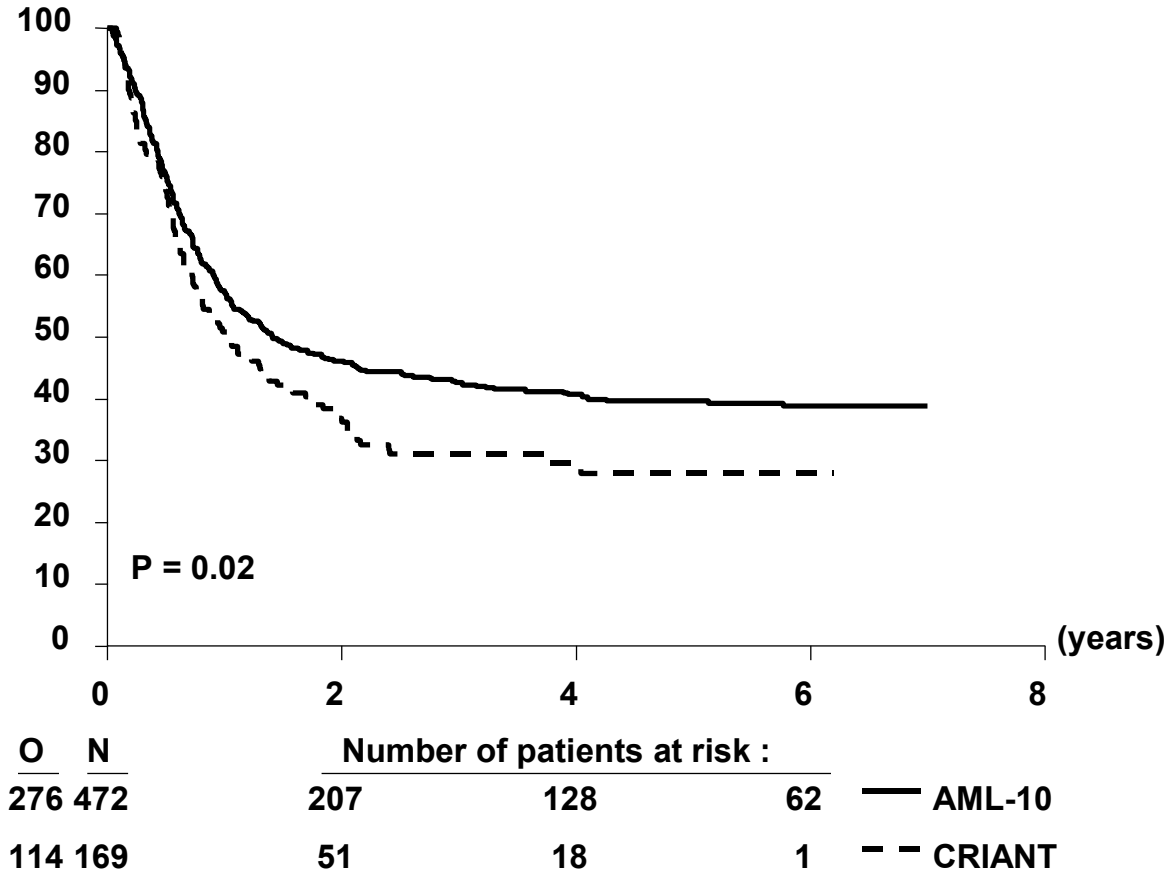


Figure 2. Disease-free survival in AML-10 and CRIANT study.



Prognostic factors

In univariate analysis performed on all 981 patients the following variables appeared to be prognostic factors for overall survival: cytogenetic risk group according to IPSS, age, performance status (WHO), FAB classification in AML patients, white blood count (WBC) (both continuous and categorical variable), number of blasts in the peripheral blood, AHD and LDH (Table 3). The hazard ratio (HR) for the intermediate vs. the good cytogenetic risk group was 1.40 with a 95% Confidence Interval (CI) of 1.09-1.78, the HR for the poor prognostic cytogenetic risk group was 2.53 (95% CI: 2.01-3.19).

The prognostic importance for survival was not significant for: study protocol (AML-10 versus CRIANT), FAB classification in MDS patients, number of cytopenias, percentage of blasts in the bone marrow, primary disease (therapy-related MDS/AML versus other), and the number of lineages with dysplastic features (data not shown). Table 3 summarizes the variables assessed in univariate analyses.

For disease-free survival the following variables appeared to be of prognostic importance: cytogenetic risk group according to IPSS, FAB in AML, WBC, age, LDH, study and primary disease. The HR for the intermediate cytogenetic risk group was 1.31 (95% CI: 0.97-1.78) and 2.68 (95% CI: 1.98-3.63) for the poor cytogenetic risk group. The time until hematological recovery (platelets > 20 x 10^9/l and PMN > 0.5 x10^9/l) from start of the consolidation course had no impact on DFS. The hazard ratio for the time to recovery ($\leq$ 4 weeks vs. > 4 weeks) was 0.84 (95% CI: 0.68-1.04) for platelet recovery and 0.99 (95% CI: 0.79-1.23) for PMN recovery.

Table 3. Univariate analyses for survival and disease-free survival.

Endpoint		Survival			Disease-free survival	
Variable	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Cytogenetic risk group IPSS			< 0.0001			< 0.0001
Good	1.00			1.00		
Intermediate	1.40	1.09-1.78		1.31	0.97-1.78	
Poor	2.53	2.01-3.19		2.68	1.98-3.62	
Unknown	1.60	1.31-1.94		1.32	1.04-1.68	
Performance status			< 0.0001			0.18
0	1.00			1.00		
1	1.23	1.03-1.46		1.04	0.84-1.29	
2	1.57	1.24-1.97		1.30	0.96-1.76	
3	2.74	1.59-4.70		1.88	0.83-4.25	
FAB in AML			< 0.0001			0.003
M0	1.00			1.00		
M1	0.88	0.57-1.37		0.81	0.41-1.58	
M2	0.57	0.37-0.87		0.52	0.27-0.99	
M4	0.57	0.36-0.89		0.48	0.24-0.94	
M5	1.04	0.67-1.61		0.87	0.44-1.70	
M6	0.81	0.43-1.51		0.56	0.22-1.41	
M7	1.32	0.62-2.83		1.05	0.33-3.36	
WBC (x 10^9/l)			< 0.0001			0.0003
< 2.5	1.00			1.00		
2.5-10	0.85	0.68-1.06		0.60	0.46-0.79	
10-25	0.82	0.63-1.07		0.57	0.41-0.79	

25-100	0.95	0.75-1.21		0.77	0.58-1.02	
≥ 100	1.71	1.28-2.28		1.04	0.69-1.58	
Blast count in blood (x 10^9/l)			< 0.0001			0.07
< 2.5	1.00			1.00		
2.5-10	0.87	0.69-1.08		0.74	0.56-0.99	
10-25	1.11	0.84-1.47		0.98	0.69-1.40	
25-100	1.05	0.83-1.31		1.05	0.80-1.39	
≥ 100	2.29	1.72-3.04		1.51	0.93-2.46	
Age (yr.)			0.0004			0.0001
15-45	1.00			1.00		
46-55	1.36	1.14-1.62		1.36	1.08-1.71	
> 55	1.39	1.13-1.70		1.70	1.32-2.20	
AHD			0.008			0.08
0-6 months	1.00			1.00		
> 6 months	1.60	1.13-2.28		1.67	0.94-2.97	
LDH			0.03			0.02
< Upper Normal Limit (UNL)	1.00			1.00		
UNL-< 2.5 x UNL	0.92	0.76-1.12		0.74	0.58-0.94	
2.5-< 5 x UNL	1.07	0.84-1.37		0.91	0.67-1.24	
5-< 10 x UNL	1.18	0.86-1.62		0.72	0.45-1.15	
≥ 10 x UNL	1.85	1.15-2.98		1.61	0.98-2.92	
Study			0.26			0.02
AML-10	1.00			1.00		
CRIANT	1.10	0.93-1.31		1.30	1.05-1.62	
FAB in MDS			0.52			0.84
RAEB < 10% blasts	1.00			1.00		

RAEB ≥ 10% blasts	1.45	0.74-2.86		1.21	0.56-2.63	
RAEBt	1.46	0.76-2.82		1.08	0.51-2.27	
Number of cytopenias			0.17			0.32
0/1	1.00			1.00		
2	0.88	0.72-1.08		0.83	0.65-1.07	
3	1.04	0.85-1.28		0.94	0.72-1.23	
Blast percentage in bone marrow			0.38			0.12
< 5	1.00					
5-10	1.15	0.33-4.01		1.00		
10-20	1.39	0.44-4.42		1.20	0.61-2.39	
20-30	1.63	0.51-5.22		1.44	0.71-2.92	
30-50	1.20	0.38-3.81		0.82	0.41-1.61	
50-75	1.33	0.43-4.18		0.97	0.51-1.86	
75-100	1.54	0.49-4.81		0.95	0.50-1.79	
Primary disease			0.24			0.04
MDS/AML	1.00			1.00		
Therapy-related MDS/AML	1.24	0.87-1.77		1.54	1.01-2.34	

Multivariate analyses

To correct for the imbalance in poor performance status (PS=3) between both studies, 0 (CRIANT) versus 18 patients (AML-10), the latter patients have been excluded from the subsequent analyses. Study effect remained practically unchanged regarding overall survival and DFS (data not shown). In multivariate analysis cytogenetics, WBC, age and study protocol appeared to be of prognostic importance for both overall survival and DFS, whereas initial performance status was important only for survival (Table 4). For survival the estimated hazard ratio for the presence of poor prognostic cytogenetic abnormalities was 2.52 (95% CI: 1.99-3.20). The hazard ratio for the intermediate prognostic cytogenetic abnormalities was 1.54 (95% CI: 1.20-1.99).

The importance of AHD was not assessable in a model containing both the variables AHD and study protocol, since all patients with an AHD of longer than 6 months were included in the CRIANT study. Therefore, a separate multivariate analysis for survival in both studies is given in table 5. Cytogenetics, WBC and age appeared highly prognostic in both studies. In the CRIANT study an AHD with a duration of longer than 6 months negatively influenced survival. The number of cytopenias was of prognostic importance in the CRIANT study, but not in the AML-10 study. On the other hand the FAB subtype M2/M4 and cytogenetic abnormalities inv(16)/t(8;21) predicted for a better prognosis in the AML-10 study, but these variables were not applicable to the CRIANT study. Performance status appeared highly predictive only in the AML-10 study. The presence of poor prognostic cytogenetic features had a greater impact on survival in the CRIANT study (hazard ratio 3.51) compared to the AML-10 study (hazard ratio 1.75, when corrected for baseline).

Table 4. Results of Cox's proportional hazards models for outcome in all patients with an initial performance status < 3.

Endpoint	Survival			Disease-free survival		
Variable	Hazard Ratio[a]	95% CI	P-value	Hazard Ratio[a]	95% CI	P-value
Cytogenetics (IPSS)						
Good[b]	1.00			1.00		
Intermediate	1.54	1.20-1.99	0.0008	1.48	1.05-2.09	0.03
Poor	2.52	1.99-3.20	< 0.0001	2.59	1.86-3.60	< 0.0001
Unknown	1.64	1.33-2.02	< 0.0001	1.49	1.13-1.95	0.004
WBC (x 10^9/l)						
< 25	1.00			1.00		
25-100	1.31	1.07-1.60	0.009	1.40	1.07-1.84	0.01
$\geq$ 100	2.31	1.76-3.02	< 0.0001	1.97	1.29-3.02	0.002
Age (yr.)						
15-45	1.00			1.00		
46-55	1.42	1.18-1.70	0.0002	1.40	1.09-1.81	0.009
> 55	1.56	1.26-1.94	< 0.0001	1.82	1.36-2.44	< 0.0001
PS (0, 1, 2)	1.21	1.08-1.36	0.001	1.05	0.90-1.23	0.55
Study						
AML-10	1.00			1.00		
CRIANT	1.23	1.01-1.50	0.04	1.33	1.02-1.75	0.04

[a]: A value >1 indicates that the outcome is worse for that category in comparison with the baseline

[b]: Patients with inv(16) and t(8;21) included

Table 5. Results of Cox's proportional hazards model for survival in AML-10 and CRIANT study.

Study	AML-10			CRIANT		
Variable	Hazard Ratio[a]	95% CI	P-value	Hazard Ratio[a]	95% CI	P-value
Cytogenetics (IPSS)						
inv(16), t(8;21)	1.00					
Good	1.52	0.94-2.46	0.08	1.00		
Intermediate	2.03	1.24-3.32	0.005	1.79	1.15-2.78	0.009
Poor	2.66	1.60-4.41	0.0002	3.51	2.43-5.07	< 0.0001
Unknown	2.17	1.39-3.40	0.0007	1.57	0.97-2.55	0.07
WBC (x 10^9/l)						
< 100 (< 25)[b]	1.00			1.00		
$\geq$ 100 ($\geq$ 25)[b]	1.77	1.35-2.32	< 0.0001	2.01	1.21-3.32	0.007
FAB						
M0, M1, M5, M6, M7	1.53	1.25-1.86	< 0.0001			
M2, M4	1.00					
FAB unknown	0.79	0.32-1.91	0.60			
Age (yr.)						
15-45	1.00			1.00		
46-55	1.27	1.02-1.57	0.03	1.91	1.29-2.81	0.001
> 55	1.26	0.96-1.66	0.10	2.16	1.41-3.30	0.0004
PS (0, 1, 2)	1.24	1.08-1.41	0.002			
Number of cytopenias						
0-2				1.00		
3				1.70	1.24-2.32	0.0009
AHD (months)						
0-6				1.00		
> 6				1.54	1.04-2.29	0.03

[a]: A value >1 indicates that the outcome is worse for that category in comparison with the baseline
[b]: For the CRIANT study the cut-point 25 x 10^9/l was considered, as only 3 patients had a WBC > 100 x 10^9/l

Prognostic scores

For both studies a prognostic score was created based on the multivariate analyses in table 5: ∑(variable x ln(hazard ratio)). For the AML-10 study the following variables were incorporated in the scoring system: cytogenetic risk group, WBC, FAB in AML, age and PS. In the AML-10 study the cut-point for WBC was 100 x 10^9/l, as the prognosis was

very similar for patients with a WBC < 25 x 10^9/l and 25-100 x 10^9/l, whereas for the CRIANT study the cut-point 25 x 10^9/l was retained, since only 3 patients had a WBC > 100 x 10^9/l. The score values are given in table 6.

Table 6. Prognostic scores for overall survival in AML-10 study and CRIANT study.

Variable	Points AML-10	Points CRIANT
Cytogenetics IPSS		
inv(16), t(8;21)	0	0
Good	15	0
Intermediate	30	20
Poor	40	40
Unknown	30	20
WBC (x 10^9/l)		
< 25	0	0
25-100	0	20
≥ 100	25	20
FAB		
M0, M1, M5, M6, M7	15	0
M2, M4	0	0
FAB unknown	7	0
Age (yr.)		
15-45	0	0
46-55	10	20
> 55	10	22
Performance status		
0	0	0
1	10	0
2	20	0
AHD > 6 months	0	13
Number of cytopenias		
0/1	0	0
2	0	0
3	0	15

In the AML-10 study 3 groups were distinguished: score < 20, score 20 - < 60, score ≥ 60. The 5-year estimated survival rates were 54% (s.e. = 7.0%), 38% (s.e. = 2.5%), and 19% (s.e = 2.9%) respectively for the 3 groups (Figure 3).

The model was validated on a group of 677 AML patients not included in the present analysis. These patients were treated in the AML-10 study with a different anthracycline: mitoxantrone instead of idarubicin. In the patients receiving mitoxantrone the 5-year estimated survival rates were 72% (s.e. = 6.5%), 37% (s.e. = 2.5%), and 21% (s.e. = 3.0%) respectively for the 3 groups (p<0.0001) (Figure 4).

Figure 3. Prognostic score in AML-10 study.

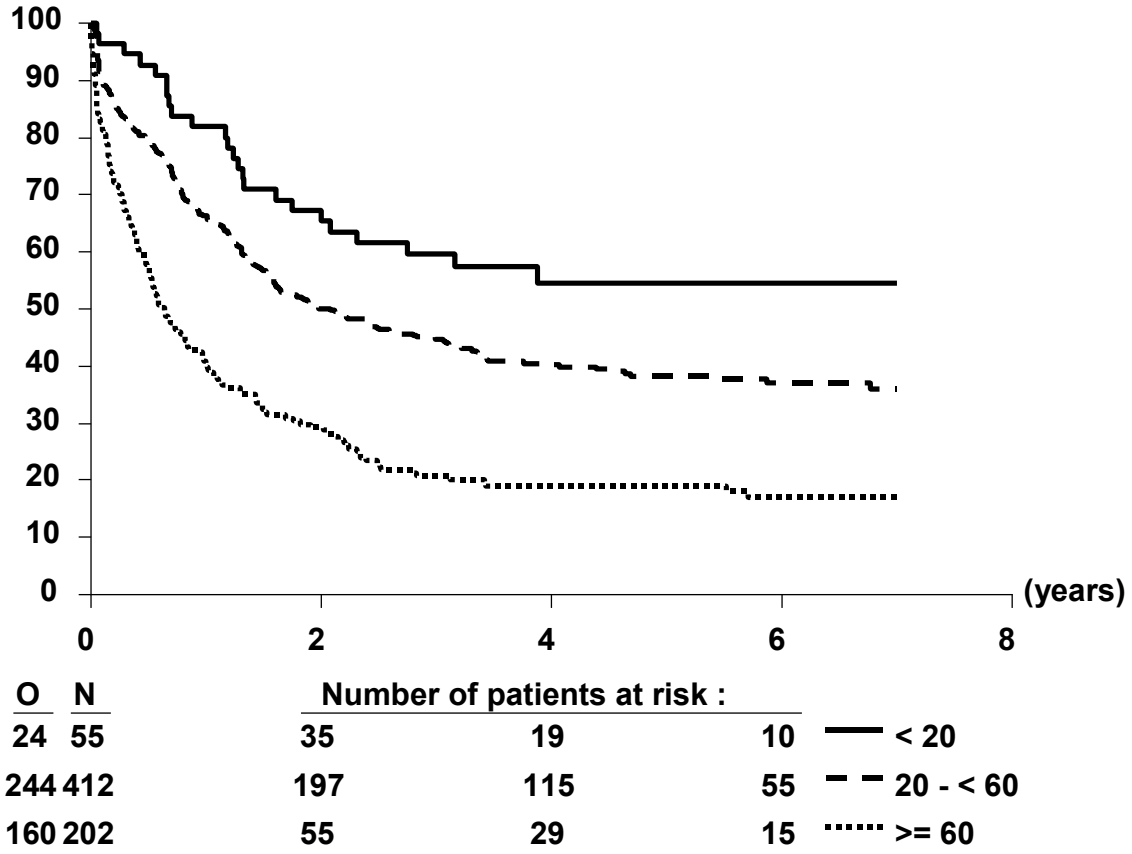
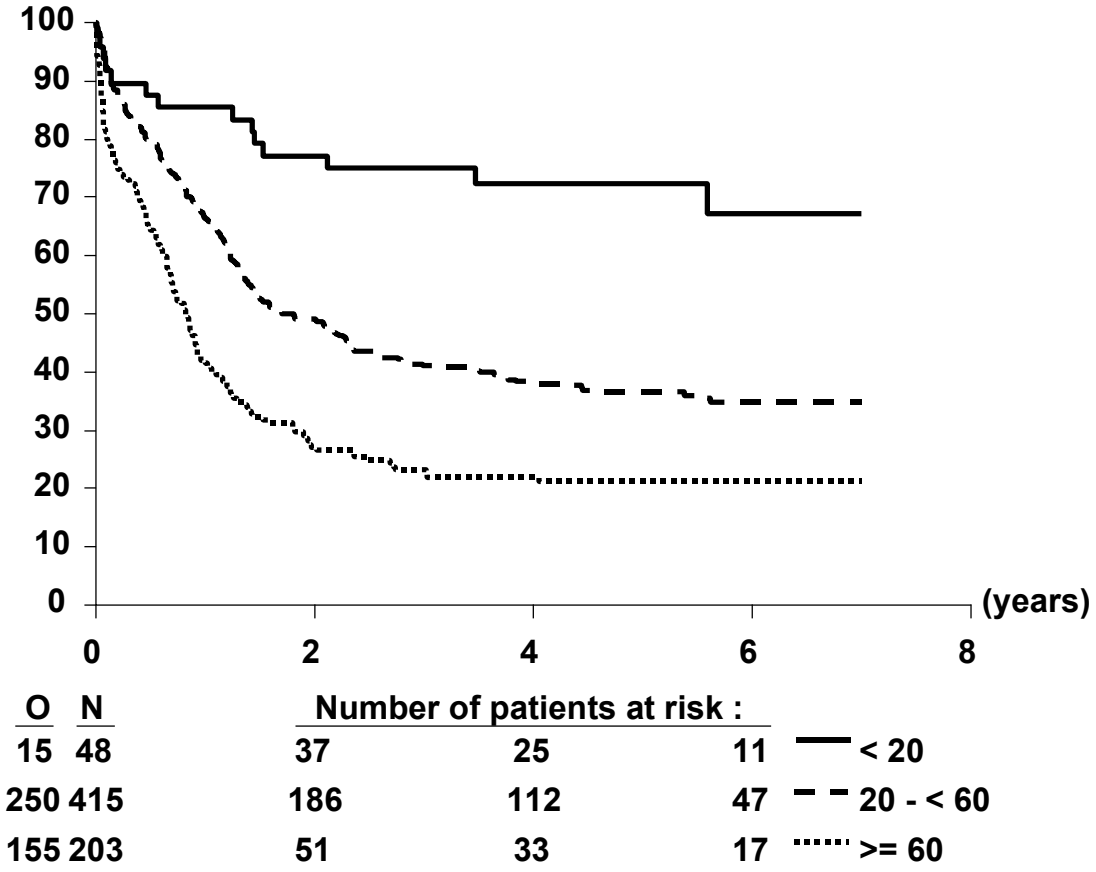
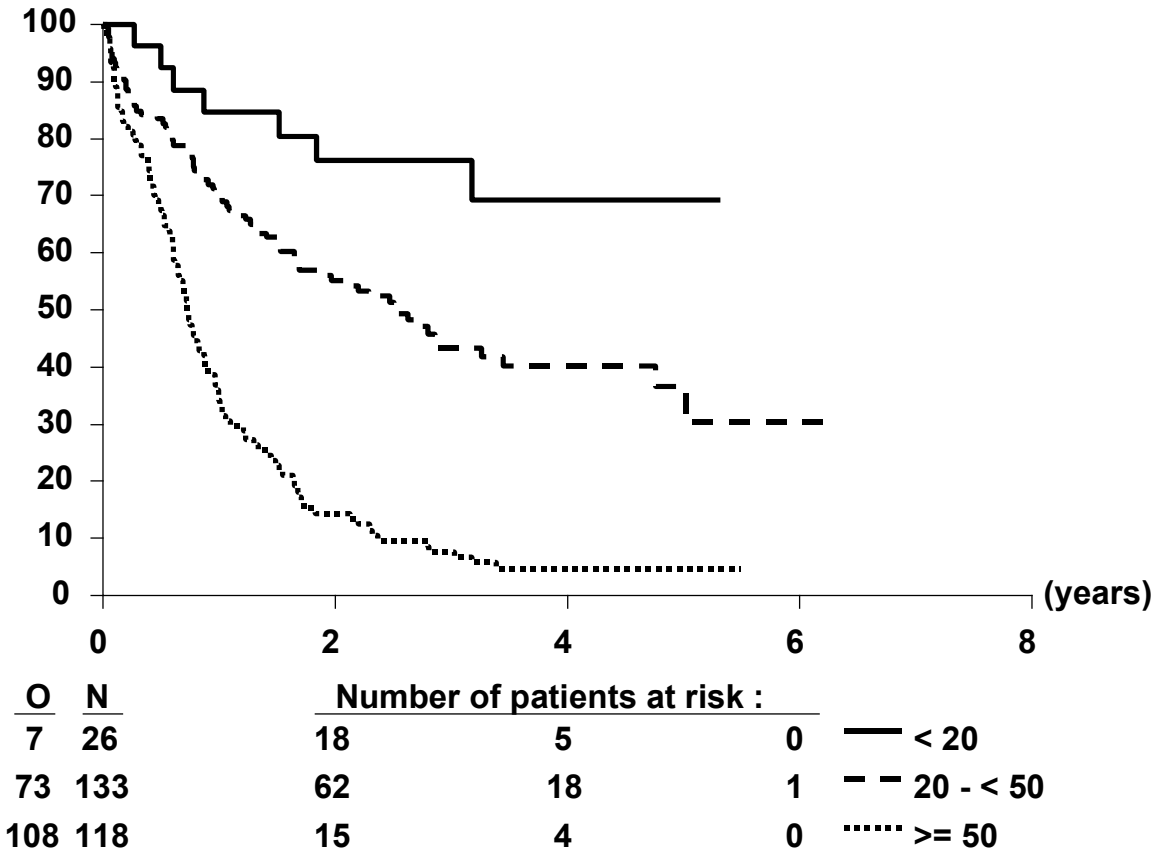


Figure 4. External validation of prognostic score in mitoxantrone arm of the AML-10 study.



For the CRIANT study the following variables were incorporated in the scoring system: cytogenetic risk group according to IPSS, WBC, age, number of cytopenias and AHD. Performance status was not incorporated in the model, since PS appeared not to be of any prognostic importance. Three groups were distinguished: score < 20, score 20 - < 50, score ≥ 50. In the CRIANT study the 5-year estimated survival rates were 69% (s.e. = 10.2%), 37% (s.e. = 5.6%), and 5% (s.e = 2.1%) for the 3 groups (Figure 5).

Figure 5. Prognostic score in CRIANT study.



DISCUSSION

The FAB classification separates MDS as a distinct disorder from AML.[1] Nowadays high-risk MDS is recognized as a clonal stem cell disorder that shares genetic, molecular and clinical features with AML generally arising in older individuals.[24] This had led to the concept that MDS and AML are part of a continuous disease spectrum rather than distinct disorders. Nevertheless, the use of intensive antileukemic treatment is less widely accepted in high-risk MDS patients than in de novo AML patients due to the reported worse outcome.[13] The treatment outcome is determined both by patient-related factors and by disease-related factors. Age, co-morbidity, performance status and genetic variations in drug-metabolism can be considered as patient-related factors, while disease-related factors comprise factors related to the characteristics of the stem cells involved like cytogenetic abnormalities and molecular aberrations. The question is whether the disease-related factors differ between MDS and AML and whether poor prognostic factors occur more often in MDS compared to AML. The present analysis was designed to identify clinical and biologic prognostic factors reflecting the underlying disease-related and patient-related factors. To our knowledge this study is the first to address this question in a large group of MDS and AML patients, who received identical remission-induction and consolidation treatment in two different clinical studies. The analysis included primary MDS patients, de novo AML patients, secondary AML patients and patients with therapy-related MDS and AML.

In multivariate analysis in the combined study group, the presence of cytogenetic abnormalities, age, white blood count and treatment in the AML-10 or CRIANT study appeared prognostic for both overall survival and DFS. Performance status was predictive for overall survival, but not for DFS. Poor prognostic cytogenetic abnormalities appeared to be the most important prognostic factor for outcome in both patient groups. Unfortunately, in 45% of AML-10 patients data on cytogenetics were missing. This was due to the lack of data on cytogenetic examinations in some smaller participating centres and not because cytogenetic data were missing in patients who died early. Some other factors appeared prognostic in only one of the studies. In the CRIANT study the number of cytopenias and the presence of an AHD with a duration of longer than 6 months negatively influenced survival, while in the AML-10 study, FAB subtype M2/M4 and the presence of inv(16)/t(8;21) independently predicted for a better survival. Performance status was predictive in the AML-10 study, but not in the CRIANT study. In this analysis

poor prognostic cytogenetic features produced a more pronounced effect in the CRIANT study (Hazard ratio: 3.51) compared to the AML-10 study (Hazard ratio: 1.75). The observed differences in prognostic factors between MDS and AML suggest that despite an overlap between MDS and AML, the diseases are intrinsically different.

Multilineage dysplasia is considered as a hallmark of MDS, but dysplastic features are also observed in de novo AML and have been associated with an unfavourable prognosis in some analyses.[3,25,26] In the present analysis only limited data on dysplasia were available and no firm conclusions could be drawn. Recently, Haferlach et al. demonstrated in a group of 614 patients with de novo AML the association of dysplastic features with poor prognostic cytogenetic features without independent prognostic importance for outcome.[27] In general, interpretation of different studies on the prognostic value of dysplastic features in AML and MDS is laborious due to subjective and variable criteria used for the definition of dysplasia.[28]

The M.D. Anderson Cancer Center reported on 530 patients with AML, RAEB and RAEBt.[15] Complex cytogenetic abnormalities involving chromosome 5 and/or 7 were more frequently found in RAEBt (17%) and particularly RAEB (35%) than in AML (11%). Multivariate analysis indicated the prognostic value of cytogenetic abnormalities, age, AHD, performance status and applied treatment on survival and event-free survival (EFS). Their main conclusion was that outcome after intensive chemotherapy is not different for MDS and AML patients after adjustment for the poor-prognostic disease-related and patient-related factors. Our analysis confirms that AHD is an independent disease-related prognostic factor in MDS.

In our analysis treatment in the AML-10 study predicted for a better outcome than treatment in the CRIANT study. Although patients in both studies received identical remission-induction and consolidation courses, we cannot discard that the differences in outcome are influenced by differences in post-consolidation treatment. In the AML-10 study 36% of patients underwent allogeneic or autologous stem cell transplantation in first remission compared to 23% of patients in the CRIANT study.

The clinical outcome of MDS and AML patients after intensive antileukemic treatment shows similarities. However, important biologic differences have been reported. Several studies showed that apoptosis is a contributing factor to the ineffective hematopoiesis in MDS.[29-31] The highest apoptotic rates are found in RA, RARS, and RAEB with a progressive decline in apoptosis when the disease progresses to acute leukemia. Albitar et al. studied 802 patients with newly diagnosed AML or MDS. Apoptosis as measured by

annexin V expression in CD34 positive cells was significantly higher in all subtypes of MDS compared with AML and patients with high apoptotic activity were more likely not to respond to applied chemotherapy.[21]

The higher incidence of the multidrug resistance 1 gene (MDR1) expression in MDS compared to de novo AML may be another explanation for the inferior response to chemotherapy.[32-35] MDR1 codes for the transmembrane efflux pump P-glycoprotein (Pgp). When overexpressed in leukemic cells, P-glycoprotein reduces intracellular accumulation of several anticancer drugs. A French study demonstrated that response to chemotherapy is worse in Pgp-positive patients.[32] Wattel et al. employed quinine as a Pgp modulator in patients with high-risk MDS and secondary AML. In a subgroup of Pgp-positive cases a significantly better survival was observed in patients treated with quinine in combination with chemotherapy.[36]

Apart from stem cell abnormalities, abnormalities in the hematopoietic microenvironment are involved in the pathogenesis of hematopoietic failure in MDS. Bone marrow stroma plays a regulatory role by direct contact mediated by adhesion molecules and through the production of cytokines. Increased levels of TNF-alpha are observed and are able to induce apoptosis via free radical formation and upregulation of Fas expression.[37,38] We hypothesized that a longer duration of hypoplasia after intensive chemotherapy might reflect the influence of pre-existing stroma damage in MDS after chemotherapy. The time to platelet and PMN recovery after the consolidation course was significantly longer in the CRIANT study compared to the AML-10 study. The longer post-consolidation marrow hypoplasia in MDS patients might have interfered with post-consolidation therapy in some patients, but this did not translate in an inferior DFS. We noticed in an earlier analysis of the AML-10 study that patients with higher numbers of mobilized $CD34^+$ cells and a short post-consolidation hypoplasia had a poor outcome due to a higher relapse risk.[39]

A second aim of this analysis was to predict the outcome of an individual patient. Based on the prognostic factors in multivariate analysis, a prognostic score has been developed for each of the studies. According to this score, 48% of patients in the CRIANT study show a 5-year survival rate of approximately 40%, when treated with AML-like therapy. A minority of younger patients, lacking poor prognostic cytogenetic features and profound cytopenias, with a short AHD and a low WBC has a good prognosis, with an estimated 5-year survival 69%. On the other hand, this study identifies a subgroup of 43% of MDS and 30% of AML patients, with a poor prognosis despite intensive chemotherapy with or without stem cell transplantation. These patients are characterized by the presence of

poor prognostic cytogenetic features according to IPSS, age over 45 years, multiple cytopenias, AHD with a duration of longer than 6 months, FAB subtype other than M2, M4 and/or a high WBC.

To our opinion the scoring system for the CRIANT patients is a valuable alternative for the IPSS, since the IPSS gives considerable weight to the blast percentage in the bone marrow, while this seems less prognostic in intensively treated patients. The scoring systems may help to identify both MDS and AML patients with an estimated 5-year survival of less than 20%. For these high-risk patients current treatment modalities are unsatisfactory. In recent years, progress has been made in knowledge of the molecular mechanisms that underlie the ineffective hematopoiesis and leukemic transformation in MDS. Insight gained from this molecular analysis may provide the basis for a more targeted therapeutic approach. Novel treatment strategies should be offered to these poor prognosis MDS and AML patients in the context of prospective clinical trials.

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CHAPTER 7

Summary and conclusions

Samenvatting

Dankwoord

Curriculum Vitae

List of Publications

SUMMARY

The myelodysplastic syndromes (MDS) form a heterogeneous group of clonal stem cell disorders characterized by a hypercellular bone marrow, peripheral blood cytopenias and dysplastic features in blood and bone marrow. The natural history of the disease ranges from an indolent course over several years to a rapid course toward leukemic progression. Since 1982 the myelodysplastic syndromes have been classified according to FAB (French-American-British) criteria. Five subgroups have been described: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEBt), and chronic myelomonocytic leukemia (CMML). This classification was a milestone in MDS-related research. Numerous studies have demonstrated the diagnostic usefulness and the prognostic impact of the FAB classification. Nonetheless, this classification has several weaknesses. In the FAB classification, both the definition of chronic myelomonocytic leukemia (CMML) and its inclusion in the scheme are problematic, since many patients with CMML have features resembling a myeloproliferative disorder rather than a myelodysplastic disorder. The definition of CMML is based primarily on the peripheral blood monocyte count with less consideration of marrow findings. The FAB distinction between RAEBt and acute myeloid leukemia (AML) has been criticized as unimportant, since there are little differences between RAEBt and AML in terms of prognosis and response to therapy. On the other hand, the category of RAEB includes a fairly heterogeneous group of patients with a blast percentage ranging from five to twenty percent.

In 1997 a new classification system has been proposed by the World Health Organization (WHO), which attempts to correct some of the imperfections of the FAB classification. The conventional FAB classification has been used throughout this thesis.

Since the introduction of the FAB classification, multiple scoring systems have been proposed to predict the natural history of an individual patient. At present, the most widely accepted system is the International Prognostic Scoring System (IPSS). This score is based on data of 816 patients with de novo MDS, who primarily received supportive care. The IPSS distinguishes four risk groups for survival and AML evolution, based on cytogenetic features, percentage of blasts in the bone marrow and the number of cytopenias. Median survival for the low risk group is 5.7 years, 3.5 years for the

intermediate-1 risk group, 1.2 years for the intermediate-2 risk group and 0.4 years for the high-risk group. Age is an additional risk factor for survival, but not for AML evolution.
The majority of MDS patients are aged over 60 years. For most of these patients supportive care and/or low-intensity regimens is the mainstay of treatment. This thesis discusses intensive treatment strategies, mainly used with the aim to cure younger MDS patients.

Chapter one of this thesis describes the classification of the myelodysplastic syndromes (MDS) according to the French-American-British (FAB) classification and the newer World Health Organization (WHO) classification. Data on incidence and aetiology are given. Poor risk MDS patients can be identified by the International Prognostic Scoring System (IPSS). Patients belonging to the intermediate-1, intermediate-2 and high-risk groups of the IPSS may be considered as potential candidates for intensive treatment strategies. Different treatment strategies are discussed in this chapter. Allogeneic stem cell transplantation (SCT) is the treatment of choice in young patients with an HLA-identical sibling donor. Approximately 40% of patients are likely to be cured after allogeneic stem cell transplantation. Long-term disease-free survival (DFS) can be attained if the transplant is performed in an early stage of the disease. An increased blast percentage and poor prognostic cytogenetic features are associated with an increased risk of relapse and a shorter disease-free survival. Longer disease duration, advanced patient age, therapy-related MDS and the use of alternative donors are associated with increased non-relapse mortality. Reduced Intensity Conditioning (RIC) regimens are currently investigated, in view of the high treatment-related mortality after conventional myeloablative conditioning regimens. Through lack of HLA-identical sibling donors in the majority of MDS patients, alternative donor sources like unrelated donors and mismatched family donors have been used. Transplant-related mortality is higher after alternative donor SCT, resulting in a disease-free survival of circa 30%. The transplant-related mortality is significantly influenced by age.
For patients lacking a suitable donor intensive chemotherapy with AML-like schedules may be an alternative approach. Although the remission rate has improved over the past years, the remission duration is short due to a high relapse rate. For disease-free survival karyotype appears to be the most important prognostic factor. In view of the high relapse rate after chemotherapy, transplantation with autologous stem cells has been applied in an attempt to intensify the post-remission therapy. Although the data on autologous SCT

in MDS are still limited, DFS after autologous SCT seems comparable with DFS after allogeneic SCT with alternative donors. The high incidence of relapse in autologous SCT is counterbalanced by the high treatment-related mortality after alternative donor SCT. A prerequisite for autologous SCT is entering a complete remission before transplantation and harvesting a sufficient number of stem cells. For a patient who fulfils these criteria, autologous SCT is a valid option. For patients who fail to enter complete remission, allogeneic SCT with an alternative donor may constitute an alternative.

The primary curative treatment option for patients with MDS is allogeneic SCT with an HLA-identical sibling donor. However, the reported superior results after allogeneic transplantation may be due to selection of patients fit enough to undergo SCT and by excluding patients with an early relapse. The value of SCT compared to alternative treatment options has never been defined. Randomisation, the classical approach to test the value of different treatment strategies is not feasible. An alternative approach is registration at a fixed point in time: the time of HLA-typing of patient and siblings.

Chapter 2 describes a prospective registration study by the EBMT (European Group for Blood and Marrow Transplantation). The physicians were asked to give the intention-to-treat depending on the outcome of the donor search at time of registration. In case of an HLA-identical sibling donor, the possibilities were immediate SCT (without preceding chemotherapy), SCT after remission-induction chemotherapy or SCT at progression of disease. In case no donor was available, the options were search for an alternative donor, intensive chemotherapy only, chemotherapy followed by autologous SCT or supportive care. The registration forms have been collected before the outcome was known. Since the number of registered patients was not sufficient for statistical analysis, the HLA-typing laboratories have been asked to report all MDS patients, who had HLA family typing in their centre. The physicians have been asked to provide us with the clinical data of the patients and the intention-to-treat according to the policy of the centre depending on the availability of a donor. In all, 11 European centres have registered 248 patients, who were untreated at time of HLA-typing. A matched family donor has been identified in 52% of patients. On intention-to-treat basis outcome was not significantly different for patients with and without a donor, with estimated 3-year survival rates of 46% and 43%, respectively. Seventy-eight percent of patients with a donor received the intended allogeneic SCT. In patients without a donor a lower percentage received the intended treatment; 46% of patients underwent the intended alternative donor SCT, 50%

underwent autologous SCT, 67% underwent intensive chemotherapy only and 97% of patients received supportive care. In multivariate analysis age, chromosomal abnormalities and RA(RS) FAB subtype appeared prognostic for survival, while intended treatment was not prognostic for survival. On intention-to-treat basis the estimated 3-year survival was 48% for immediate allogeneic SCT, 34% for allogeneic SCT after remission-induction chemotherapy, 37% for alternative donor SCT, 36% for autologous SCT, and 35% for patients intended for chemotherapy only. This analysis confirms that alternative donor SCT, autologous SCT and high-dose chemotherapy may provide an alternative therapy for patients lacking a matched family donor.

The prognosis of high-risk MDS patients resembles that of patients with AML. However, outcome of AML-like therapy is generally disappointing in MDS patients, and is worse than observed in de novo AML. The poor results raise the question of the value of transplantation in first complete remission in these patients. The purpose of **chapter 3** is to compare continued chemotherapy and transplantation in first CR in patients under age 60 years with high-risk MDS or secondary AML (sAML). Patients have been treated by the Leukemia group of the EORTC (European Organization for Research and Treatment of Cancer) or at the M.D. Anderson Cancer Center. All patients received AML-like chemotherapy in order to achieve a CR. Subsequently, after an intensive consolidation course, patients treated by the EORTC centres received an allogeneic transplant in case of an HLA-identical sibling donor, or an autologous transplant in the absence of an HLA-identical sibling donor. In contrast, patients treated at M.D. Anderson continued to receive AML-like therapy without a transplant. One hundred and eighty-four patients have been treated in the EORTC 06921 study and 215 comparable patients at M.D. Anderson. The M.D. Anderson patients were older and more likely to have a poor performance status and secondary AML, while EORTC patients were more likely to have MDS. Abnormalities of chromosomes 5 and/or 7 were more common at M.D. Anderson (37% versus 21%). The hemoglobin level and platelet count at the start of therapy were lower in M.D. Anderson patients, while the white blood count was higher. The complete remission rates were 54% (100/184) in the EORTC and 63% (135/215) at M.D. Anderson (p=0.09). In the EORTC study, 28 patients received an allograft from an HLA-identical donor, 36 patients have been autografted and one patient underwent matched unrelated donor transplantation in first CR after the consolidation course. Thirty-five out of 100 patients in CR after remission-induction chemotherapy did not reach the transplantation step. The

outcome of patients with an HLA-identical donor did not significantly differ from the outcome of patients without an HLA-identical donor. Therefore, for the purpose of this study, we did not discriminate between allogeneic and autologous SCT and considered it as one strategy.
Survival form the start of treatment was not statistically different between the EORTC and M.D. Anderson patients. The 4-year survival estimates were 26.0% versus 18.4% (p=0.16). However, DFS in patients achieving CR was superior in the EORTC cohort, the 4-year DFS estimates were 28.9% versus 17.3% (p=0.02). To investigate whether the different outcome reflects the different treatment regimens in the EORTC and at M.D. Anderson or, rather differences in the two patients groups, a multivariate analysis has been performed including the following variables: treatment site (EORTC or M.D. Anderson), cytogenetics, age, white blood count, disease category (RA, RARS, RAEB vs. RAEBt, CMML vs. sAML), hemoglobin and performance status. Multivariate analysis confirmed that chemotherapy followed by transplantation in first CR is associated with longer disease-free survival. Nevertheless, in this analysis overall survival was not improved by a regimen including transplantation in first remission.

In **Chapter 4** we use the framework of the EORTC 06921 study to investigate the outcome of patients with and without an HLA-identical sibling donor on an intention-to-treat basis. After a common remission-induction and consolidation course, patients with an HLA-identical sibling donor were scheduled for allogeneic transplantation and patients lacking a donor for autologous transplantation. Only patients alive at 8 weeks from the start of treatment were selected since these patients were candidates for transplantation and the availability of an HLA-identical sibling donor would be known by this time. Out of 159 patients, alive at 8 weeks from the start of treatment, 52 had an HLA-identical sibling, 65 did not have an HLA-identical sibling donor and in 42 patients the availability of a donor was unknown. The majority of the patients in the unknown donor group (83%) were aged over 50 years. In these patients, the availability of a donor was not explored, since it was the intention to treat these patients without allogeneic SCT. The complete remission rate in the unknown donor group was only 45%, reflecting the older age of this group, with a survival rate at 4 years of 10%.
Thirty-nine out of 52 patients (75%) with a donor and 42 out of 65 (65%) patients without a donor attained CR after remission-induction chemotherapy. Overall, 36 patients (69%) with an HLA-identical donor underwent allogeneic SCT and 32 patients (49%) without an

HLA-identical donor underwent autologous SCT. Nine patients without an HLA-identical donor received an allograft from an alternative donor (one in first CR, two after relapse and six in partial response or resistance).

The actuarial survival rate at 4 years of the 52 patients with a donor was 33.3% versus 39.0% for the 65 patients without a donor (p=0.18). In the 81 patients who reached CR, the DFS rate was 30.8% in the donor group and 33.3% in the no donor group. The cumulative incidences of relapse at 4 years from CR were 42.6% and 64.3% in the two groups, respectively. The cumulative incidences of death in first CR were 26.5% and 2.4%.

In this analysis cytogenetic abnormalities were highly predictive for survival. Patients with good and intermediate cytogenetic risk scores according to IPSS had a 4-year survival rate of 51% and 38%, respectively, whereas in patients with poor prognostic cytogenetic features the 4-year survival rate was only 10%. In the subgroup of 29 patients with poor prognostic cytogenetic features, we were unable to demonstrate a survival difference for patients with and without a donor.

In all, 18 patients with an HLA-identical donor were alive at the end of follow-up. Sixteen patients survived in CR: one patient did not receive any post-consolidation therapy, twelve patients underwent SCT according to the protocol and three as salvage treatment. Eight of 16 patients presented with good-risk cytogenetic abnormalities, five with intermediate-risk cytogenetic abnormalities and two patients with poor prognostic cytogenetic abnormalities. Cytogenetic analysis has failed in one patient.

A total of 28 patients without an HLA-identical sibling donor were alive at the end of follow-up. In total, 20 patients survived in CR: four patients did not receive any post-consolidation treatment, ten patients received an autograft according to the protocol and six patients received an allogeneic SCT from an unrelated donor. Of 20 patients, 11 showed good-risk cytogenetic abnormalities, three intermediate cytogenetic abnormalities and one poor-risk cytogenetic abnormality. Cytogenetic analysis has failed in five patients.

The results of this analysis show that patients may benefit from intensive treatment strategies including allogeneic or autologous SCT. We were unable to demonstrate a survival advantage for patients with an HLA-identical donor over patients without a donor. Patients with a donor have a lower relapse risk compared to patients without a donor. Unfortunately, this advantage is neutralised by a substantially higher treatment-related mortality after allogeneic transplantation.

The International Prognostic Scoring System (IPSS) is a valuable instrument to predict the natural history in MDS. However, the IPSS is based on data from patients treated with transfusions, biological response modifiers and low-dose oral chemotherapy. Patients treated with intensive chemotherapy and/or stem cell transplantation and patients with therapy-related MDS are not incorporated in the scoring system. **Chapter 5** is a retrospective analysis of 306 untreated MDS patients who have been referred to our hospital, many of whom subsequently received intensive antileukemic treatment consisting of AML-like chemotherapy with or without autologous SCT, or allogeneic SCT with or without preceding chemotherapy. Patients have been classified according to the IPSS and survival has been compared with survival of the IPSS workshop patients. The principle aim of the study was to investigate whether the IPSS predicts the outcome of patients aged less than 61 years treated with intensive therapy, and whether the scoring system discriminates between subgroups of patients who benefit from these intensive treatment strategies. In patients aged less than 61 years, median survival in the low-risk group was comparable in the Nijmegen and the IPSS workshop patients (11.1 years versus 11.8 years) and in the intermediate-2 risk group (1.4 years versus 1.8 years). However, the median survival in the intermediate-1 risk group was lower in the Nijmegen patients (2.5 years versus 5.2 years), and median survival in the high-risk group was better for the Nijmegen patients (0.9 years versus 0.3 years). Out of 176 patients, aged less than 61 years, 159 belonged to the intermediate-1, intermediate-2 and high-risk group. These patients may be considered as candidates for intensive treatment. Seventy-six patients received supportive care only (48%). Eighty-three patients (52%) received intensive treatment consisting of chemotherapy only in 30 patients, chemotherapy followed by autologous SCT in 7 patients and allogeneic SCT in 46 patients. The median age of the intensively treated patients was 45 years versus 53 years for patients receiving supportive care only. In the intensive treatment group, median survival from diagnosis was 2.6 years for the intermediate-1 risk group, 3.4 years for the intermediate-2 risk group and 0.9 years for the high-risk group. The estimated 4-year survival rates were 46%, 40% and 19%, respectively. In patients, who received no intensive treatment, median survival was 2.2 years for the intermediate-1 risk group, 0.8 years for the intermediate-2 risk group and 0.7 years for the high-risk group. The estimated 4-year survival rates were 37%, 11% and 0%, respectively. These results have to be interpreted with caution, since no randomisation has been performed between intensive treatment and supportive care. Opponents of intensive treatment often argue

that the reported results are biased by selection of patients with a relatively good prognosis. In the present analysis we demonstrate that survival of non-intensively treated patients did not deteriorate in subsequent periods during which the percentage of intensively treated patients increased substantially. This supports that we have not selected patients with a relatively good prognosis for intensive treatment.
Multivariate analysis in patients who received supportive care only, confirmed the prognostic value of the IPSS. However, in the subgroup of 83 intensively treated patients aged < 61 years the IPSS was not prognostic for survival. The hazard ratio for the high-risk group compared with the intermediate-1 risk group was 1.81 (p=0.63), the hazard ratio for the intermediate-2 risk group being 0.83 (p=0.78). This suggests that patients belonging to the intermediate-2 risk group, in particular benefit from intensive treatment strategies.

The use of intensive antileukemic treatment is less common in high-risk MDS compared to de novo AML, due to the reported inferior results. It is questionable whether the reported poorer outcome of high-risk MDS patients compared to de novo AML patients reflects an intrinsic property of the stem cells involved (disease-related factors like cytogenetic abnormalities and molecular aberrations) or reflects an increased incidence of patient-related poor prognostic factors (like advanced age and poor performance status) in MDS.
In **chapter 6** we compare outcome of 981 patients with MDS and AML, who received identical remission-induction and consolidation treatment in two different studies. Patients with de novo AML have been treated in the AML-10 study and patients with high-risk MDS or secondary AML after MDS of at least 6 months in the CRIANT study. In both studies, post-consolidation therapy consisted of allogeneic SCT for patients aged < 45-55 years if an HLA-identical family donor was available. In the AML-10 study patients lacking an HLA-identical donor in continuous CR after the consolidation course were eligible for autologous bone marrow transplantation (ABMT). In 1994, a second randomisation has been introduced comparing ABMT with autologous peripheral blood stem cell transplantation (APSCT). In the CRIANT study, patients lacking an HLA-identical donor in continuous CR after the consolidation course were randomised between APSCT and a second consolidation course. The purpose of this analysis was to identify prognostic clinical and biologic factors for outcome. The estimated 5-year survival rates were 34% (AML-10) versus 27% (CRIANT) (p=0.26). The estimated 5-year DFS rate was higher in

the AML-10 study (40%) compared to the CRIANT study (28%) (p=0.02). In multivariate analysis in the overall group cytogenetic risk group according to IPSS, white blood count (WBC) and age appeared highly prognostic for both overall survival and DFS. Initial performance status was prognostic for survival as well. In the overall group, treatment in the AML-10 study predicted for a better overall survival and DFS than treatment in the CRIANT study. Apart from these shared variables, some variables appeared prognostic in one of the studies. Therefore, a separate multivariate analysis for survival was performed for the AML-10 and the CRIANT study. In the AML-10 study performance status, FAB subtype M2/M4 and cytogenetic abnormalities inv(16)/t(8;21) predicted for a better survival, while in the CRIANT study the number of cytopenias and the presence of an Antecedent Hematologic Disorder (AHD) of more than 6 months were prognostic. Our finding that prognostic factors differ in MDS and AML supports the hypothesis that MDS and AML are intrinsically different disorders. For both studies a prognostic score has been created based on the multivariate analyses. For the AML-10 study the following variables have been incorporated in the score: cytogenetic abnormalities, WBC, FAB classification, age and performance status. Three groups were distinguished with an estimated 5-year survival rate of 54%, 38%, and 19%, respectively. The score for the CRIANT study included cytogenetic abnormalities according to IPSS, WBC, age, number of cytopenias and AHD. Performance status was not incorporated in this model, since it appeared not predictive for survival. Three groups were distinguished with an estimated 5-year survival rate of 69%, 37%, and 5%, respectively.

The present analysis demonstrates that 48% of patients with high-risk MDS show a 5-year survival rate of approximately 40%, when treated with AML-like therapy. A minority of younger patients, lacking poor prognostic cytogenetic features and profound cytopenias, with a short AHD and a low WBC has a good prognosis, with an estimated 5-year survival 69%. On the other hand, this study identifies a subgroup of 43% of MDS patients and 30% of AML patients, with a 5-year survival of less than 20% despite intensive chemotherapy combined with stem cell transplantation. These patients are characterized by the presence of poor prognostic cytogenetic features according to IPSS, age over 45 years, multiple cytopenias, AHD over 6 months, FAB subtype other than M2, M4 and/or a high WBC. To our opinion the scoring system for the CRIANT patients is a valuable alternative for the IPSS, since the IPSS gives considerable weight to the blast percentage in the bone marrow, while this seems less prognostic in intensively treated patients. The presented prognostic scores enable us to identify patients with a poor

prognosis. Novel treatment strategies have to be offered to these patients in the context of prospective clinical trials.

CONCLUSIONS

The myelodysplastic syndromes (MDS) form a heterogeneous group of clonal stem cell disorders. Since the introduction of the FAB (French-American-British) classification in 1982, multiple scoring systems have been proposed to predict the natural history of an individual patient. At present the most widely used system is the International Prognostic Scoring System (IPSS), based on the percentage of blasts in the bone marrow, the number of cytopenias and the presence of cytogenetic abnormalities. MDS is predominantly diagnosed in elderly patients. Intensive treatment strategies, as described in this thesis, aiming at eradication of the malignant clone are restricted to younger patients in a good clinical condition. Patients belonging to the intermediate-1, intermediate-2 and high-risk groups of the IPSS may be considered as candidates for intensive treatment strategies. A major challenge lies in predicting which patient is most likely to respond favourably to which treatment.

Allogeneic stem cell transplantation (SCT) is considered as the only curative treatment option by many clinicians. In the first part of this thesis we demonstrated that survival of patients with and without an HLA-identical sibling donor was not different on intention-to-treat basis. Therefore, alternative treatment options like SCT with mismatched family donors and matched unrelated donors, autologous SCT and high-dose chemotherapy have to be considered in patients lacking an HLA-identical family donor. In another analysis we compared the outcome of patients with high-risk MDS and secondary AML, who received AML-like chemotherapy with or without stem cell transplantation. Although survival of patients treated with AML-like chemotherapy only or with AML-like chemotherapy followed by stem cell transplantation was not different, disease-free survival was significantly longer after treatment including SCT.

In the second part of this thesis, we focused on the value of the IPSS in predicting the outcome of patients. We confirmed that the IPSS is an improved scoring system for patients receiving supportive care. However, the scoring system does not seem to be the best method for predicting outcome in younger patients after intensive antileukemic treatment. In particular, intermediate-2 risk patients may benefit from intensive treatment.

Finally, we compared outcome of high-risk MDS and AML patients, who received identical remission-induction and consolidation treatment in two different studies, to identify prognostic clinical and biologic factors for outcome. In the combined studies, cytogenetic risk group according to IPSS, white blood count, age and performance status appeared highly prognostic for outcome. However, some variables appeared prognostic in only one of the studies. Our finding that prognostic factors differ in AML and MDS supports that the diseases are intrinsically different. Based on the multivariate analyses two prognostic scores have been developed: one for the AML-10 study and one for the CRIANT study. To our opinion the scoring system for the CRIANT patients is a valuable alternative for the IPSS, since the IPSS gives considerable weight to the blast percentage in the bone marrow, while this seems less important in intensively treated patients. The scores enable us to predict survival after intensive treatment including SCT and to identify patients with a poor prognosis. In recent years, progress has been made in the knowledge of the molecular mechanisms that underlie the ineffective hematopoiesis and leukemic transformation in MDS. Insight gained from this molecular analysis may provide the basis for a more targeted approach.

FUTURE PERSPECTIVES

Considerable progress has been made in the treatment of MDS patients over the last years, especially in the field of allogeneic stem cell transplantation. New insights in the biology of MDS open the way to new treatment approaches.

Improvement of intensive chemotherapy

Gemtuzumab ozogamicin is an anti-CD33 antibody, which is linked to calicheamicin, a potent cytotoxic agent. The drug has shown encouraging results in relapsed AML patients. Clinical trials with gemtuzumab in combination with other drugs as first-line treatment in MDS patients are under investigation.

An alternative approach is to overcome drug resistance with new Pgp (P-glycoprotein) inhibitors like zosuquidar.

Reduction of treatment-related mortality after allogeneic stem cell transplantation

Supportive care has improved over the years. Better diagnosis and (pre-emptive) treatment of opportunistic infections may reduce the treatment-related mortality after SCT.

The risk of severe Graft versus Host Disease after unrelated donor transplantation is reduced by refined HLA-typing of patient and donor at the DNA level. This may ameliorate the outcome after unrelated donor transplantation.

The introduction of reduced intensity conditioning (RIC) schedules is a promising development, with a lower reported transplant-related mortality compared with myeloablative conditioning regimens. However, whether this treatment will improve long-term outcome of patients has to be proven in prospectiverandomised trials.

Use of novel agents

In the last decade, the therapeutic arsenal for MDS has been extended. New molecular targets have been identified as the mosaic of pathophysiologic pathways in MDS is being unraveled. Several new agents with anti-angiogenic properties (thalidomide, lenalidomide, bevacizumab), anti-apoptotic properties (infliximab), farnesyl transferease inhibitors (tipifarmib, lonafarmib), DNA methyltransferase inhibitors (5-azacytidine, 5-aza-2'-deoxycytidine), and tyrosine kinase inhibitors have shown encouraging results and may offer durable benefit to patients with MDS. Up till now, these drugs are used as single agents and in general without the intention to cure the patients. The challenge lies in combining these agents with existing treatment modalities.

SAMENVATTING

De myelodysplastische syndromen (MDS) vormen een heterogene groep van klonale afwijkingen van de hematopoïetische stamcel die gekenmerkt wordt door een toegenomen celrijkdom in het beenmerg, deficiënte cellijnen in het bloed (=cytopenieën) en dysplastische afwijkingen in bloed en beenmerg. Het ziektebeloop van MDS is variabel en varieert van een indolent verloop gedurende vele jaren tot een snelle overgang naar een acute leukemie.

Sinds 1982 wordt de “French-American-British” (FAB) classificatie gebruikt om de verschillende vormen van MDS in te delen. De FAB classificatie onderscheidt vijf groepen: refractaire anemie (RA), refractaire anemie met ringsideroblasten (RARS), refractaire anemie met toename van blasten (RAEB), refractaire anemie met toename van blasten in transformatie (RAEBt) en chronische myelomonocyten leukemie (CMML). De FAB classificatie was een doorbraak in het onderzoek naar MDS. Talrijke studies toonden aan dat deze indeling zeer bruikbaar was en dat hiermee een inschatting van de prognose gemaakt kon worden. Deze classificatie heeft echter ook een aantal beperkingen. De definitie van chronische myelomonocyten leukemie kan problematisch zijn, omdat CMML vaak een mengbeeld is met zowel dysplastische als myeloproliferatieve kenmerken. Daarnaast is de definitie alleen gebaseerd op het aantal monocyten in het bloed en wordt er minder aandacht besteed aan het percentage onrijpe cellen (=blasten) in het beenmerg. De FAB classificatie onderscheidt RAEBt van acute myeloïde leukemie. Sommigen vinden dit onderscheid onbelangrijk omdat de prognose en de behandelingsresultaten weinig van elkaar verschillen. Daarentegen vormen de patiënten met RAEB een heterogene groep met een blastenpercentage variërend van vijf tot twintig procent.

In 1997 heeft de “World Health Organization“ (WHO) een nieuw classificatievoorstel gedaan, waarin een aantal van de genoemde kritiekpunten is verbeterd. In dit proefschrift wordt echter gebruik gemaakt van de oorspronkelijke FAB classificatie.

Talrijke scoringssystemen zijn ontwikkeld sinds de introductie van de FAB classificatie met als doel om de overleving van een individuele patiënt beter te kunnen voorspellen. Tegenwoordig is de “International Prognostic Scoring System” (IPSS) vrij breed geaccepteerd. Deze score is gebaseerd op de klinische gegevens van 816 patiënten met MDS, die voor het merendeel behandeld zijn met alleen supportieve zorg. De IPSS maakt gebruik van het percentage blasten in het beenmerg, het type cytogenetische

afwijkingen en het aantal cytopenieën in het bloed om de levensverwachting en de kans op het ontwikkelen van een acute myeloïde leukemie te voorspellen. Er worden vier groepen onderscheiden. De mediane overleving voor de laag risicogroep is 5.7 jaar, intermediair-1 risico 3.5 jaar, intermediair-2 risico 1.2 jaar en 0.4 jaar voor de hoog risicogroep. Daarnaast is leeftijd een extra risicofactor voor overleving, maar niet voor het ontwikkelen van leukemie.
De meerderheid van de patiënten met MDS is ouder dan 60 jaar. Deze patiënten hebben naast hun hematologische ziekte vaak ook andere, bij de leeftijd horende, aandoeningen. De standaardbehandeling voor de meerderheid van de oudere patiënten bestaat uit ondersteunende behandeling met bloedtransfusies en antibiotica. Dit proefschrift beschrijft intensieve behandelingen, die vooral worden toegepast met de intentie om jonge patiënten te genezen.

In **hoofdstuk 1** van dit proefschrift worden de FAB classificatie en de WHO classificatie beschreven. Gegevens over het voorkomen van MDS en de ontstaanswijze worden besproken. Patiënten met een intermediair-2 en een hoog risicoscore volgens de IPSS hebben onbehandeld een zeer slechte prognose. Patiënten met een intermediair-1, intermediair-2 en een hoog risicoscore volgens de IPSS kunnen in aanmerking komen voor intensieve behandeling. Verschillende vormen van intensieve behandeling worden besproken. Allogene stamceltransplantatie, waarbij gebruik wordt gemaakt van de stamcellen van een HLA-identieke familiedonor (meestal een broer of een zus) is de behandeling van voorkeur, indien de patiënt over een donor beschikt. Met deze behandeling is het mogelijk om circa 40% van de patiënten te genezen. Langdurige ziektevrije overleving wordt bereikt wanneer de behandeling vroeg in het ziektebeloop wordt toegepast. Een toegenomen aantal blasten en prognostisch slechte cytogenetische afwijkingen vergroten de kans op terugkeer (=recidief) van de ziekte. Een langere ziekteduur voor transplantatie, hogere leeftijd, een MDS ontstaan na eerdere behandeling met chemotherapie en/of bestraling alsmede het gebruik van alternatieve donoren verhogen de kans op overlijden na de transplantatie. Als voorbehandeling voor de transplantatie wordt veelvuldig gebruik gemaakt van een zogenaamde myeloablatieve conditionering. Hierbij wordt het beenmerg van de patiënt bijna volledig afgebroken door de toegepaste chemotherapie. Omdat de sterfte gerelateerd aan de behandeling hoog is, na deze myeloablatieve conditionering, wordt onderzoek gedaan naar de effecten van

minder intensieve voorbehandeling, de zogenaamde “Reduced Intensity Conditioning” (RIC).
Aangezien slechts een minderheid van de patiënten beschikt over een identieke familiedonor, wordt gebruik gemaakt van niet volledig identieke familie donoren en van onverwante donoren uit de donorbank. De behandeling gerelateerde sterfte is hoger na transplantatie met onverwante donoren, waardoor de ziektevrije overleving circa 30% bedraagt. De behandeling gerelateerde sterfte is sterk leeftijdsafhankelijk.
Patiënten zonder donor kunnen behandeld worden met intensieve chemotherapie, zoals ook bij acute myeloïde leukemie wordt toegepast. De resultaten van deze behandeling zijn in de afgelopen jaren verbeterd, maar de kans is groot dat de ziekte na behandeling terugkeert. Dit risico wordt met name bepaald door de aanwezigheid van cytogenetische afwijkingen. Om de behandeling met chemotherapie te intensiveren, wordt autologe stamceltransplantatie toegepast, waarbij de stamcellen van de patiënt zelf worden terug gegeven na intensieve chemotherapie. De ervaring met autologe transplantatie bij MDS is nog beperkt, maar de ziektevrije overleving lijkt vergelijkbaar met de ziektevrije overleving na allogene stamcel transplantatie waarbij gebruik wordt gemaakt van alternatieve donoren. Na autologe transplantatie is de recidiefkans hoger dan na allogene transplantatie met een alternatieve donor, maar dit nadeel wordt tenietgedaan doordat het risico van overlijden na autologe transplantatie veel lager ligt dan na allogene transplantatie met een alternatieve donor. Hierdoor is de ziektevrije overleving vergelijkbaar voor beide behandelingen. Een voorwaarde voor autologe transplantatie is dat een complete remissie van de ziekte wordt bereikt voor de transplantatie en dat voldoende stamcellen worden geoogst. Indien de patiënt geen complete remissie bereikt is een allogene transplantatie met een alternatieve donor een optie.

De behandeling van voorkeur bij patiënten met een MDS is een allogene transplantatie met een HLA-identieke familiedonor. Echter, bij rapportage van behandelingsresultaten van allogene transplantatie treedt een vorm van selectie op. Dit komt doordat alleen patiënten met een donor die fit genoeg zijn voor de transplantatie worden getransplanteerd en dat patiënten, die door bijvoorbeeld andere ziektes of een recidief voor de transplantatie niet aan de transplantatie toekomen, niet worden gerapporteerd. Onderzoeken waarbij transplantatie direct met andere behandelingen wordt vergeleken zijn niet uitgevoerd. De beste manier om verschillende behandelingen met elkaar te vergelijken is om bij patiënten met een identieke familiedonor door loting vast te stellen (=

randomiseren) of patiënten een allogene stamceltransplantatie ondergaan of een ander soort behandeling. Dit is echter in de praktijk niet goed mogelijk. Een alternatief is om alle patiënten te registreren op het moment dat er gekeken wordt of ze een identieke familiedonor hebben, het tijdstip van HLA-typering. **Hoofdstuk 2** is als een registratiestudie door de EBMT (Europese groep voor Bloed en Beenmerg Transplantatie) ontworpen. Patiënten zijn aangemeld op het moment dat de HLA-typering plaats vond. Aan de behandelende dokters werd gevraagd welke behandeling zij voorstelden aan een patiënt indien hij/zij wel over een familiedonor beschikte en ook indien geen familiedonor beschikbaar zou zijn, voordat de uitslag van de HLA-typering bekend was. Zo zijn de behandelingsintenties (intention-to-treat) verkregen. Indien de patiënt wel een donor had waren de behandelingsmogelijkheden: directe transplantatie, transplantatie na voorbehandeling met chemotherapie en transplantatie bij verergering van de ziekte. Als geen identieke familiedonor werd gevonden waren de behandelingsmogelijkheden: zoeken naar een alternatieve donor, intensieve chemotherapie, autologe transplantatie of supportieve zorg. Helaas zijn er niet genoeg patiënten aangemeld om een statistisch verantwoorde analyse uit te voeren. Daarom werd aan diverse laboratoria, waar HLA-typering wordt verricht, gevraagd om alle patiënten te rapporteren met een MDS waarbij HLA-typering heeft plaats gevonden. Daarna is de vragenlijst voorgelegd aan de behandelend arts. Op deze manier zijn de gegevens verkregen van 248 MDS patiënten uit 12 centra in Europa. Een HLA-identieke familie donor was aanwezig in 52% van de patiënten. De uitkomst van de patiënten met en zonder donor bleek niet verschillend te zijn wanneer gekeken werd naar de behandelingsintentie. De geschatte overleving na 3 jaar bedroeg 46% voor patiënten met een donor en 43% voor patiënten zonder donor. Van de patiënten met een donor onderging 78% uiteindelijk een allogene stamceltransplantatie. In de patiëntengroep zonder donor bereikte een lager percentage de geplande behandeling: 46% van de patiënten waarbij de behandelingsintentie een alternatieve donor transplantatie was, onderging deze behandeling ook daadwerkelijk, 50% van de patiënten onderging de geplande autologe stamceltransplantatie, 67% onderging intensieve chemotherapie en 97% van de patiënten werd behandeld met supportieve zorg. In multivariate analyse waren leeftijd, cytogenetische afwijkingen en FAB classificatie RA(RS) prognostisch voor overleving, terwijl de behandelingsintentie niet prognostisch was. Uitgaande van de behandelingsintenties bedroeg de geschatte 3-jaars overleving 48% voor directe stamceltransplantatie, 34% voor transplantatie na voorbehandeling met chemotherapie,

37% voor transplantatie met een alternatieve donor, 36% voor autologe transplantatie en 35% voor supportieve zorg. Deze analyse laat zien dat transplantatie met een alternatieve donor, autologe transplantatie en intensieve chemotherapie goede behandelingsalternatieven kunnen zijn voor patiënten die niet over een HLA-identieke familie donor beschikken.

De prognose van patiënten met een hoogrisico MDS verschilt weinig van de prognose van een patiënt met acute myeloïde leukemie. Echter de behandelingsresultaten van intensieve chemotherapie bij MDS patiënten zijn vaak teleurstellend en over het algemeen slechter dan bij behandeling van patiënten met acute myeloïde leukemie. Het is de vraag, of stamceltransplantatie de resultaten verbetert. Het doel van **hoofdstuk 3** was om intensieve chemotherapie en intensieve chemotherapie gevolgd door stamceltransplantatie in eerste remissie bij patiënten onder de 60 jaar met hoog risico MDS en secundaire acute myeloïde leukemie met elkaar te vergelijken. De patiënten zijn behandeld in een grote Europese studie (EORTC 06921) en in het M.D. Anderson Cancer Center in Houston, Texas. Alle patiënten ondergingen intensieve chemotherapie om de ziekte in remissie te brengen, gevolgd door een consolidatiekuur. De EORTC patiënten ondergingen vervolgens een allogene stamceltransplantatie of een autologe stamceltransplantatie, afhankelijk van de beschikbaarheid van een donor. De patiënten in het M.D. Anderson werden doorbehandeld met chemotherapie in een lagere dosering zonder transplantatie. In de EORTC studie werden 184 patiënten behandeld en 215 patiënten in het M.D. Anderson. De M.D. Anderson patiënten waren ouder, hadden vaker een slechtere algemene conditie (=performance status) en leukemie na een voorfase van MDS, terwijl de EORTC patiënten vaker MDS hadden. Afwijkingen aan chromosoom 5 of 7 werden vaker gezien in het M.D. Anderson (37% versus 21%). Het hemoglobinegehalte en het aantal bloedplaatjes waren lager in het M.D. Anderson, terwijl het aantal witte bloedcellen hoger was. Het remissiepercentage na de eerste kuur bedroeg 54% in de EORTC en 63% in het M.D. Anderson (p=0.09). In de EORTC studie ondergingen 28 patiënten een allogene stamceltransplantatie met een HLA-identieke donor, 36 patiënten een autologe transplantatie en 1 patiënt werd getransplanteerd met een onverwante donor. Van de 100 patiënten die een complete remissie behaalden kwamen 35 patiënten niet toe aan de transplantatie. De uitkomst van de patiënten met een HLA-identieke donor verschilde niet van de uitkomst van de patiënten zonder donor. Daarom werd in deze studie geen onderscheid gemaakt tussen allogene en autologe transplantatie, en

werd dit als één behandelingstrategie beschouwd. De overleving vanaf de start van behandeling was niet verschillend voor de EORTC en M.D. Anderson patiënten. De geschatte 4-jaars overleving was 26.0% versus 18.4% (p=0.16). Echter de ziektevrije overleving was beter in de EORTC studie, namelijk 28.9% versus 17.3% (p=0.02). Omdat de twee onderzoeksgroepen verschillend waren, werd er een multivariate analyse uitgevoerd waarin de volgende variabelen zijn opgenomen: studie (EORTC of M.D. Anderson), cytogenetica, leeftijd, aantal witte bloedcellen, FAB classificatie (RA, RARS, RAEB vs. RAEBt, CMML vs. sAML), hemoglobinegehalte en performance status. De multivariate analyse bevestigde dat patiënten die intensieve chemotherapie gevolgd door transplantatie ondergaan, een betere ziektevrije overleving hebben dan patiënten die alleen chemotherapie krijgen toegediend. Helaas konden we niet aantonen dat deze behandeling ook tot een betere overleving leidt.

In **hoofdstuk 4** wordt de studieopzet van de EORTC 06921 studie gebruikt om de uitkomst te vergelijken van patiënten met en zonder HLA-identieke donor volgens de geplande behandelingsstrategie (=intention-to-treat principle). Nadat alle patiënten een remissie-inductie kuur en consolidatiekuur hadden ondergaan, was het de bedoeling om patiënten met een HLA-identieke donor allogeen te transplanteren en patiënten zonder donor autoloog te transplanteren. In deze analyse werden de patiënten die 8 weken na start van de behandeling nog in leven waren geïncludeerd omdat deze patiënten in aanmerking kwamen voor transplantatie en de resultaten van de HLA-typering op dit tijdstip bekend waren. Acht weken na start van de behandeling waren er nog 159 patiënten in leven: 52 patiënten beschikten over een HLA-identieke donor, 65 patiënten hadden geen donor en van 42 patiënten was niet bekend of ze een donor hadden. De meerderheid van de patiënten met een onbekende donor (83%) was ouder dan 50 jaar. Kennelijk had HLA-typering niet plaatsgevonden omdat de behandelend arts van mening was dat de patiënt niet in aanmerking kwam voor een allogene stamceltransplantatie. Doordat de groep met een onbekende donor voornamelijk uit oudere patiënten bestond, was het complete remissie percentage aanzienlijk lager (45%) en bedroeg de 4-jaar overleving slechts 10%.
In de groep met een HLA-identieke donor bereikten 39 van de 52 patiënten (75%) een complete remissie na de remissie-inductie kuur tegenover 42 van de 65 patiënten (65%) zonder donor. Zesendertig patiënten (69%) in de groep met een donor ondergingen een allogene transplantatie en 32 patiënten (49%) in de groep zonder donor ondergingen een

autologe transplantatie. Negen patiënten in de groep zonder donor ondergingen een transplantatie met een alternatieve donor.

De 4-jaars overleving voor de 52 patiënten met een donor was 33.3% versus 39.0% voor de 65 patiënten zonder donor (p=0.18). In de 81 patiënten die een complete remissie bereikten bedroeg de ziektevrije overleving 30.8% in de donor groep en 33.3% in de groep zonder donor. De kans op een recidief bedroeg respectievelijk 42.6% en 64.3% voor de beide groepen. Het risico van overlijden in complete remissie bedroeg 26.5% versus 2.4%.

In deze studie hadden cytogenetische afwijkingen een grote invloed op de overleving. Patiënten in de prognostisch goede en intermediaire cytogenetische risicogroep volgens de IPSS toonden een 4-jaars overleving van 51% en 38%, terwijl in de prognostisch slechte cytogenetische groep de 4-jaars overleving slechts 10% bedroeg. In de subgroep van 29 patiënten met prognostisch slechte cytogenetische afwijkingen bleek geen verschil in overleving te bestaan tussen patiënten met en zonder donor.

Uiteindelijk waren nog 18 patiënten met een donor in leven aan het einde van de studie. Zestien patiënten verkeerden in complete remissie: 1 patiënt zonder transplantatie, 12 patiënten na transplantatie volgens het protocol en 3 patiënten na transplantatie als rescue behandeling. Acht van de 16 patiënten behoorden tot de groep met prognostisch goede cytogenetische afwijkingen, 5 patiënten tot de groep met intermediaire cytogenetische afwijkingen en 2 patiënten met slechte cytogenetische afwijkingen. Het cytogenetische onderzoek was in 1 patiënt mislukt.

Van de patiënten zonder donor waren er 28 nog in leven aan het einde van de studie. Twintig patiënten verkeerden in complete remissie: 4 patiënten zonder transplantatie, 10 patiënten hadden autologe transplantatie ondergaan volgens het protocol en 6 patiënten een allogene transplantatie met een onverwante donor. Van deze 20 patiënten behoorden 11 patiënten tot de groep met prognostisch goede cytogenetische afwijkingen, 3 tot de groep met intermediaire cytogenetische afwijkingen en 1 patiënt met slechte cytogenetische afwijkingen. Het cytogenetische onderzoek was in 5 patiënten mislukt.

De resultaten van deze studie laten zien dat de prognose van patiënten met MDS en secundaire AML verbetert met intensieve behandeling inclusief allogene of autologe stamcel transplantatie. Wij konden geen overlevingsvoordeel aantonen voor patiënten met een HLA-identieke donor in vergelijking met patiënten zonder donor. Weliswaar hebben patiënten met een donor een lagere kans op een recidief van de ziekte, maar dit wordt tenietgedaan door de hogere kans op overlijden na een allogene transplantatie.

De International Prognostic Scoring System (IPSS) is een waardevol instrument om het beloop te voorspellen van een MDS patiënt, die geen intensieve behandeling ondergaat. Het is echter de vraag of de IPSS ook geschikt is voor patiënten die intensieve behandeling ondergaan en voor patiënten die een secundaire MDS hebben na eerdere behandeling met chemotherapie of bestraling in verband met een andere aandoening. **Hoofdstuk 5** is een retrospectieve analyse van 306 onbehandelde MDS patiënten die naar het UMC St. Radboud zijn verwezen. Een aanzienlijk deel van deze patiënten is behandeld met intensieve chemotherapie al dan niet gevolgd door autologe transplantatie of allogene transplantatie met of zonder voorafgaande chemotherapie. De patiënten werden geclassificeerd volgens de IPSS criteria en de overleving is vergeleken met de overleving van de patiënten uit de oorspronkelijke IPSS workshop. Het doel van de studie was om te onderzoeken of de IPSS ook bruikbaar is om de overleving te voorspellen van patiënten jonger dan 61 jaar, die een intensieve behandeling ondergaan. Daarnaast was de vraag of binnen de IPSS groepen kunnen worden geïdentificeerd, die het meest profiteren van intensieve behandeling. In de patiënten onder de 61 jaar was de mediane overleving van de Nijmeegs patiënten in de laag risico groep (11.1 versus 11.8 jaar) en in de intermediair-2 risicogroep (1.4 vs. 1.8 jaar) vergelijkbaar met de overleving van de IPSS workshop patiënten. Daarentegen was de mediane overleving in de intermediair-1 risicogroep lager in de Nijmeegse patiënten (2.5 vs. 5.2 jaar), en de mediane overleving in de hoog risicogroep beter in de Nijmeegse patiënten (0.9 vs. 0.3 jaar). Van de 176 patiënten onder de 61 jaar, behoorden er 159 tot de intermediair-1, intermediair-2 en hoog risicogroep. Deze patiënten zijn potentiële kandidaten voor intensieve behandeling. Zesenzeventig patiënten (48%) zijn behandeld met alleen supportieve zorg. Drieëntachtig patiënten (52%) hebben intensieve behandeling ondergaan bestaande uit chemotherapie (30 patiënten), chemotherapie gevolgd door autologe transplantatie (7 patiënten) en allogene stamcel-transplantatie (46 patiënten). De mediane leeftijd van de intensief behandelde patiënten bedroeg 45 jaar, de mediane leeftijd van de niet-intensief behandelde patiënten bedroeg 53 jaar. In de intensief behandelde groep bedroeg de mediane overleving vanaf diagnose 2.6 jaar voor de intermediair-1 risicogroep, 3.4 jaar voor de intermediair-2 risicogroep en 0.9 jaar voor de hoog risicogroep. De geschatte 4-jaars overleving bedroeg 46%, 40% en 19%, respectievelijk. In de patiënten groep die geen intensieve behandeling onderging, was de mediane overleving 2.2 jaar voor de intermediair-1 risicogroep, 0.8 jaar voor de intermediair-2 risicogroep en 0.7 jaar voor de hoog risicogroep. De geschatte 4-jaars overleving bedroeg 37%, 11% en 0%,

respectievelijk. Uit deze resultaten kan niet zonder meer geconcludeerd worden dat intensieve behandeling beter is, omdat de patiëntengroepen mogelijk niet vergelijkbaar zijn en geen randomisatie heeft plaats gevonden tussen intensieve en niet-intensieve behandeling. Tegenstanders van intensieve behandeling zijn van mening dat de resultaten vertekend zijn, doordat alleen de patiënten die in goede conditie verkeren en die goed hebben gereageerd op de voorbehandeling, worden getransplanteerd. De huidige analyse toont aan dat de resultaten van de groep patiënten, die geen intensieve behandeling hebben ondergaan, niet zijn verslechterd in de loop van de tijd. Dit ondersteunt dat niet alleen de goede patiënten voor behandeling zijn geselecteerd.
In de patiëntengroep die geen intensieve behandeling heeft ondergaan bleek in multivariate analyse, dat de IPSS een goede maat is om de prognose van een patiënt te voorspellen. Echter in de subgroep van 83 patiënten onder de 61 jaar, die intensief zijn behandeld, was de IPSS niet voorspellend voor overleving. De hazard ratio voor de hoog risicogroep in vergelijking met de intermediair 1 risicogroep was 1.81 (p=0.63), de hazard ratio voor de intermediair-2 risicogroep was 0.83 (p=0.78). Deze analyse suggereert dat patiënten in de intermediair-2 risicogroep het meest profiteren van intensieve behandeling.

Intensieve behandelingsopties worden bij hoog risico MDS patiënten minder vaak toegepast dan bij patiënten met AML (acute myeloïde leukemie), omdat de resultaten slechter zijn. Het is de vraag of dit komt door verschillen in de aangedane stamcel (ziekte-gerelateerde faktoren zoals genetische afwijkingen of moleculaire veranderingen) of doordat ongunstige variabelen die de uitkomst beïnvloeden, zoals oudere leeftijd, en een slechte algehele conditie, nu eenmaal vaker voorkomen bij MDS dan bij AML (patiënt-gerelateerde faktoren). In **hoofdstuk 6** worden de uitkomsten vergeleken van 981 patiënten met hoog risico MDS en AML, die in twee verschillende studies van de EORTC Leukemia Groep zijn behandeld en een zelfde remissie-inductie en consolidatiekuur hebben gekregen. Patiënten met primaire AML zijn behandeld in de AML-10 studie en patiënten met hoog risico MDS en secundaire AML na een MDS voorstadium van tenminste 6 maanden in de CRIANT studie. De postconsolidatie behandeling in beide studies bestond uit allogene stamceltransplantatie bij patiënten jonger dan 45-55 jaar, die over een HLA-identieke donor beschikken. In de AML-10 studie ondergingen de patiënten zonder donor een autologe stamceltransplantatie. Vanaf 1994 werden de patiënten zonder donor gerandomiseerd tussen autologe

beenmergtransplantatie (ABMT) en autologe perifere bloed stamceltransplantatie (APSCT). In de CRIANT studie werden de patiënten zonder donor gerandomiseerd tussen APSCT en een tweede consolidatiekuur. Het doel van deze studie was om klinische en biologische factoren te identificeren, die voorspellend zijn voor de uitkomst van patiënten. De geschatte 5-jaars overleving bedroeg 34% (AML-10) versus 27% (CRIANT) (p=0.26). De geschatte 5-jaars ziektevrije overleving was langer in de AML-10 studie (40%) vergeleken met de CRIANT studie (28%) (p=0.02). In multivariate analyse waren de volgende factoren van belang voor overleving en ziektevrije overleving: cytogenetische risicogroep, leukocytenaantal en leeftijd. In de gehele groep was de overleving en ziektevrije overleving beter voor patiënten die in de AML-10 studie zijn behandeld, dan voor patiënten die in de CRIANT studie zijn behandeld. Echter naast deze gemeenschappelijke variabelen die voor beide studies van belang waren, waren sommige variabelen slechts in één van de studies van belang. Om deze reden is een aparte multivariate analyse voor overleving in beide studies verricht. In de AML-10 studie hadden patiënten met een goede performance status (PS), FAB subtype M2/M4 en met de cytogenetische afwijkingen inv(16)/t(8;21) een betere prognose, terwijl in de CRIANT studie het aantal cytopenieën en het tijdsinterval tussen het begin van de ziekte en het starten van intensieve behandeling (=Antecedent Hematologic Disorder) van belang waren. Onze bevinding dat prognostische factoren verschillen in MDS en AML geeft steun aan onze veronderstelling dat MDs en AML verschillende ziektes zijn. Voor beide studies is een prognostische score ontwikkeld gebaseerd op de multivariate analyse. De score voor de AML-10 studie omvatte de volgende variabelen: cytogenetische afwijkingen, leukocytenaantal, FAB classificatie, leeftijd en performance status. De drie onderscheiden groepen hadden een geschatte 5-jaars overleving van 54%, 38%, en 19%, respectievelijk. De score voor de CRIANT studie omvatte cytogenetische afwijkingen, leukocytenaantal, leeftijd, aantal cytopenieën, en Antecedent Hematologic Disorder. Performance status was niet opgenomen in het model, omdat dit in de CRIANT studie niet van belang bleek te zijn voor overleving. De drie groepen hadden een geschatte 5-jaars overleving van 69%, 37%, en 5%, respectievelijk.

Deze analyse toont aan dat 48% van de hoog risico MDS patiënten een 5-jaars overleving van circa 40% hebben, wanneer zij worden behandeld met intensieve chemotherapie. Een minderheid van vooral jongere patiënten zonder slecht prognostische cytogenetische afwijkingen en ernstige cytopenieën, met een korte ziektegeschiedenis en een laag leukocytenaantal hebben een relatief goede prognose

met een 5-jaars overleving van 69%. Daartegenover onderscheidt deze studie 43% van de CRIANT patiënten en 30% van de AML-10 patiënten die een geschatte 5-jaars overleving hebben van minder dan 20% ondanks intensieve behandeling. Deze patiënten worden gekenmerkt door slecht prognostische cytogenetische afwijkingen, leeftijd boven de 45 jaar, meerdere cytopenieën, een ziektegeschiedenis langer dan 6 maanden, FAB classificatie anders dan M2/M4 en/of een hoog leukocytenaantal.
Wij zijn van mening dat de risico score voor de CRIANT studie als alternatief kan dienen voor de IPSS. De IPSS geeft veel gewicht aan het percentage beenmergblasten, terwijl dit percentage minder van belang lijkt voor intensief behandelde patiënten. De huidige scores stellen ons in staat om patiënten met een slechte prognose te onderscheiden. Nieuwe behandelingsstrategieën bij deze patiëntenpopulatie dienen plaats te vinden in de context van prospectieve klinische studies, waarbij de intensiteit van de behandeling aangepast kan worden aan de prognose van de patiënt.

CONCLUSIES

De myelodysplastische syndromen (MDS) vormen een heterogene groep van klonale afwijkingen in de hematopoïetische stamcel. Sinds de introductie van de FAB (“French-American-British”) classificatie in 1982, zijn meerder scoringssystemen ontworpen om het natuurlijk verloop van de ziekte bij een individuele patiënt te voorspellen. Vandaag de dag wordt de International Prognostic Scoring System (IPSS), gebaseerd op het aantal blasten in het beenmerg, het aantal cytopenieën en het type cytogenetische afwijkingen, het meest gebruikt.
MDS is een ziekte die vooral bij oudere patiënten voorkomt. Dit proefschrift beschrijft intensieve behandelingsmethoden, die als doel hebben om de kwaadaardige kloon uit te roeien. Deze behandelingen worden alleen bij jongere patiënten in een goede conditie toegepast. Patiënten die tot de intermediair-1, intermediair-2 en hoog risicogroep van de IPSS behoren, komen in aanmerking voor intensieve behandeling. Het is een uitdaging om te voorspellen welke patiënt de meeste baat heeft bij welke behandeling.
Veel clinici beschouwen allogene stamceltransplantatie (SCT) als de enige curatieve optie. In het eerste deel van dit proefschrift laten we zien dat de overleving van patiënten met en zonder een HLA-identieke donor niet van elkaar verschilt, wanneer de behandelingsintentie als uitgangspunt wordt genomen. Andersoortige behandelingen, zoals stamceltransplantatie met niet HLA-identieke familieleden en onverwante donoren,

autologe SCT en intensieve chemotherapie, vormen een alternatief voor patiënten zonder HLA-identieke donor. In een volgende analyse hebben we de uitkomsten vergeleken van patiënten met hoog risico MDS en acute leukemie na een voorstadium van MDS, die zijn behandeld met intensieve chemotherapie met of zonder stamceltransplantatie. Hoewel de overleving van patiënten die behandeld zijn met chemotherapie in combinatie met transplantatie, niet langer is dan de overleving van patiënten die alleen chemotherapie krijgen toegediend, is de ziektevrije overleving langer in de patiëntengroep die met SCT wordt behandeld.

Het tweede gedeelte van dit proefschrift onderzoekt de waarde van de IPSS in het voorspellen van de prognose van een individuele patiënt. We bevestigen dat de IPSS een waardevol instrument is om de overleving van niet-intensief behandelde patiënten te voorspellen. Echter de IPSS is minder geschikt om de uitkomst na intensieve behandeling te voorspellen. We laten zien dat patiënten in de intermediair-2 risicogroep de meeste baat hebben bij intensieve behandeling.

Tenslotte vergelijken we de uitkomst van patiënten met hoogrisico MDS en AML, die in twee verschillende studies zijn behandeld met identieke remissie-inductie en consolidatiekuren, met als doel om voorspellende klinische en biologische factoren te onderscheiden. In de gecombineerde patiëntengroep zijn cytogenetische risicogroep, leukocytenaantal, leeftijd en performance status van belang voor de uitkomst. Echter, een aantal andere factoren is slechts in één van de studies van belang. Gebaseerd op deze factoren hebben we twee prognostische scores ontwikkeld: één voor de AML-10 studie en één voor de CRIANT studie. De score voor de CRIANT studie kan een goed alternatief zijn voor de IPSS, omdat de IPSS veel gewicht geeft aan het percentage blasten in het beenmerg, terwijl dit minder van belang is bij patiënten die intensieve behandeling ondergaan. De scores stellen ons in staat om de overleving te voorspellen na intensieve behandeling inclusief stamceltransplantatie en om patiënten te identificeren met een slechte prognose na behandeling. In de afgelopen jaren is de kennis van de moleculaire mechanismen, die verantwoordelijk zijn voor de ineffectieve aanmaak van bloedcellen en de leukemische ontaarding toegenomen. Deze kennis kan leiden tot een meer oorzakelijke behandeling van de ziekte. Nieuwe behandelingsstrategieën bij patiënten met een slechte prognose dienen toegepast te worden in de context van klinische studies, waarbij de intensiteit van de behandeling aangepast kan worden aan de prognose van de patiënt.

TOEKOMSTIGE ONTWIKKELINGEN

In de afgelopen jaren is er een aanzienlijke winst geboekt in de behandeling van MDS patiënten, met name door het toepassen van allogene stamceltransplantaties. Nieuwe inzichten in het biologisch gedrag van MDS bieden mogelijkheden voor nieuwe behandelingsmethodes.

Verbeteren van intensieve chemotherapie

Gemtuzumab ozogamicine is een antistof gericht tegen CD33, gebonden aan calicheamicine en heeft een sterk celdodend effect. De resultaten van behandeling van patiënten met een recidief AML zijn bemoedigend. Nieuwe studies met gemtuzumab in combinatie met andere cytostatica als eerste lijnsbehandeling bij MDS worden momenteel gestart.

Een alternatieve benaderen is het combineren van chemotherapie met Pgp (P-glycoproteïne) remmers zoals zosuquidar om chemotherapie-resistentie tegen te gaan.

Verminderen van de transplantatie-gerelateerde sterfte na allogene transplantatie

De supportieve zorg is in de afgelopen jaren sterk verbeterd. Een intensievere monitoring en effectievere behandeling van potentiële infecties heeft geleid tot een lagere transplantatie-gerelateerde mortaliteit.

De kans op ernstige omgekeerde afstoting na SCT met een onverwante donor is verminderd sinds HLA-typering op DNA-niveau wordt verricht. Mede hierdoor zijn de resultaten van transplantatie met een onverwante donor sterk verbeterd.

Het toepassen van de zogenaamde “Reduced Intensity Conditioning” (RIC) schema’s is veelbelovend, omdat de transplantatie-gerelateerde sterfte lager is dan na zogenaamde myeloablatieve conditionering. Echter, of deze behandeling de lange termijn uitkomst van patiënten zal verbeteren, moet nog worden onderzocht in prospectief gerandomiseerde studies.

Toepassen van nieuwe geneesmiddelen

In de laatste 10 jaar zijn een aantal nieuwe geneesmiddelen ontwikkeld. Deze middelen grijpen min of meer specifiek aan op moleculaire mechanismen, die van belang zijn voor het ontstaan van MDS. De resultaten van behandeling met deze nieuwe middelen (angiogenese-remmers, farnesyl-transferase remmers, hypomethylerende middelen,

tyrosine kinase remmers, anti-apoptose middelen) zijn bemoedigend. Echter, tot nu toe zijn deze middelen als monotherapie getest in verschillende studies, in de meeste gevallen zonder de intentie om de ziekte te genezen. De uitdaging is om deze nieuwe geneesmiddelen te combineren met bestaande behandelingen.

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CURRICULUM VITAE

De schrijfster van dit proefschrift werd op 8 november 1964 in Amersfoort geboren. Zij woonde achtereenvolgens in Groede en Ameide. In 1970 verhuisde zij naar Engwierum, waar de lagere school werd afgemaakt. Het VWO diploma werd in 1982 in Dokkum behaald (Christelijke scholengemeenschap Oostergo). In datzelfde jaar werd gestart met de studie Scheikunde aan de Rijksuniversiteit Groningen. In 1984 werd gestart met de studie Geneeskunde aan de Rijksuniversiteit Groningen. Het doctoraalexamen werd in 1988 behaald en het artsexamen (cum laude) in 1991.

In de zomer van 1991 startte zij als arts-assistent niet in opleiding in het toenmalige Bonifatius hospitaal in Leeuwarden (thans Medisch Centrum Leeuwarden). Vanaf 1 oktober 1992 was ze in opleiding tot internist in de regio Noord-Oost Nederland (opleider Prof. dr. W.D. Reitsma). Zij was van 1992 tot 1996 werkzaam in het Sophia Ziekenhuis in Zwolle (opleider Dr. T. Tjabbes) en van 1996-1997 in het Medisch Spectrum Twente in Enschede (opleider Prof. dr. D.J. Richel). In 1997 verhuisde zij naar Nijmegen om te starten met het aandachtsgebied hematologie (hoofd Prof. dr. T.J.M. de Witte). Registratie als internist vond op 1 oktober 1998 plaats (opleider Prof. dr. J.W.M. van der Meer). Registratie als hematoloog vond plaats op 18 maart 2003.

Van 1 oktober 1997 tot 1 mei 2005 is zij verbonden aan de afdeling Hematologie van het Universitair Medisch Centrum Sint Radboud. In deze periode werd ook het onderzoek verricht dat is beschreven in dit proefschrift.

Vanaf 1 mei 2005 zal zij als internist werkzaam zijn in het Elkerliek ziekenhuis in Helmond.

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10. Oosterveld M, de Witte TJM. Een fase-II-studie voor de evaluatie van de behandeling van anemie met recombinant erythropoietine (Aranesp®) bij patiënten met een myelodysplastisch syndroom. Nederlands tijdschrift voor Hematologie 2004; 3: 121-123.

11. Van de Loosdrecht AA, Oosterveld M. Het myelodysplastisch syndroom: behandelingsprotocollen in Nederland anno 2004. Nederlands tijdschrift voor Hematologie 2004; 4: 162-165.

12. De Witte T, Oosterveld M. Myelodysplastic Syndromes. Hematopoietic stem cell transplant strategies in patients with myelodysplastic syndrome and secondary acute myeloid leukemia: the role of reduced intensity conditioning regimens. Hematology 2004;: 308-317