Reduced-toxicity conditioning with treosulfan and fludarabine in allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes: final results of an international prospective phase II trial

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ABSTRACT

Background

An alternative reduced-toxicity conditioning regimen for allogeneic transplantation, based on treosulfan and fludarabine, has recently been identified. The rationale for this study was to investigate the efficacy and safety of this regimen prospectively in patients with a primary myelodysplastic syndrome.

Design and Methods

A total of 45 patients with primary myelodysplastic syndromes were conditioned with 3×14 g/m² treosulfan and 5×30 mg/m² fludarabine followed by allogeneic hematopoietic stem cell transplantation. Subtypes of myelodysplastic syndromes were refractory anemia with excess blasts-2 (44%), refractory cytopenia with multilineage dysplasia (27%), refractory anemia (9%), refractory anemia with ringed sideroblasts (4%), refractory cytopenia with multilineage dysplasia and ringed sideroblasts (4%), refractory anemia with excess blasts-1 (2%), and myelodysplastic syndrome with isolated del (5q) (2%). The myelodysplastic syndrome was unclassified in 7% of the patients. Forty-seven percent of the patients had a favorable karyotype, 29% an unfavorable one, and 18% an intermediate karyotype. Patients were evaluated for engraftment, adverse events, graft-*versus*-host disease, non-relapse mortality, relapse incidence, overall survival and disease-free survival.

Results

All but one patient showed primary engraftment of neutrophils after a median of 17 days. Non-hematologic adverse events of grade III-IV in severity included mainly infections and gastrointestinal symptoms (80% and 22% of the patients, respectively). Acute graft-*versus*-host disease grade II-IV developed in 24%, and extensive chronic graft-*versus*-host disease in 28% of the patients. After a median follow-up of 780 days, the 2-year overall and disease-free survival estimates were 71% and 67%, respectively. The 2-year cumulative incidences of non-relapse mortality and relapse were 17% and 16%, respectively.

Conclusions

Our safety and efficacy data suggest that treosulfan-based conditioning therapy is a promising treatment option for patients with myelodysplastic syndromes.
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Key words: reduced-toxicity conditioning, treosulfan, fludarabine, hematopoietic stem cell transplantation, myelodysplastic syndrome.

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The online version of this article has a Supplementary Appendix.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative approach for patients with a myelodysplastic syndrome (MDS). The incidence of MDS is age-dependent and the vast majority of MDS patients are older than 50 years. For many years, only a small minority of MDS patients qualified for allogeneic HSCT due to procedure-related toxicity after standard total body irradiation or busulfan-based conditioning, associated particularly with increasing age of the patients. During the past years the number of MDS patients who undergo allogeneic HSCT has increased considerably,[1] which might reflect substantial advances in supportive care, but is in particular connected to the development of reduced intensity conditioning (RIC) regimens. Evaluating the benefit of a particular conditioning regimen in MDS is, however, complicated by the diversity of regimens in use as well as inclusion of populations of patients with heterogeneous disease characteristics, such as primary and therapy-related MDS or secondary acute myeloid leukemia (AML) arising from MDS, and different prognostic profiles of the patients. Moreover, most of the published studies on conditioning regimens for allogeneic HSCT in MDS patients are retrospective in nature.[2] RIC regimens mainly aim at inducing sufficient immunosuppression to enable engraftment, and rely largely on the graft-*versus*-malignancy effect for the cure of the patient. Most RIC protocols include fludarabine in combination with reduced doses of either an alkylating agent (e.g., busulfan) or total body irradiation.[2] Compared to standard-dose conditioning, the potential, as yet unproven, benefit of RIC relies on the reduction of acute regimen-related non-hematologic toxicity and its inherent mortality. With a few exceptions,[3] a major obstacle to successful transplantation after RIC is the higher risk of relapse compared with that after standard conditioning regimens.[2,4-8]

Treosulfan is a bifunctional alkylating prodrug with proven myelotoxic and immunosuppressive properties and demonstrated strong activity against hematopoietic stem cells.[9-11] Treosulfan-based conditioning regimens have recently been shown to have a favorable safety profile and to enable fast and sustained engraftment.[12-16] Low transplantation-related morbidity and sustained engraftment have also been reported in children, even in those with non-malignant diseases and at high risk of both regimen-related toxicity and graft failure.[17-21] A dose-escalation study in adult patients with a variety of hematologic malignancies qualifying for allogeneic HSCT but with a substantial risk of regimen-related toxicity revealed that a treosulfan dose of 3×14 g/m² in combination with fludarabine 5×30 mg/m² was a safe and effective conditioning regimen.[22] Based on the available data on low toxicity in combination with myeloablative properties, we consider *reduced-toxicity conditioning* an appropriate term to characterize this regimen. The current prospective phase II study was designed to investigate the safety and efficacy of this regimen in primary MDS patients with an indication for allogeneic HSCT. The final results of the study are reported after all surviving patients have been observed for at least 1 year after transplantation of the last patient included in the study.

Design and Methods

Patients' eligibility

Between November 2004 and July 2007, 45 MDS patients were enrolled in this prospective non-randomized phase II study at 11 study centers in four European countries. Written informed consent to all aspects of the study was obtained from all patients before enrollment. The study was approved by the appropriate independent ethics committees and competent authorities and was performed in accordance with the Declaration of Helsinki.

Patients between 18-65 years of age with MDS according to the World Health Organization (WHO) 2001 classification and an indication for allogeneic HSCT according to institutional policy were included. Patients with therapy-related MDS or AML were not to be included. Detailed eligibility criteria are given in the *Online Supplementary Appendix*.

Outcome parameters were followed until 1 year after transplantation of the last patient included in the study.

Donors and grafts

Either HLA-identical siblings or matched unrelated donors were allowed (matching for eight out of eight antigens, Table 1). Serological typing was required for class I (HLA-A/-B) and molecular typing for class II (HLA-DRB1/-DQB1) antigens.

Conditioning regimen and transplantation

All patients received intravenous (IV) fludarabine 30 mg/m² from day -6 to day -2 (total dose: 150 mg/m²) and treosulfan (medac GmbH, Hamburg, Germany) 14 g/m² IV on days -6, -5, and -4 (total dose: 42 g/m²) before transplantation. Allogeneic hematopoietic stem cells either from peripheral blood or from bone marrow were given on day 0 (Table 1).

Supportive care

Graft-*versus*-host disease (GvHD) prophylaxis consisted of cyclosporin (3 mg/kg/day IV) starting 1 day before transplantation in combination with a short-course methotrexate (15 mg/m² IV on day +1 and 10 mg/m² IV on days +3 and +6). If an unrelated donor was used, anti-T-cell globulin (ATG-Fresenius (S)®, Fresenius Biotech, Graefelfing, Germany) was administered at a dose of 10 mg/kg IV from day -4 to day -2. Supportive care was given according to center-specific guidelines. The use of human recombinant granulocyte growth factors was not recommended unless clinically indicated.

Engraftment, graft failure and chimerism analysis

Engraftment and graft failure were defined as previously described.[22] Chimerism analysis was performed in the total bone marrow according to established methods of the participating institutions.[22]

Complete chimerism was defined as 95% or more donor cells as quantified by dual color XY chromosome fluorescence *in situ* hybridization in opposite sex donor-recipient pairs or by variable number of tandem repeats analysis in sex concordant donor-recipient combinations.

Adverse events

Adverse events including serious adverse events were evaluated from the start of conditioning (day -6) to day +28. In addition, serious adverse events occurring after day +28 had to be reported, if at least a possible relation to the conditioning regimen was suspected. Changes in laboratory values were not included in the adverse event analysis, but were documented separately.

Apart from hepatic veno-occlusive disease, all adverse events were assessed using the National Cancer Institute Common

Terminology Criteria for Adverse Events (CTCAE, version 3.0). Hepatic veno-occlusive disease was evaluated according to standard criteria.[23,24]

Assessment of response/relapse

Treatment response and relapse were evaluated according to standard criteria.[25]

Graft-versus-host disease

GvHD was diagnosed and graded according to standard criteria.[26-28] Depending on whether the GvHD developed before or after day +100, it was classified as acute or chronic.

Sample size and statistical considerations

The primary aim of this study was to evaluate the efficacy and safety profile of a treosulfan-based conditioning regimen. With a sample size of 45 patients, an expected neutrophil engraftment rate of 95% could be estimated with a precision of ± 14 percentage points with a power of 80% using a two-sided exact Clopper-Pearson 95% confidence interval. In addition, any toxicity occurring with a probability of at least 5% had a 90% chance of being seen at least once, whereas any toxicity occurring with a probability of 3.5% had an 80% chance of being seen at least once. Time to engraftment was calculated from day 0 by means of conditional cumulative incidence curves. Day +28 rates were extracted from these curves. Estimates of chimerism, non-relapse mortality, relapse incidence, and acute and chronic GvHD were derived using cumulative incidence rates to accommodate competing risks. Disease-free survival and overall survival were analyzed using product-limit (Kaplan-Meier) estimates. Incidences of selected grade III-IV adverse events reported in the setting of allogeneic HSCT were the primary combined end-point of the study. The incidence of adverse events was calculated as the percentage of patients who experienced at least one adverse event of a certain CTCAE category out of the total number of patients. For exploratory purposes, efficacy data were stratified by type of donor (HLA-identical sibling *versus* matched unrelated donor), status prior to the conditioning regimen (treated *versus* untreated), and International Prognostic Scoring System (IPSS) risk score.[29] For the comparison of cumulative incidence curves, Gray's test was applied, whereas log-rank tests were

Table 1. Patients' demographic and disease characteristics.

	N=45 (100%) N (%)
Median age [years] (range)	50 (22-63)
Sex	
Male	21 (47)
Female	24 (53)
Donor	
HLA-identical sibling donor	15 (33)
HLA-matched unrelated donor	30 (67)
Source of stem cells	
Peripheral blood	40 (89)
Bone marrow	5 (11)
Number of $CD34^+$ cells$\times 10^6$ per kg body weight	
Median (range)	6.35 (0.89-17.9)
WHO classification at the time of transplantation	
Refractory anemia	4 (9)
Refractory anemia with excess blasts – 1	1 (2)
Refractory anemia with excess blasts – 2	20 (44)
Refractory anemia with ringed sideroblasts	2 (4)
Refractory cytopenia with multilineage dysplasia	12 (27)
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	2 (4)
MDS associated with isolated del (5q)	1 (2)
MDS unclassified	3 (7)
Median time from diagnosis to transplantation [years] (range)	0.64 (0.1-7.7)
Pre-treatment	
AML-induction-like and/or low-dose chemotherapy	8 (18)
Untreated (none, or no chemotherapy)	35 (78)
Experimental	2 (4)
IPSS risk groups	
Low risk	3 (7)
Intermediate 1 risk	20 (44)
Intermediate 2 risk	14 (31)
High risk	8 (18)
Karyotype*	
Favorable	21 (47)
Intermediate	8 (18)
Unfavorable	13 (29)
Unknown	3 (7)

**Definition of karyotypes: favorable: normal; -Y, del(5q) isolated, del(20q) isolated; unfavorable: complex karyotype (≥ 3 abnormalities); anomalies of chromosome 7; intermediate: all others AML: acute myeloid leukemia; IPSS: International Prognostic Scoring System;[29] MDS: myelodysplastic syndrome.*

Table 2. Frequency of all CTCAE grade III and IV adverse events between start of conditioning and day +28.

CTCAE Category/Term	Worst CTCAE Grade (N=45) III N (%)	IV N (%)	Total III/IV N (%)
Number of patients with any event*	35 (78)	4 (9)	39 (87)
Infection total	33 (73)	3 (7)	36 (80)
Febrile neutropenia	25 (56)	1 (2)	26 (58)
Infection with grade III/IV neutrophils	13 (29)	1 (2)	14 (31)
Infection with normal or grade I/II ANC	4 (9)	1 (2)	5 (11)
Infectious colitis	1 (2)	0 (0)	1 (2)
Infection - Other	1 (2)	0 (0)	1 (2)
Gastrointestinal total	9 (20)	1 (2)	10 (22)
Nausea	6 (13)	0 (0)	6 (13)
Diarrhea	2 (4)	0 (0)	2 (4)
Anorexia	1 (2)	0 (0)	1 (2)
Colitis	1 (2)	0 (0)	1 (2)
Mucositis/stomatitis (clinical examination)	0 (0)	1 (2)	1 (2)
Vomiting	1 (2)	0 (0)	1 (2)
Pain	6 (13)	0 (0)	6 (13)
Pulmonary/upper respiratory	4 (9)	0 (0)	4 (9)
Neurology	1 (2)	2 (4)	3 (7)
Blood/bone marrow (hemolysis)	2 (4)	0 (0)	2 (4)
Cardiac general	2 (4)	0 (0)	2 (4)
Constitutional symptoms	2 (4)	0 (0)	2 (4)
Allergy / immunology	1 (2)	0 (0)	1 (2)
Cardiac arrhythmia	1 (2)	0 (0)	1 (2)
Endocrine	1 (2)	0 (0)	1 (2)
Hemorrhage/bleeding	1 (2)	0 (0)	1 (2)
Hepatobiliary/pancreas	1 (2)	0 (0)	1 (2)
Renal/genitourinary	1 (2)	0 (0)	1 (2)

**Excluding laboratory changes (see Supplementary Appendix Table S2 for non-hematologic laboratory changes. ANC: absolute neutrophil count; CTCAE: Common Terminology Criteria for Adverse Events.*

used for the comparison of product-limit estimates. All *P*-values were derived from two-sided tests. The statistical analyses were performed using SAS software package version 9.1.3 (SAS Institute, Cary, NC, USA) and *R* version 2.2.1 (The R Foundation for Statistical Computing).

Results

Demographics

A total of 45 MDS patients were included in the study and treated in line with the study protocol. A single patient with AML was erroneously enrolled, but was excluded from the study analysis and was replaced by an additional patient fulfilling the inclusion criteria. Table 1 summarizes the characteristics of the patients and their diseases. Only two patients had significant co-morbidities as assessed by the treating physician.

Engraftment and chimerism

CTCAE grade IV neutropenia, leukocytopenia and thrombocytopenia occurred in virtually all patients. The 28-day conditional cumulative incidences of neutrophil, total white blood cell and platelet recovery reached 96% (95% CI: 85%-100%), 96% (95% CI: 87%-100%), and 87% (95% CI: 76%-98%), respectively. The median time to recovery was 16 days (range, 10-33 days) for white blood cells, 16 days (range, 6-71 days) for platelets and 17 days (range, 10-35 days) for neutrophils. The cumulative incidences of complete donor type chimerism increased from 78% on day +28 to 93% on days +56 and +100. One patient experienced primary graft failure as documented on day +28. Secondary failure of engraftment (pancytopenia) was reported in another patient. Results of engraftment and chimerism analyses are detailed in *Online Supplementary Table S1*.

Adverse events

Within the observation period (day -6 to day +28), 39 of 45 patients (87%) experienced at least one episode of grade III-IV adverse events (Table 2). The most frequently reported CTCAE categories were infection (80%) and gastrointestinal events (22%). Infections included grade III-IV febrile neutropenia (58%) and infection either with (31%) or without (11%) neutropenia. Gastrointestinal adverse events were mostly of grade III in severity and included nausea (13%) and diarrhea (4%). Only one patient (2%) experienced grade IV mucositis. All other reported grade III-IV adverse events occurred sporadically.

The incidences of selected grade III-IV adverse events reported in the setting of allogeneic HSCT were the primary combined end-point of the study. The incidences of these events were 13% (95% CI: 5%-27%) for hyperbilirubinemia, 2% (95% CI: 0%-12%) for mucositis/stomatitis, and 0% (95% CI: 0%-8%) for seizures. Two patients (4%; 95% CI: 1%-15%) experienced moderate (grade II) veno-occlusive disease, which had resolved by day +20. Changes in laboratory values were within expected ranges (*Online Supplementary Table S2*).

Beyond day +28 after transplantation, three serious adverse events assessed as at least possibly related to the conditioning regimen were reported. These were secondary graft failure (starting on day +29), reversible grade III cutaneous ulcerations on both legs secondary to skin necrosis (starting on day +29), and breast cancer (starting on day +685).

Non-relapse mortality

All patients survived the initial 28-day assessment period after transplantation. Thereafter, seven patients (16%) died from transplant-related causes. The main causes of death were infections in two patients and GvHD (acute in one patient, chronic in another). One patient experienced primary graft failure. Eight days later, she developed Epstein-Barr virus lymphoproliferative disease leading to fatal multiorgan failure. Another patient experienced secondary graft failure and developed pneumonia complicated by fatal multiorgan failure. One additional patient died on day +52 of multiorgan failure not further specified. The 100-, 360- and 720-day cumulative incidences of non-relapse mortality were 9%, 13%, and 17%, respectively (Figure 1). Non-relapse mortality was similar among patients transplanted from sibling or. unrelated donors, among patients with IPSS intermediate-1, -2 or high risk disease, and among those with untreated or chemotherapy-pretreated MDS (*Online Supplementary Table S3*).

Relapse incidence

Seven patients relapsed during follow-up, resulting in a cumulative incidence of relapse of 4% at 100 days, and 16% at 360 and 720 days (Figure 2). Five of these patients died of relapse. The 2-year cumulative incidence of relapse was 20% in patients with sibling donors compared to 13% in patients with unrelated donors (*P*=0.5665, Gray's test), 10% in patients with intermediate-1 and 13% in patients with high IPSS compared to 29% in patients with intermediate-2 IPSS (*P*=0.3512, Gray's test). Patients with previous chemotherapy and untreated patients had relapse incidences of 25% and 14%, respectively (*P*=0.4956, Gray's test, *Online Supplementary Table S4*). An additional analysis stratified by cytogenetic risk revealed comparable 2-year cumulative incidences of relapse for patients with favorable (14%), intermediate (13%), and unfavorable (15%) risk (*P*=0.9748, Gray's test).

Disease-free survival

The probabilities of disease-free survival were 87% at 100 days, 71% at 360 days, and 67% at 720 days (Figure 3). Patients with sibling donors had a 2-year probability of disease-free survival of 57% compared to 73% of the

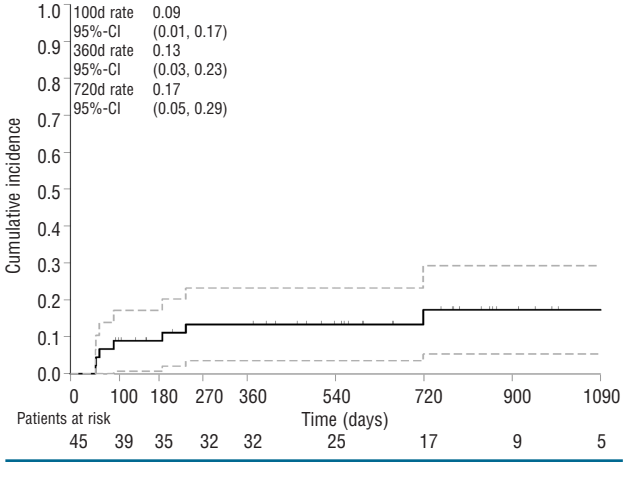

Figure 1. Cumulative incidence of non-relapse mortality and 95% confidence limits.

patients with unrelated donor. However, this difference was not statistically significant (P=0.4684, log-rank test). Comparable disease-free survival probabilities at 2 years were observed for patients within the IPSS groups intermediate-1 (70%), intermediate-2 (63%) and high risk (63%), and for previously treated and previously untreated patients (75% *versus* 67%, respectively; *Online Supplementary Table S5*). An additional analysis stratified by cytogenetic risk revealed 2-year disease-free probabilities of 88% (95% CI: 66%-100%) for patients with intermediate risk compared to 67% (95% CI: 47%-87%) for patients with favorable risk, and 55% (95% CI: 25%-85%) for patients with unfavorable risk (P=0.4561, log-rank test).

Survival

After a median follow-up period of 780 days (range of those surviving, 372-1260 days), 33 patients (73%) were alive, and 12 (27%) had died. The overall survival estimates were 91% (95% CI: 83%-99%) at 100 days, 82% (95% CI: 71%-93%) at 360 days, and 71% (95% CI: 56%-85%) at 720 days (Figure 3). A 2-year overall survival rate of 63% was observed for patients with sibling donors compared to 75% for patients with unrelated donors (P=0.5163, log-rank test). In addition, no significant differences were observed among patients within the IPSS groups intermediate-1 (70%), intermediate-2 (68%) and high risk (75%), and for patients previously treated with chemotherapy (80%) compared to untreated patients (70%; *Online Supplementary Table S6*).

Graft-versus-host disease

The day 100 cumulative incidences of grade I-IV, II-IV, and III-IV acute GvHD were 56%, 24%, and 16%, respectively (*Online Supplementary Figure S1*). The cumulative incidence of chronic GvHD at 720 days was 59%, while the cumulative incidence of extensive chronic GvHD reached 28% (*Online Supplementary Figure S2*).

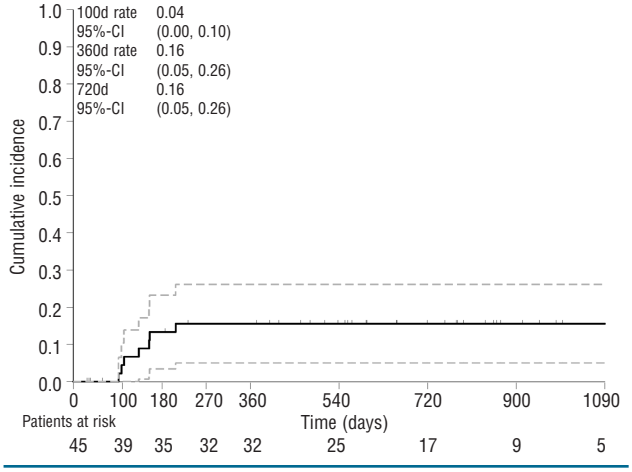

Figure 2. Cumulative incidence of relapse and 95% confidence limits.

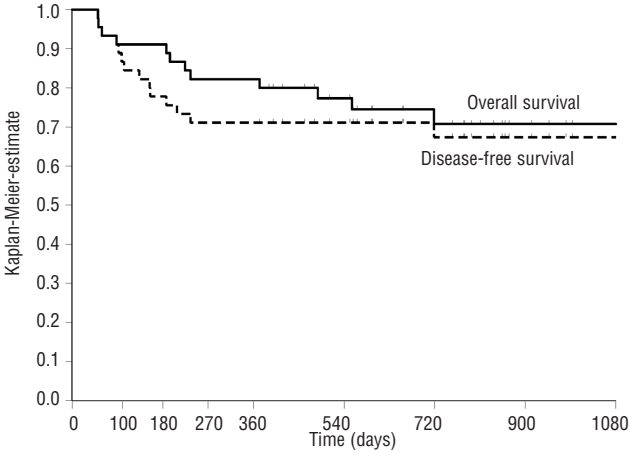

Figure 3. Kaplan-Meier estimates for disease-free and overall survival.

Discussion

The aim of developing a conditioning regimen consisting of treosulfan and fludarabine was to reduce the incidence and severity of non-hematologic acute toxicities frequently observed in allogeneic HSCT recipients after standard conditioning therapy, without compromising the antineoplastic effect. Analyzing the present study results in the context of published data, it is of note that most previous studies included not only patients with primary MDS, but also patients with secondary AML or treatment-related MDS,[30] which may substantially affect study results. As anticipated from previous studies with treosulfan-based conditioning, the acute non-hematologic toxicity of the regimen was low.[12,15,16,22,31] Grade III-IV hyperbilirubinemia was noted in 13% of the patients, and only two cases (4%) of moderate veno-occlusive disease were observed. Similarly, the incidence of severe mucositis appears very low when compared to that usually described for standard conditioning regimens. As can be expected for a standard conditioning regimen, severe infections were common as these are primarily connected to the severity and duration of marrow aplasia. Twenty-two percent of the patients had grade III-IV gastrointestinal symptoms. All other CTCAE grade III-IV toxicities occurred with low frequencies. The incidences and severities of acute and chronic GvHD were in the range of those commonly reported for allogeneic HSCT using standard conditioning regimens.[5,8,30,32] Our GvHD prophylaxis regimen contained three doses of methotrexate. Using the other common version with four doses might have somewhat influenced the incidence of GvHD, but, on the other hand, also that of engraftment and possibly the occurrence of adverse effects.

The resulting non-relapse mortality rates of 9% at 100 days and 17% at 720 days appear similar to those seen after RIC transplantation[5,7,8,30,33] and lower than those reported after standard conditioning in MDS patients, in whom 100-day rates between 19% and 27% have been observed.[5,30,34,35]

The prognosis of MDS depends strongly on the subtype of the disease as well as on other prognostic factors.[2,36] In general, outcome is considered to be more favorable in patients with refractory anemia without excess blasts than in those with an excess of blasts.[2,36-39] Certain cytogenetic abnormalities and cytopenia in more than one cell line also indicate an adverse prognosis. The IPSS for the estimation of the likelihood of leukemic transformation and survival

includes these variables.[29] Our exploratory subgroup analysis revealed no statistically significant influence of the type of donor (sibling or unrelated), IPSS, or previous MDS treatment on relapse incidence, non-relapse mortality, disease-free survival or overall survival. These results should, however, be interpreted cautiously due to the small number of patients in each subgroup. Recent results of a larger prospective randomized transplantation study showed no prognostic influence of IPSS or blast count on survival while advanced age, number of cytopenias and intermediate to high-risk cytogenetic characteristics were adverse prognostic factors.[40]

A low and encouraging 2-year relapse incidence of only 16% was observed in this study, comparing favorably with incidences in previously published series.[5,33,40] Thus far, relapses have occurred only within the first 220 days after transplantation and no relapses have been reported beyond this time. Rare late disease recurrences were noted by Nemecek *et al*. who used the treosulfan-based conditioning regimen in a prospective allogeneic HSCT protocol, which included several disease entities.[31]

The 2-year estimates of overall and disease-free survival were 71% and 67%, respectively. Approximately one half of the deaths in this study were caused by relapse. These figures appear superior to those published for the results of allogeneic HSCT using standard conditioning regimens,[5,34,35] and compare favorably with those of some studies using RIC. Ho *et al*., using fludarabine-busulfan conditioning with busulfan 8 mg/kg, reported 1-year overall and disease-free survival rates of 74% and 62%, respectively. However, a considerable proportion of the patients required donor lymphocyte infusions to treat declining donor chimerism.[33] In contrast, Alyea *et al*., using the same conditioning regimen, reported substantially inferior overall and progression-free survival estimates of 39% and 27% at 2 years after transplantation.[7] Similar results were observed by Shimoni *et al*. after RIC with fludarabine and intravenous busulfan. Two-year overall and disease-free survival estimates of 47(49)% and 43(49)%, respectively, were reported. However, that study also included patients with AML, and all MDS patients had an excess of blasts.[8] In older AML/MDS patients (≥ 55 years) similar 2-year overall and event-free survival rates of 46% and 44% were reported after RIC with fludarabine and intravenous busulfan, and the 1-year transplant-related mortality rate was 19-20%.[41]

In preclinical[9,11,42] and clinical[12,16,22,31,43,44] studies, treosulfan demonstrated strong cytotoxic activity on hematopoietic cells, while non-hematologic toxicity was generally mild. The results of the present study are in good accordance with those reports. Given the prompt engraftment, rapid achievement of full donor hematopoietic chimerism, as well as a comparatively low relapse incidence, the treosulfan/fludarabine conditioning regimen has clearly myeloablative properties, and the term *reduced-toxicity conditioning* appears most appropriate for this regimen.

In the light of the favorable outcome results with the regimen evaluated in the present study, further investigation of treosulfan and fludarabine conditioning therapy is warranted. A randomized, international phase III study comparing the treosulfan/fludarabine regimen with a conditioning regimen consisting of reduced-dose busulfan and fludarabine in a large cohort of AML and MDS patients stratified by indications is currently under way.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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