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

Tapani Ruutu,[1] Liisa Volin,[1] Dietrich W. Beelen,[2] Rudolf Trenschel,[2] Juergen Finke,[3] Marc Schnitzler,[3] Jerzy Holowiecki,[4,13] Sebastian Giebel,[4,13] Miroslaw Markiewicz,[4] Lutz Uharek,[5] Igor W. Blau,[5] Joachim Kienast,[6] Matthias Stelljes,[6] Kajsa Larsson,[7] Axel R. Zander,[8] Martin Gramatzki,[9] Roland Repp,[9] Hermann Einsele,[10] Gernot Stuhler,[10] Joachim Baumgart,[11] Heidrun A. Mylius,[11] Uwe Pichlmeier,[11] Mathias Freund,[12] and Jochen Casper[12,14]

[1]Dept. of Medicine, Helsinki University Central Hospital, Helsinki, Finland; [2]Dept. for Bone Marrow Transplantation, University of Duisburg-Essen, Essen, Germany; [3]Dept. of Medicine, Hematology, Oncology, University of Freiburg, Freiburg, Germany; [4]University Department of Hematology and BMT, Silesian Medical University, Katowice, Poland; [5]Medical Clinic III - Hematology and Oncology, Charité University Medicine Berlin, Berlin, Germany; [6]Dept. of Hematology/Oncology, University of Muenster, Muenster, Germany; [7]Centre for Allogeneic Stem Cell Transplantation and Dept. of Hematology, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden; [8]Bone Marrow Transplantation Centre, University Hospital Eppendorf, Hamburg, Germany; [9]Division for Stem Cell Transplantation and Immunotherapy, University of Kiel, Kiel, Germany; [10]Dept. of Hematology/Oncology, University of Wuerzburg, Wuerzburg, Germany; [11]medac GmbH, Hamburg, Germany; [12]Division of Hematology and Oncology, University of Rostock, Rostock, Germany; [13]present address: M. Sklodowska-Curie Memorial Cancer Center and Institute, Gliwice, Poland; [14]present address: Clinic Oldenburg, Clinic for Oncology and Hematology, Oldenburg, Germany

Citation: Ruutu T, Volin L, Beelen DW, Trenschel R, Finke J, Schnitzler M, Holowiecki J, Giebel S, Markiewicz M, Uharek L, Blau IW, Kienast J, Stelljes M, Larsson K, Zander AR, Gramatzki M, Repp R, Einsele H, Stuhler G, Baumgart J, Mylius HA, Pichlmeier U, Freund M, and Casper J. 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. Haematologica 2011;96(9):1344-1350. doi:10.3324/haematol.2011.043810

Online Supplementary Appendix

Patients' eligibility criteria

Patients' eligibility criteria included a diagnosis of myelodysplastic syndrome (MDS) according to the World Health Organization (WHO) classification 2001, an indication for allogeneic hematopoietic stem cell transplantation (HSCT) according to institutional policy, age 18-65 years, Karnofsky performance score of 80% or greater, adequate contraception in female patients of child-bearing potential, and availability of an HLA-identical sibling or matched unrelated donor. Donors and recipients were required to be HLA-matched at the following loci: HLA-A and -B (serological or DNA-based, two digits), HLA-DRB1 and -DQB1 (DNA-based, four digits). The main exclusion criteria were therapy-related MDS, more than two courses of previous cytotoxic MDS therapy, previous allogeneic transplantation, severe concomitant illnesses, active infectious disease, impaired liver function (bilirubin > upper limit of normal; transaminases > 3 × upper limit of normal), and impaired renal function (creatinine clearance < 60 mL/min; serum creatinine > 1.5 × upper limit of normal).

Online Supplementary Table S1. Conditional cumulative incidence of cell recovery (%) and cumulative incidence of chimerism (%) in 45 MDS patients.

	Day +28	Day +56	Day +100
CCI of recovery neutrophils (%) (95% CI)	96 (85, 100)	98 (94, 100)	98 (94, 100)
CCI of recovery WBC (%) (95% CI)	96 (87, 100)	98 (94, 100)	98 (94, 100)
CCI of recovery platelets (%) (95% CI)	87 (76, 98)	91 (80, 100)	94 (87, 100)
Cumulative incidence of Complete donor type chimerism (%) (95% CI)	78 (65, 91)	93 (79, 100)	93 (79, 100)

CCI: conditional cumulative incidence; C.I.: confidence interval; WBC: white blood cell count.

Online Supplementary Table S2. Frequency of CTCAE grades III/IV changes of non-hematologic laboratory values between day -6 and day +28.

Laboratory parameter	CTCAE Grade III N (%)	IV N (%)	Total III/IV N (%)
Alanine aminotransferase	4 (9%)	2 (4%)	6 (13%)
Aspartate aminotransferase	2 (4%)	1 (2%)	3 (6%)
Gamma-glutamyl transferase	1 (2%)	1 (2%)	2 (4%)
Alkaline phosphatase	1 (2%)	0 (0%)	1 (2%)
Bilirubin	6 (13%)	0 (0%)	6 (13%)
Hyperglycemia	3 (7%)	0 (0%)	3 (7%)
Hypokalemia	2 (4%)	1 (2%)	3 (6%)
Hyponatremia	3 (7%)	1 (2%)	4 (9%)

CTCAE: Common Terminology Criteria for Adverse Events.

Online Supplementary Table S3. Two-year cumulative incidence of non-relapse mortality stratified by donor type, IPSS score and previous treatment of myelodysplastic syndrome. *P* values were calculated by Gray's test.

	Cumulative incidence of NRM (95% CI)	*P* value
HLA-identical sibling donor (n=15)	23% (1%, 45%)	
HLA-matched unrelated donor (n=30)	13% (1%, 25%)	0.6669
IPSS Intermediate 1 (n=20)	20% (3%, 37%)	
IPSS Intermediate 2 (n=14)	10% (0%, 28%)	
IPSS High (n=8)	25% (0%, 53%)	0.4036
Previous chemotherapy (n=8)	0% (0%, 0%)	
Untreated (n=35)	18% (5%, 32%)	0.2499

CI: confidence interval; IPSS: International Prognostic Scoring System; NRM: non-relapse mortality

Online Supplementary Table S4. Two-year cumulative incidence of relapse stratified by donor type, IPSS score and previous treatment of myelodysplastic syndrome. *P* values were calculated by Gray's test.

	Cumulative incidence of relapse (95% CI)	*P* value
HLA-identical sibling donor (n=15)	20% (0%, 40%)	
HLA-matched unrelated donor (n=30)	13% (1%, 25%)	0.5665
IPSS Intermediate 1 (n=20)	10% (0%, 23%)	
IPSS Intermediate 2 (n=14)	29% (5%, 52%)	
IPSS High (n=8)	13% (0%, 33%)	0.3512
Previous chemotherapy (n=8)	25% (0%, 53%)	
Untreated (n=35)	14% (3%, 26%)	0.4956

CI: confidence interval; IPSS: International Prognostic Scoring System.

Online Supplementary Table S5. Two-year Kaplan-Meier estimate of disease-free survival stratified by donor type, IPSS score and previous treatment of myelodysplastic syndrome. *P* values were calculated by log-rank test.

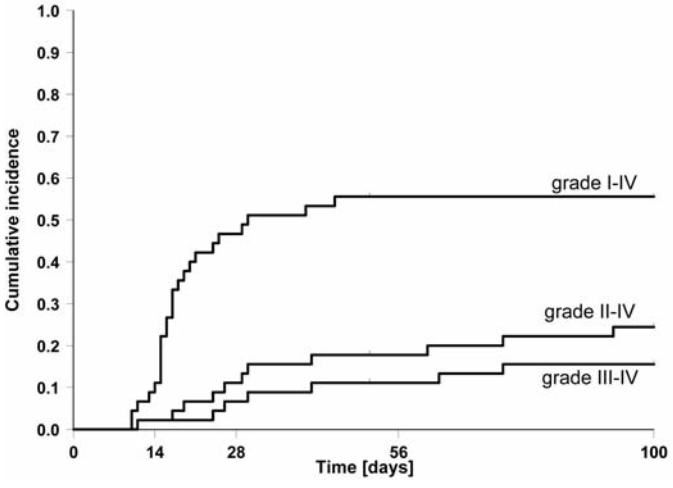
	Kaplan-Meier estimate of DFS (95% C.I.)	*P* value
HLA-identical sibling donor (n=15)	57% (31%, 84%)	
HLA-matched unrelated donor (n=30)	73% (58%, 89%)	0.4684
IPSS Intermediate 1 (n=20)	70% (50%, 90%)	
IPSS Intermediate 2 (n=14)	63% (37%, 88%)	
IPSS High (n=8)	63% (31%, 94%)	0.9009
Previous chemotherapy (n=8)	75% (47%, 100%)	
Untreated (n=35)	67% (51%, 84%)	0.7733

CI: confidence interval; DFS,: disease-free survival; IPSS: International Prognostic Scoring System.

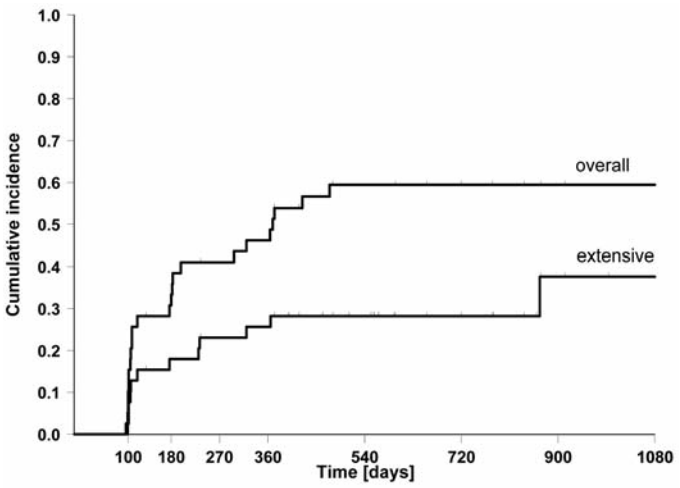
Online Supplementary Table S6. Two-year Kaplan-Meier estimate of overall survival stratified by donor type, IPSS score and previous treatment of myelodysplastic syndrome. *P* values were calculated by log-rank test.

	Kaplan-Meier estimate of OS (95% CI)	*P* value
HLA-identical sibling donor (n=15)	63% (37%, 89%)	
HLA-matched unrelated donor (n=30)	75% (59%, 91%)	0.5163
IPSS Intermediate 1 (n=20)	70% (50%, 90%)	
IPSS Intermediate 2 (n=14)	68% (42%, 93%)	
IPSS High (n=8)	75% (47%, 100%)	0.9356
Previous chemotherapy (n=8)	80% (49%, 100%)	
Untreated (n=35)	70% (53%, 86%)	0.3608

CI: confidence interval; IPSS: International Prognostic Scoring System; OS: overall survival.



Online Supplementary Figure S1. Cumulative incidences of acute graft-*versus*-host disease.



Online Supplementary Figure S2. Cumulative incidences of chronic graft-*versus*-host disease (overall and extensive only)