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Allogeneic transplantation after reduced conditioning in high risk patients is complicated by a high incidence of acute and chronic graft-versus-host disease

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Background and Objectives. We studied the toxicity and efficacy of reduced intensity conditioning followed by allogeneic stem cell transplantation in 50 patients over 50 years old or with relative contraindications against myeloablative regimens. Diagnoses were chronic myeloid leukemia (n=15), acute myeloid leukemia (n=9), myelodysplastic syndromes (n=9), lymphoma (n=11) and refractory solid tumors (n=6).

Design and Methods. Donors were identical siblings (n=25), non-identical family members (n=6) and unrelated volunteers (n=19). Peripheral blood stem cells (n=36) or bone marrow (n=14) were transplanted. The conditioning regimen consisted of fludarabine 180 mg/m^2, busulphan 8 mg/kg and rabbit antithymocyte globulin 40 mg/kg (Fresenius). Graft-versus-host disease (GVHD) prophylaxis was carried out with cyclosporin A (CSA) alone (n=17) or in combination with methotrexate (n=18) or mycophenolate mofetil (n=15).

Results. Neutrophil counts >0.5/nL and platelet counts > 20/nL were reached after 17 (range 0-66) and 19 days (range 0-111), respectively. Three graft failures occurred. Fever lasted for a median of 2 days (range 0-15). Six patients developed veno-occlusive disease of the liver. Acute GVHD grade II-IV occurred in 47% of the patients and chronic GVHD in 46%. The 1-year overall survival probability was 44% (95% CI: 30-58%). GVHD-related complications were a major cause of the probability of 1-year non-relapse mortality of 31% (95% CI: 16-46%).

Interpretation and Conclusions. In conclusion, the regimen itself can be carried out safely in patients with relative contraindications against myeloablative conditioning. However, GVHD causes significant non-relapse mortality in high risk patients.
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Key words: allogeneic stem cell transplantation, reduced intensity conditioning.

In 1998, Slavin *et al.* published data on 26 patients who received hematopoietic stem cell transplants (SCT) after dose-reduced conditioning treatment.[1] They observed the development of a stable chimerism in all patients without early procedure-related mortality and successful eradication of malignant and genetically abnormal hematopoietic cells in the host. Severe graft-versus-host disease (GVHD) after early discontinuation of cyclosporin (CSA) was the only major complication. However, the median age in this group of patients was low (32 years, range 1-56 years) and four patients did not suffer from malignant diseases. We adopted the protocol for patients with relative contraindications against the use of a myeloablative regimen because of age, precedent autologous transplantation or significant comorbidity. Thereby, we investigated whether the excellent tolerability could be reproduced in a larger group of high risk patients. This report focuses on toxicity, GVHD and clinical outcome.

Design and Methods

Patients

Between March 1998 and September 2000, 50 patients were transplanted at the Charité, Campus Virchow Klinikum, Berlin and the Universitäts-Krankenhaus Eppendorf, Hamburg. Their median age was 50 years (range 20-64 years). Twenty-six patients were male and 24 female. Diagnoses were chronic myeloid leukemia (n=15), acute myeloid leukemia (n=9), myelodysplastic syndromes (n=9), malignant lymphoma (n=11), refractory germ cell cancer (n=5) and breast cancer (n=1). All patients had at least one relative contraindication against a conventional myeloablative conditioning regimen. Twenty patients (40%) had received prior high-dose therapy and autologous stem cell transplantation. Infections were a contraindication in 19 patients (38%): a history of recent invasive fungal infection (n=9), tuberculosis (n=2), toxoplasmosis (n=1), neutropenic fever at the beginning of conditioning therapy (n=3), chronic osteomyelitis (n=1), post-stenotic pneumonia (n=2) and chronic hepatitis B (n=1). Twenty-two patients (44%) had medical contraindications mostly related to cardiovascular diseases or to extensive cytotoxic pretreatment.

Donors

Donors were 25 HLA-identical siblings, 6 non-HLA-identical family members, 16 matched unrelated donors and 3 unrelated donors with one minor mismatch. Twenty-five CMV-seronegative patients had 15 seronegative and 10 seropositive donors. Among 25 CMV-seropositive patients, 12 had seropositive donors and 13 had seronegative donors.

Preparative regimen and stem cell products

The conditioning regimen consisted of fludarabine (180 mg/m^2), busulphan (8 mg/kg) and rabbit antithymocyte globulin (ATG) (40 mg/kg, Fresenius Inc.) as published by Slavin in 1998. Granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSC) were transplanted in 36 patients. The median count of CD34$^+$ cells in PBSC-products was 5.2×10^6 CD34$^+$ cells/kg (range 2.2-12.6×10^6). Fourteen patients with unrelated donors received bone marrow (BM) with a median count of mononuclear cells (MNC) of 1.2×10^8 MNC /kg (range 0.7-4.4×10^8).

Supportive care and GVHD prophylaxis

Supportive care was carried out in a center-specific manner. In brief, for infection prophylaxis patients received oral quinolones and amphotericin B suspension. Empiric antibiotic treatment for neutropenic fever consisted of broad-spectrum antibiotics. Intravenous amphotericin B was added for refractory neutropenic fever or if fungal infection was suspected or documented. In order to control allergic reactions to ATG infusion, patients received prophylactic intravenous medication consisting of pethidine 100 mg, ranitidine 50 mg, dimethyndenmaleate 4 mg and prednisolone 100 mg. GVHD prophylaxis was carried out with CSA alone (n=17), CSA plus short course methotrexate (MTX) (n=18) or CSA plus mycophenolate mofetil (MMF) (n=15). Red blood cell transfusions were given to maintain a hemoglobin level of 8 g/dL and single donor platelet concentrates were transfused to keep a platelet count of 10/nL in afebrile patients, and of 20/nL in febrile patients.

Chimerism studies

Donor chimerism in the peripheral blood was analyzed every week during the first three months using a multiplex-polymerase chain reaction (PCR).[2]

Definitions

Toxicity was graded according to the *Common Toxicity Criteria*, applying the special items for bone marrow transplantation. A diagnosis of veno-occlusive disease (VOD) of the liver was made according to the Baltimore criteria.[3] GVHD was graded according to common clinical criteria.[4] GVHD persisting beyond day +100 or *de novo* GVHD occurring after day +100 was classified as chronic GVHD. We defined non-relapse mortality as death not related to progression of the malignant disease.

Statistical analysis

All data were computed with SPSS statistical software (SPSS Inc., Chicago, Illinois, USA). Comparisons of groups regarding mucositis and GVHD were performed with the χ^2 and Fisher's exact test. Multivariate analysis of risk factors for GVHD was carried out with a binomial logistic regression model. Kaplan-Meier product-limit estimates were used to analyze overall survival, treatment-related death and the cumulative incidence of GVHD. For the analysis of treatment-related death and of the incidence of GVHD, surviving patients and patients who died from relapse were censored at the day of last follow-up.

Results

Cytopenia, transfusion requirements

Forty-seven patients were evaluable for engraftment, while three patients died before day +14. Neutrophil counts >0.5/nL were reached after a

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median of 17 days (range 0-66) and platelet counts >20/nL after 19 days (range 0-111). Three patients (6%) did not experience neutropenia <0.5/nL at all, while 14 patients (30%) had neutrophils <0.5/nL lasting for ≥20 days. Seven patients (15%) did not show thrombocytopenia <20/nL, while 15 patients (32%) had platelets <20/nL lasting for ≥20 days. Until day +30, a median number of 9.5 red blood cell concentrates (range 0-24) and 6 single donor platelet apheresis concentrates (range 0-30) were given. One patient did not require red blood cell transfusions and 9 patients (18%) did not need platelet support.

Chimerism and engraftment failures

The conditioning regimen enabled fast conversion to complete overall donor chimerism as shown in Figure 1. Primary graft failure occurred in one patient (UPN 800) with chronic myeloid leukemia, who received bone marrow from a matched unrelated donor. After reconditioning and intensified immunosuppression a second transplant from the same donor engrafted successfully. We observed two secondary graft failures (UPN 848 and 556). Both patients engrafted and reached full donor chimerism within 4 weeks. However, CMV-reactivation and treatment with ganciclovir might have contributed to secondary graft failure and fatal infectious complications.

Infections

Between day 0 and day +30, patients had a median of 2 days (range 0-15) with fever of more than 38°C. Twelve patients (24%) did not develop fever at all. There was one fatal infection during the first 30 days in a patient with refractory acute myeloid leukemia. Nine patients died due to infectious complications at a median of 146 days (range 11-252) after transplantation. Causative micro-organisms were: CMV (n=1), *Toxoplasma gondii* (n=1), aspergillus species (n=2) and unknown organisms (n=5). CMV-reactivation as detected by antigenemia and/or PCR was observed in 16 patients (32%). Two of these patients presented with CMV-hepatitis and one with CMV-pneumonia.

Acute side-effects of cytostatic treatment

Chemotherapy induced mild, short-lasting nausea and vomiting. One patient experienced grade III vomiting. Application of ATG caused fever and rigors together with tachycardia and tachypnea, which required additional intravenous medication and therefore was classified as grade III allergic toxicity in 18 patients (36%).

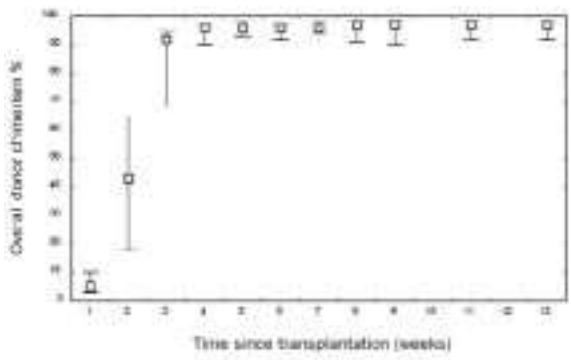

Figure 1. Development of overall donor chimerism: median value (boxes) and 25-75% quartile ranges (whiskers) are indicated.

Mucositis, liver and urogenital toxicity

The severity of mucositis was associated significantly with the use of MTX as GVHD-prophylaxis. Twelve out of 19 patients (63%) with MTX as GVHD prophylaxis, compared to 4 out of 32 patients (12.5%) without MTX, experienced grade III/IV mucositis (Fisher's exact test, $p<0.001$). Regarding the criteria for veno-occlusive disease (VOD), an increase of bilirubin ≥2 mg/dL was documented in 32/50 patients within the first 30 days. Weight gain of >5% of body weight was seen in 13 patients, hepatomegaly in 10 patients and liver tenderness or pain in 9 patients. A diagnosis of VOD according to the Baltimore criteria was made in 6 patients (moderate, n=4; severe, n=2). During the first 30 days after transplantation 4 patients had an increase in creatinine ≥2 mg/dL. This was related to major ABO incompatible bone marrow transfusion in one patient and to infection and antibiotic treatment in three patients. Mild to moderate hemorrhagic cystitis occurred in 5 patients with grade II/III dysuria and grade II hematuria.

Acute and chronic GVHD

Acute GVHD grade II–IV was observed in 22 of 47 evaluable patients (47%) and acute GVHD grade III-IV in 5 patients (11%). The median onset of acute GVHD was on day +24 (range 12-94) after transplantation. Patients frequently showed clinical features of acute and chronic GVHD simultaneously. Limited chronic GVHD was seen in 10 of 41 evaluable patients (24%), while 9 patients (22%) suffered from extensive GVHD. Chronic GVHD occurred almost always (16/19) in patients

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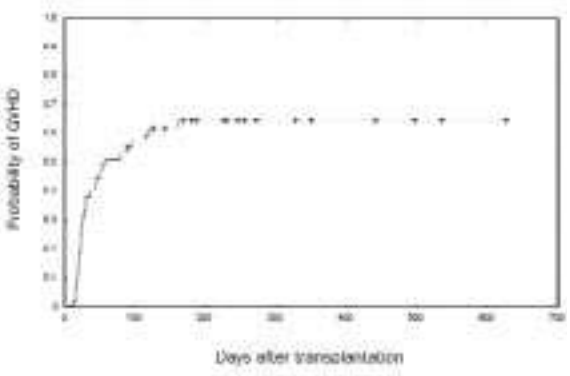

Figure 2. Probability of acute and *de novo* chronic GVHD (all grades).

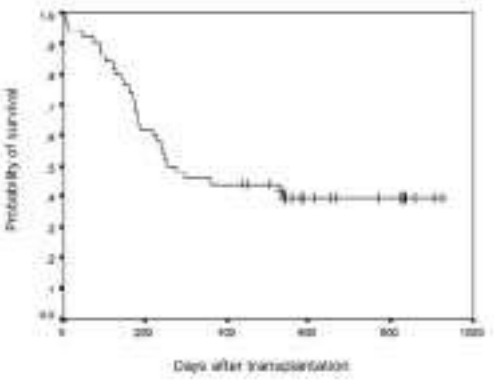

Figure 3. Probability of overall survival.

who had suffered already from acute GVHD. Onset and cumulative probability of acute and chronic GVHD are shown in Figure 2. The addition of short course MTX or MMF to CSA as GVHD-prophylaxis resulted in a significant reduction in acute GVHD grade II-IV (p=0.012) and GVHD (p=0.047) (Table 1). In a multivariate analysis of the impact of the combined prophylaxis compared to CSA alone, including match status (HLA-identical siblings vs. non-identical donors) and graft type (BM vs PBSC), only the type of GVHD prophylaxis was associated with the incidence of GVHD. For acute GVHD grade II-IV the relative risk of CSA alone compared to combined prophylaxis with MTX and MMF was 8.2 (95% CI: 1.9-35.7, p=0.005) and for chronic GVHD the relative risk of CSA alone was 5.4 (95% CI 1.2-25.1, p=0.029).

Response

Twelve out of 15 patients with chronic myeloid leukemia achieved molecular remissions, demonstrated by nested PCR for the bcr/abl hybrid mRNA. The two patients with refractory acute myeloid leukemia had no response. Among 9 patients with myelodysplastic syndrome, complete remissions were achieved in 4 patients. Four out of 11 patients with malignant lymphoma transplanted in refractory or relapsed disease achieved a complete remission. Out of 6 patients with advanced stages of germ cell cancer (n=5) or breast cancer (n=1) only one patient experienced a partial remission.

Mortality and causes of death

After a median observation period of 21 months (range 14–31), 20 patients are alive and 30 patients have died. Causes of death were disease progression in 16 patients and treatment-related complications in 14 patients. The overall survival at 1 year was 44% (95% CI: 30-58%). The probability of overall survival at 2 years was 39% (95% CI: 25-53%) (Figure 3). The probability of non-relapse mortality was 11% (95% CI: 2-20%) at day +100, 31% (95% CI: 17-45%) at 1 year and 35% (95% CI: 19-51%) at 2 years after transplantation (Figure 4). Treatment-related death occurred a median of 171 days after transplantation (range 9-537) and GVHD was regarded as the underlying cause of death in 11 patients (78.5%). Table 2 shows the causes of death in detail.

Discussion

During the last three years several conditioning regimens of reduced dose-intensity in conjunction with allogeneic stem cell transplantation have been studied.[1,5,6] Development of complete donor chimerism and the induction of a graft-versus-malignancy effect were shown in patients with

Table 1. Numbers of patients with acute and chronic GVHD.

	n=	*aGVHD grade 0-I*	*aGVHD grade II-IV*	
CSA-mono	16	4	12	p=0.012
CSA+MTX/MMF	17/14	11/10	6/4	
	n=	*no cGVHD*	*cGVHD*	
CSA-mono	15	5	10	p=0.047
CSA+MTX/MMF	15/11	10/7	5/4	

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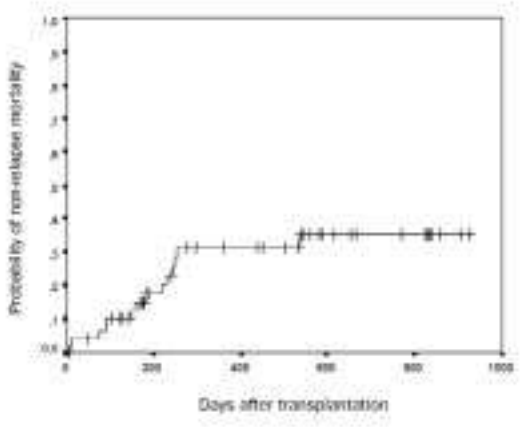

Figure 4. Probability of non-relapse mortality.

Table 2. Causes of non-relapse mortality.

UPN	*Primary cause*	*Secondary cause*	*Final event*	*Day*
10014	HIT	–	myocardial infarction	9
727	VOD	–	aspergillosis	11
556	GVHD	CMV-reactivation, secondary graft-failure toxoplasmosis	toxoplasmosis	90
10017	GVHD	–	aspergillosis	92
848	VOD	CMV-reactivation, secondary graft-failure	sepsis	106
876	GvHD	CMV-hepatitis	sepsis	146
698	GvHD	ITP, toxoplasmosis	intracranial bleeding	159
10002	GvHD	COPD	CMV-pneumonia	183
10006	GvHD	–	liver-failure	218
728	GvHD	COPD, ITP	lung-bleeding	229
806	GvHD	MAHA	sepsis	241
792	GvHD	–	sepsis	247
775	GvHD	restrictive pulmonary disease	pneumonia	252
724	GvHD	ITP	intracranial bleeding	537

HIT=heparin-induced thrombocytopenia; VOD=veno-occlusive disease of the liver; ITP=idiopathic thrombocytopenic purpura; COPD=chronic obstructive pulmonary disease; MAHA=micro-angiopathic hemolytic anemia.

various hematologic malignancies.[7,8,9] Preliminary results suggest that the toxicity and morbidity of reduced dose-intensity conditioning in the context of allogeneic stem cell transplantation is lower than that of classical intensive conditioning regimens. There is hope that these new regimens will make allogeneic transplantation applicable to older patients and to patients with relative contraindications against myeloablative treatment. Our aim was to reproduce the favorable data of Slavin *et al.* which were obtained in a group of 26 patients with a median age of 32 years suffering from malignant and non-malignant diseases.[1] We, therefore, studied engraftment and toxicity of allogeneic transplantation after conditioning with fludarabine, busulphan and ATG in patients with a median age of 50 years (range 20-64) and relative contraindications to myeloablative conditioning regimens. We observed no primary graft failure in 24 patients who received grafts from HLA-identical siblings and one primary graft failure in 23 patients with non-identical related donors or unrelated donors. This is in accordance with data from Slavin and Nagler who observed a 100% rate of engraftment in 54 HLA-identical sibling and 16 matched unrelated transplantations and indicates that the regimen provides intensive immunosuppression.[10,11]

The introduction of dose-reduced conditioning nourished the hope that patients would experience less GVHD after reduced intensity conditioning.[12, 13] This was based on the hypothesis that less tissue injury would occur due to lower doses of cytotoxic agents and that the induction of mixed chimerism could reduce the incidence of GVHD.[14, 15] Regarding our data, we found acute GVHD grade II-IV in 47% and chronic GVHD in 46% of our patients. Allogeneic transplantation after myeloablative regimens in high-risk patients led to rates of acute GVHD grade II-IV between 55 and 85%.[16,17, 18,19] Regarding non-myeloablative allogeneic transplants in high-risk patients with HLA-identical related donors, the Seattle team reported rates of 47 % for acute GVHD grade II-IV and of 74 % for chronic GVHD.[6] Our data are within this range. Thus, today no empirical evidence exists that reduced dose-intensity conditioning is associated with a lower incidence and severity of GVHD.

Despite our patients' high risk of infectious complications at study entry, fatal infections during the first 30 days after transplantation were rare in our trial (2%) compared to the early infectious mortality rate of between 10-20 % after dose intensive conditioning regimens.[16,20] However, regarding the whole follow-up period fatal infections occurred in 9 patients (18%) who were free from progression of their malignant disease. Apart from one patient, all of them suffered from GVHD. This comparatively high incidence of fatal infections during the first year after transplantation leads to

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the suggestion that the immune system is heavily compromised during the first year even after reduced intensity conditioning. First of all, this might be a result of the high incidence and severity of acute and chronic GVHD. Although our day +100 mortality was low, there was a 31% probability of non-relapse mortality at 1 year and a 35% one at 2 years. Again, our observations correspond with data obtained in older patients and patients who were transplanted after failure of a first autologous transplant.[16,17,19,20,21] Childs *et al.* studied 84 consecutive patients after non-myeloablative allogeneic stem cell transplantation.[22] They found an overall survival of 34 % with a non-relapse mortality of 36 % in patients ≥49 years. Similar to our observations, non-relapse mortality was associated with GVHD. A non-relapse mortality of 6.7 % after a median follow-up of 417 days was observed by McSweeney *et al.* in older patients with hematologic malignancies after conditioning with 200 cGy total body irradiation and CSA/MMF after HCT. Although the incidence and severity of GVHD were comparable to those in our patients, GVHD-related mortality was much lower. This advantage might be explained partly by the transplantation strategy. However, the two groups of patients differ in many aspects.

Our data suggest that a GVHD-prophylaxis consisting of cyclosporin A combined with short course MTX or MMF lowers the incidence of acute and chronic GVHD compared to that following cyclosporin A alone, as published by Slavin *et al.*[1] However, the number of patients included in this trial was too small to analyze outcome variables such as disease-specific response rates and overall survival in relation to the applied GVHD prophylaxis. Thus, it is not known whether the reduction of GVHD translates into a survival benefit. In conclusion, the combination of fludarabine, busulphan and ATG proved to be a conditioning regimen with little drug toxicity even in high-risk patients and allows for stable donor cell engraftment. However, the predominant problem was the occurrence of acute and chronic GVHD which caused significant non-relapse mortality during the first year after transplantation. The focus of future investigations should, therefore, be the prevention of GVHD and the search for more effective measures against it without abrogating a graft-versus-malignancy effect. In this context, stimulation of tumor-specific T-cell activity instead of the induction of global alloreactivity would be desirable.

Contributions and Acknowledgments

All authors were involved in the collection and interpretation of the data and in the revision of the manuscript. All have given their final approval. WS designed the study. Care and clinical assessment of the patients was done by NK, TZ, JS, TKH, OR and ARZ. Donor chimerism was analyzed by CT, MB and GE. Data management and statistical analyses were carried out by JS, AK and MD. JS wrote the manuscript. We thank the staff of the bone marrow transplantation units for the excellent care they provided and U. Löwel, M. Hartwig and P. Grassmel for excellent technical assistance in chimerism analyses.

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Disclosures

Conflict of interest: we received financial support from Amgen, Germany and Fresenius HemoCare, Germany.

Redundant publications: yes, < 50%.

References

1. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998; 91:756-63.
2. Thiede C, Florek M, Bornhäuser M, Ritter M, Mohr B, Brendel C, et al. Rapid quantification of mixed chimerism using multiplex amplification of short tandem repeat markers and fluorescence detection. Bone Marrow Transplant 1999; 23:1055-60.
3. Jones RJ, Lee KS, Beschorner WE, Vogel VG, Grochow LB, Braine HG, et al. Venoocclusive disease of the liver following bone marrow transplantation. Transplantation 1987; 44:778-83.
4. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995; 15:825-8.
5. Carella AM, Cavaliere M, Lerma E, Ferrara R, Tedeschi L, Romanelli A, et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral-blood hematopoietic stem-cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol 2000; 18: 3918-24.
6. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood 2001; 97:3390-400.
7. Nagler A, Slavin S, Varadi G, Naparstek E, Samuel S, Or

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R. Allogeneic peripheral blood stem cell transplantation using a fludarabine-based low intensity conditioning regimen for malignant lymphoma. Bone Marrow Transplant 2000; 25:1021-8.
8. Peggs KS, Williams CD, Chopra R, et al. Non-myeloablative allogeneic transplantation with adjuvant dose escalated donor lymphocyte infusions for multiple myeloma. Blood 2000; 96 Suppl 1:781[abstract].
9. Ehninger G, Kiehl M, Siegert W, et al. Dose-reduced conditioning for allografting in 45 patients with CML: a retrospective analysis. Blood 2000; 96 Suppl 1: 783 [abstract].
10. Slavin S, Nagler A, Naparstek B, et al. Well-tolerated nonmyeloablative fludarabine-based protocols for the treatment of malignant and non-malignant disorders with allogeneic bone marrow or blood stem cell transplantation. Blood 1999; 94 Suppl 1:351[abstract].
11. Nagler A, Aker M, Or R, Naparstek E, Varadi G, Brautbar C, et al. Low-intensity conditioning is sufficient to ensure engraftment in matched unrelated bone marrow transplantation. Exp Hematol 2001; 29:362-70.
12. Barrett J, Childs R. Non-myeloablative stem cell transplants. Br J Haematol 2000; 111:6-17.
13. Champlin R, Khouri I, Shimoni A, Gajewski J, Kornblau S, Molldrem J, et al. Harnessing graft-versus-malignancy: non-myeloablative preparative regimens for allogeneic haematopoietic transplantation, an evolving strategy for adoptive immunotherapy. Br J Haematol 2000; 111:18-29.
14. Storb R, Yu C, Wagner JL, Deeg HJ, Nash RA, Kiem HP, et al. Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. Blood 1997; 89:3048-54.
15. Hill RS, Petersen FB, Storb R, Appelbaum FR, Doney K, Dahlberg S, et al. Mixed hematologic chimerism after allogeneic marrow transplantation for severe aplastic anemia is associated with a higher risk of graft rejection and a lessened incidence of acute graft-versus-host disease. Blood 1986; 67:811-6.
16. Tsai T, Goodman S, Saez R, Schiller G, Adkins D, Callander N, et al. Allogeneic bone marrow transplantation in patients who relapse after autologous transplantation. Bone Marrow Transplant 1997; 20:859-63.
17. Ringden O, Labopin M, Frassoni F, Sanz G, Demeocq F, Prentice H, et al. Allogeneic bone marrow transplant or second autograft in patients with acute leukemia who relapse after an autograft. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 1999; 24:389-96.
18. Du W, Dansey R, Abella EM, Baynes R, Peters WP, Klein J, et al. Successful allogeneic bone marrow transplantation in selected patients over 50 years of age: a single institution's experience. Bone Marrow Transplant 1998; 21:1043-7.
19. Deeg HJ, Shulman HM, Anderson JE, Bryant EM, Gooley TA, Slattery JT, et al. Allogeneic and syngeneic marrow transplantation for myelodysplastic syndrome in patients 55 to 66 years of age. Blood 2000; 95:1188-94.
20. Klingemann HG, Storb R, Fefer A, Deeg HJ, Appelbaum FR, Buckner CD, et al. Bone marrow transplantation in patients aged 45 years and older. Blood 1986; 67:770-6.
21. Radich JP, Gooley T, Sanders JE, Anasetti C, Chauncey T, Appelbaum FR. Second allogeneic transplantation after failure of first autologous transplantation. Biol Blood Marrow Transplant 2000; 6:272-9.
22. Childs RW, Bahceci E, Eniafe R. Older patient age remains a risk factor for transplant related mortality following nonmyeloablative allogeneic stem cell transplantation. Blood 2000; 96 Suppl 1:520 [abstract].

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Jordi Sierra, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Dr. Sierra and the Editors. Manuscript received November 16, 2001; accepted January 14, 2002.

What is already known on this topic

Hematopoietic transplantation after reduced intensity conditioning regimen is a feasible option in patients not candidates for conventional transplants.

What this study adds

This study confirms previous experiences on this subject. Interestingly, this approach may be safely performed using unrelated donors and marrow as stem cell source.

Potential implications for clinical practice

Graft-versus-host disease prophylaxis should include the combination of two immunosuppresive drugs. This approach may be extended to transplants from unrelated donors.

Jordi Sierra, Deputy Editor