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Allogeneic transplantation of G-CSF mobilized peripheral blood stem cells from unrelated donors: a retrospective analysis.

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ABSTRACT

Background and Objectives. **Allogeneic peripheral blood stem cell transplantation (PBSCT) from matched siblings has lead to clinical results comparable to those of standard bone marrow transplantation (BMT). We report the outcome of 79 patients transplanted with PBSC from unrelated donors.**

Design and Methods. **In 61 cases PBSC were used for primary transplantation whereas 18 patients were treated for relapse or graft-failure. In 35 patients receiving primary transplants, T-cell depletion (TCD) using CD34 positive selection of PBSC with or without additional T-cell depletion had been performed to reduce the risk of graft-versus-host-disease (GvHD).**

Results. **The rate of primary graft-failure was higher (20%) in the TCD group than in that receiving unmanipulated grafts (UM) (5%, *p*=0.007). Patients with standard risk (n=34) receiving first transplants had a significantly better overall (60.4% vs. 24%, *p*=0.02) and disease-free survival (57.2% vs. 22.3%, *p*=0.006) compared to a high risk group of patients (n=21). There were no differences in the speed of neutrophil and platelet engraftment between TCD and UM transplants. As expected, the cumulative risk for acute GvHD grade II.-IV was significantly higher in the patients who had received UM grafts (71.8% vs. 38.1%, *p*=0.005). Although a trend towards a better survival rate was observed after TCD transplantation (52.2%) compared to the UM group (38.1%), this difference was not statistically significant. The probability of relapse was significantly higher in patients after UM transplants (38.8% vs. 8.4%). This apparent paradox is explained by the higher number of high-risk patients in this group (*p*=0.03). Multivariable analysis of disease-free survival revealed risk category (*p*=0.02) and use of ATG (*p*=0.03) to be of significant impact. All patients (n=6) with non-malignant diseases are alive with full donor chimerism.**

Interpretation and Conclusions**. These data show that PBSC from unrelated donors can be transplanted either unmanipulated or CD34 selected. Prospective studies comparing BMT with PBSCT from unrelated donors are needed in defined disease categories.**

Key words: allogeneic transplantation, peripheral blood stem cells, unrelated donor

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There are several reports on the outcome of patients with hematologic malignancies after allogeneic transplantation of peripheral blood stem cells (PBSC) from HLA-matched sibling donors.[1-3] In preliminary studies the outcomes of patients after allogeneic PBSC transplantation and bone marrow transplantation (BMT) have been compared. These retrospective investigations suppose a faster hematopoietic engraftment with no differences in the rate of acute graft-versus-host disease (GvHD) and early mortality.[4,5] In contrast, the rate of chronic GvHD associated with PBSC transplantation was reported to be significantly higher.[6] Although there are some hints on a more pronounced antileukemic effect of PBSC,[7] no significant differences in the overall- and leukemia-free survival of standard risk patients have been found so far.[8] Nevertheless, there is some evidence that there might be an advantage of PBSC compared to BM in patients with unfavorable diseases.[9]

The comparable rate of acute GvHD and the improved speed of engraftment have prompted several transplant physicians to explore the feasibility of allogeneic PBSC from unrelated donors especially in high-risk patients with progressed leukemia. A further argument had been the improved survival rate of patients after unrelated BMT receiving higher-doses of CD34 positive cells.[11] CD34 positive selection combined with others methods of T-cell depletion (TCD) has been used by different groups to minimize the risk of acute GvHD known to occur from historical reports on BMT in the matched unrelated setting.[12-14] The increased rate of graft failure was supposed to be overcome by the higher numbers of CD34 positive progenitors transfused.

Although there is still a lot of debate on its safety, granulocyte colony-stimulating factor (G-CSF) has

been approved for the use in healthy donors in Europe recently. Since then, the *German Bone Marrow Donor Center* (DKMS) has faced an increasing number of requests for G-CSF mobilized PBSC either for primary transplantation or treatment of relapse. We performed a retrospective analysis on the outcome of 79 patients receiving grafts from the first donors willing to donate G-CSF mobilized PBSC. Special emphasis was put on the speed of engraftment, the rate of acute GvHD and the early mortality associated with PBSC from unrelated donors. Patients receiving first transplants with unmanipulated PBSC (UM PBSC) were compared to those transplanted with T-cell depleted PBSC (TCD PBSC).

Design and Methods

Patients

All patients had given informed consent before being included in the programs of the different transplant centers. In 49 cases CD34 positive selection with or without further T-cell depletion was performed. Thirty patients received unmanipulated PBSC. The patients' characteristics and disease status are summarized in Table 1. Fourteen patients were below the age of 20 with a higher percentage of children in the TCD group (p=0.07). The median observation time in the whole group is 12 months (range, 6-34). In 61 patients PBSC were the primary transplant whereas 18 patients received PBSC as a second donation from the same person for relapsing disease or graft-failure after transplantation. Most patients had acute or chronic myelogenous leukemia. Patients with first or subsequent complete remission (CR) of AML and ALL as well as patients with CML in 1st chronic phase or paroxysmal nocturnal hemoglobinuria (PNH) were categorized as standard-risk patients. The rest of the patients (MDS, AML/ALL not in remission, CML accelerated or blastic phase) belong to the high-risk category. All patients with severe aplastic anemia (SAA, n=5), PNH (n=2) and inborn errors (n=2) received TCD PBSC. SAA and inborn errors were grouped as non-malignant diseases. The TCD group contained fewer high-risk patients (n=8) than the UM group (n=13).

Donor/recipient cytomegalovirus (CMV) status and HLA matching

Table 2 provides the details concerning CMV status of donor and recipient. In 14 cases recipient and donor had been positive for anti-CMV IgG whereas in 31 pairs both had been negative. In most cases (n=34) either recipient (n=18) or donor (n=16) had been CMV positive prior to transplantation. HLA matching was performed by serologic typing for HLA-A, B, and C, whereas high-resolution typing was performed for DRB1, DQB1 and DRB3.[15] With this typing strategy 59 donor/recipient pairs could be matched completely. There were 10 pairs with a serologic HLA-C mismatch. In 10 patients class II micromismatches were accepted (4 DRB1/DQB1, 5 DQB1 and 1 DRB3/DQB1 micromismatch). There were no significant differences in HLA-match grades between the UM and the TCD group.

Table 1. Patient characteristics.

	All	*TCD*	*UM*	*p (TCD vs. UM)*
No. of patients	79	49	30	
Age, years, median (range)	35 (4-58)	36 (4-58)	34 (8-55)	
Age groups				
1 (0-10)	7	6	1	1-2: 0.07
2 (11-20)	7	6	1	
3 (21-30)	18	7	11	3-6: 0.07
4 (31-40)	20	11	9	
5 (41-50)	21	15	6	
6 (51-60)	6	4	2	
Recipient sex F/M	27/52	15/34	12/18	
Sex mismatched/matched	23/56	17/ 32	8/22	
Diagnoses				
Acute myeloid leukemia	28 (35%)	14 (29%)	14 (47%)	0.64
CR1	7	5	2	0.7
CR2	8	4	4	0.47
CR3	1	/	1	0.38
PR	6	2	4	0.19
1st relapse	3	2	1	1.0
≥2nd relapse	3	1	2	
Acute lymphoid leukemia	10 (13%)	6 (12%)	4 (13%)	1.0
CR1	2	2	/	0.52
CR2	2	1	1	1.0
CR3	1	1	/	1.0
PR	2	1	1	1.0
1st relapse	1	/	1	0.38
≥2nd relapse	2	1	1	1.0
Chronic myeloid leukemia	25 (31%)	17 (38%)	8 (27%)	0.62
cp1	16	12	4	0.39
cp2	3	3	/	0.28
accelerated phase	5	2	3	0.36
blast crisis	1	/	1	0.38
Myelodysplastic syndrome	5 (6%)	2 (4%)	3 (10%)	0.36
Severe aplastic anemia	4 (6%)	4 (10%)	/	0.15
Non Hodgkin's lymphoma	3	2	1	1.0
PNH	2	2	/	0.52
Wiskott-Aldrich syndrome	1	1	/	1.0
x-ALD	1	1	/	1.0
High-risk pts. receiving first tx.	*21*	*8*	*13*	*0.03*
Reason for transplantation				
Primary PBSC	61 (77%)	40 (84%)	21 (70%)	0.17
For relapse	13 (15%)	6 (12%)	7 (20%)	0.36
For graft failure	5 (8%)	2 (4%)	3 (10%)	0.36

Abbreviations: CR = complete remission; PR = partial remission; cp = chronic phase; UM = unmanipulated; TCD-T cell depleted.

Table 2. CMV status/HLA matching.

	All	*TCD*	*UM*	*p*
HLA typing				
HLA identical	59 (75%)	36 (73%)	23 (77%)	0.8
Mismatch	20 (25%)	13 (26%)	7 (23%)	
HLA C	10	7	3	
Micromismatch				
DRB1	4	4		
DQB1	6	2	4	
DRB3	1	1		
Cytomegalovirus serology				
Recipient pos/Donor pos	14	9	5	
Recipient neg/Donor neg	31	21	10	0.48
Recipient pos/Donor neg	18	10	8	
Recipient neg/Donor pos	16	9	7	

Abbreviations: CR = complete remission; PR = partial remission; cp = chronic phase; UM = unmanipulated; TCD-T cell depleted.

PBSC mobilization and T-cell depletion

Mobilization of PBSC was performed using 7.5 µg/kg lenograstim for 5 days and two subsequent aphereses on days 5 and 6 of the stimulation period. The mobilization protocol was approved by the ethical board of the University Hospital in Dresden. In 38 cases CD34 positive selection of PBSC was performed using an immunomagnetic device (CliniMACS®, Miltenyi Biotec, Bergisch Gladbach, Germany) according to the manufacturer's instructions. Briefly, PBSC were washed once to reduce platelet contamination. The washed cells were incubated with QBEND-10 antibody (mouse antihuman CD34) for 30 minutes at room temperature. Two centrifugation steps followed to reduce unbound antibody. The labeled cells were loaded onto the CliniMACS® column and a semiautomated separation process was started. Marked cells were bound in the column and flushed out with buffer after removing the column from the magnetic field. The negative fraction was recovered and stored as was the CD34 positive fraction.

In 11 cases an immunoaffinity column (Ceprate SC®, CellPro) was used for CD34 purification as described elsewhere.[16] This step was followed by further depletion of CD 3 positive cells by magnetic activated cell sorting (MACS, Miltenyi Biotec, Bergisch Gladbach, Germany). Purity and content of CD3 positive T-cells of each graft were measured by flow cytometric analysis.

Preparative regimen, GvHD prophylaxis and supportive care

All regimens used for primary transplants (n=55) are summarized in Table 3. The percentage of patients receiving radiation-based conditioning therapies was 40% in both groups. Most non-TBI (total body irradiation) containing regimens consisted of busulfan and cyclophosphamide. Anti-thymocyte globulin (ATG) was used in 40 patients with no differences between the two groups. GvHD prophylaxis was performed with conventional cyclosporin A (CsA) based protocols in most patients. Significantly more patients in the TCD group received either CsA only (p=0.002) or no immunosuppressive treatment at all (p=0.002). Methotrexate was used more often in the UM group either combined with CsA or with steroids. The patient without GvHD prophylaxis in the UM PBSC group was treated for relapsing disease. Most patients (n=47) received G-CSF to support neutrophil engraftment post-transplantation with no differences between the two groups analyzed. All centers tested for cytomegalovirus (CMV) pp65 antigen by immunofluorescence once a week after engraftment to detect viral reactivation. Organ involvement (pneumonia, enteritis, hepatitis) was classified as CMV disease.

Statistical analysis

Acute and chronic GvHD were evaluated and graded according to standard criteria.[17,18] All analyses were performed after a median observation time of 12 months (range 5-34). Fisher's exact test and the Mann Whitney-U test were used to compare quantitative parameters and median values of the UM and the TCD group, respectively. Cox regression analysis was used to determine the effect of various variables on the end-point disease-free survival in the 55 patients receiving first transplants, since we felt second transplants should not be included in this analysis. All 79 patients were included in a multivariable analyis for the end-points acute and chronic GvHD and hematopoietic recovery. The probabilities of overall and event-free survivals were calculated according to the Kaplan-Meier method and differences in outcome were compared using the Mantel-Haenszel test.[19] A minimum of 100 days follow-up was requested for the observation of chronic GvHD.

Table 3. Conditioning and GvHD prophylaxis.

	All	*TCD*	*UM*	*p*
No. of patients	55	35	20	
Conditioning				
Pat. with TBI	22 (39%)	14 (39%)	8 (40%)	0.51
TBI/ATG/VP16	1	1	/	1.0
TBI/ATG/Thio/Melph	1	1	/	1.0
TBI/Cy	8	1	7	0.004
TBI/Cy/ATG	10	9	1	0.08
TBI/Cy/ATG/VP16	4	2	2	0.63
TBI/Cy/ATG/Thio	5	5	/	0.15
TBI/Cy/VP16	1	1	/	1.0
Cy/Bu	6	1	5*	0.03
Cy/Bu/ATG	12	9°	3	0.14
Cy/Bu/ATG/VP16	6	4	2	1.0
Bu/ATG/VP16	1	1	/	1.0
GvHD Prophylaxis				
CSA alone	11	10	1	0.002
CSA + Mtx	12	4	8	0.003
CSA + Mtx + Steroids	4	/	4	0.002
CSA + Mtx + Others	4	1	3	0.15
CSA + Steroids	5	3	2	1.0
CSA + Steroids + Others	4	3	1	0.63
None	15	14	1	0.002

*TBI: total body irradiation; Cy: cyclophosphamide; Thio: thiotepa; VP16: etoposide; Melph: melphalan; Bu: busulphan; Flud: fludarabine. *One patient received Melph; °one patient received radioimmun-ablation; #one case treated with Ara-C instead of fludarabine.*

Results

Cell yield of the transplanted grafts

The doses of transfused CD34 and CD3 positive cells/kg are provided in Table 4. There was a wide range of CD34 positive cells infused because adults donating for pediatric patients were included in the analysis. The amount of CD34 positive cells/kg infused was comparable in both groups. As expected the amount of CD3 positive T cells transfused with the unmanipulated grafts was significantly higher with a considerable range in both groups. At the time of writing, no donor has experienced serious side effects or long-term impairments.

Engraftment and clinical course

The engraftment parameters are summarized in Table 5. Seven patients in the TCD group experienced graft failure whereas only one case was observed in the UM group (p=0.04). The median dose of CD3 positive cells transplanted into patients with graft-failure in the TCD group was not lower than in those patients with

Table 4. Cell dose infused.

	TCD	UM	p
CD34+, median (range)	5.6 (1.78-28.5)	6.8 (1.92-19.1)	0.8
CD3+, median (range)	0.01 (0.0003-0.58)	320 (2.2-150)	0.0001

Abbreviations: CR = complete remission; PR = partial remission; cp = chronic phase; UM = unmanipulated; TCD-T cell depleted.

Table 5. Engraftment, transfusions and GvHD.

	All	TCD	UM	p
Graft-failure	8	7 (20%)	1 (5%)	0.04
Engraftment				0.1
Days to ANC >0.5×10⁹/L, median (range)	13 (7-35)	12 (7-35)	14 (10-27)	
Platelets >50×10⁹/L, median (range)	21 (11-57)	21 (11-57)	22 (14-53)	
Transfusions				
No. of RBC units transfused	9 (1-136)	10 (1-136)	9 (2-26)	
No. of platelet units transfused	13 (0-68)	13 (0-67)	13 (4-68)	
Day of discharge, median (range)	30 (3-98)	28 (13-98)	36 (3-85)	0.017
GCSF application	57	38 (78%)	19 (63%)	0.2
GvHD				
acute GvHD grades	0	21	16	5
I	8	6	2	
II	15	11	4	
III	7	1	6	
IV	4	1	3	
GvHD grade 0-II	44	33	11	0.001
GvHD grade III+IV	11	2	9	
chronic GvHD	15	8	7	0.59

Abbreviations: CR = complete remission; PR = partial remission; cp = chronic phase; UM = unmanipulated; TCD-T cell depleted.

TCD grafts who had stable engraftment. There was no difference between both groups in the speed of neutrophil and platelet engraftment which occurred on day 13 (range, 7-35) and 21 (range, 11-57), respectively. The number of red blood cell (RBC) and platelet transfusions also did not differ significantly between the two groups. Patients receiving TCD PBSC were discharged 8 days earlier than the UM group (28 vs. 36 days, p=0.017). The cumulative risk of acute GvHD was 71.8% in the UM group compared to 38.1% in the TCD group (p=0.005). No difference in the incidence of chronic GvHD was observed between the two groups. The plots for acute and chronic GvHD are provided in Figure 1. There was no difference in the rate of graft failure between patients receiving ATG and those not but there was a trend towards less acute GvHD in patients having received ATG (66.2% vs. 49%, p=0.06).

Complications and causes of death

Nine patients developed bacteremia and 11 patients invasive fungal infections with no differences between the two groups. As shown in Table 6, 17 patients developed pneumonia and 4 patients CMV disease. There was a trend towards more patients with CMV antigenemia in the TCD group (27%) compared to the UM group (13%, p=0.26). Relapse was the cause of death in 6 patients with no differences between the TCD and the UM group.

Overall and disease-free survival

Figure 2 depicts the Kaplan-Meier estimation for overall and disease-free survival in the whole group. With a median observation time of 12 months (range 4-34) the projected overall and disease-free survival (OS and DFS) for patients with non-malignant diseases at one year is 100%. Patients with primary transplantation for malignant diseases (n=55) achieved 47.3% OS and 42 % DFS whereas the 18 patients treated for graft-failure or relapse obtained only 11.8% OS and DFS. Figure 3 shows the survival plots for patients receiving their first transplant, comparing those with standard risk (AML, ALL at 1st or

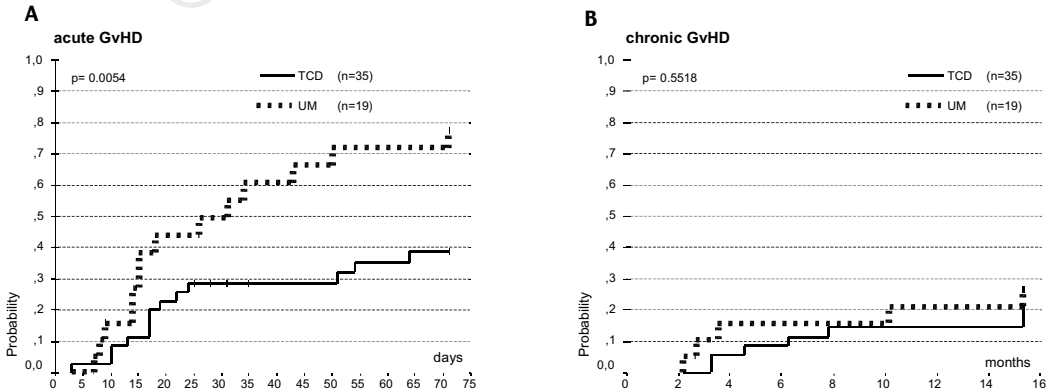

Figure 1. Acute and chronic GvHD. Graph A depicts the cumulative risk of the development of acute GvHD according to graft manipulation. The risk of developing chronic GvHD is provided in graph B. *UM=unmanipulated graft, TCD=T-cell depleted graft*.

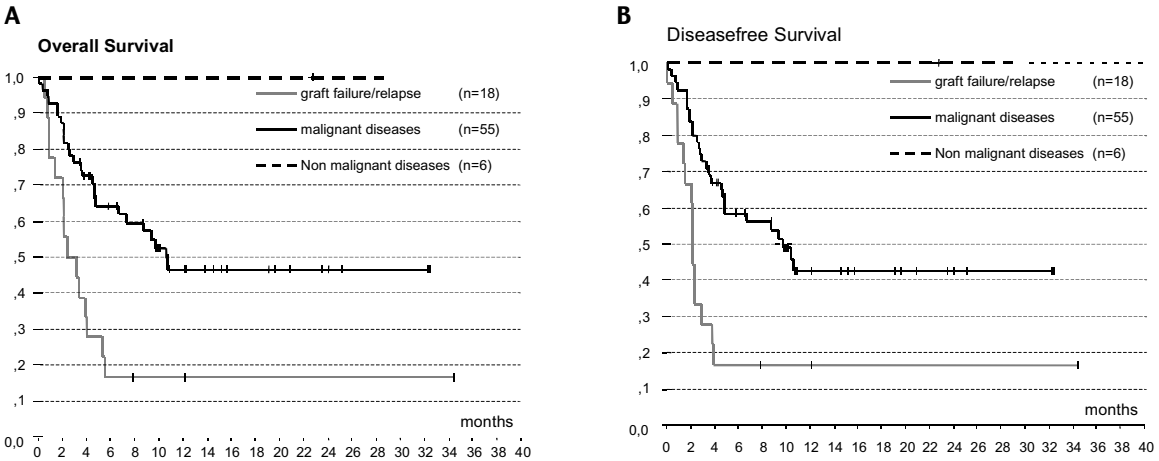

Figure 2. Survival of patients with non-malignant, malignant diseases and second transplants. Graphs A and B show overall- and disease-free survival for patients with non-malignant diseases (n=6), malignant diseases and first transplantation (n=55) as well as for 18 patients who received PBSC as second transplants from the same unrelated donor for relapse or graft-failure.

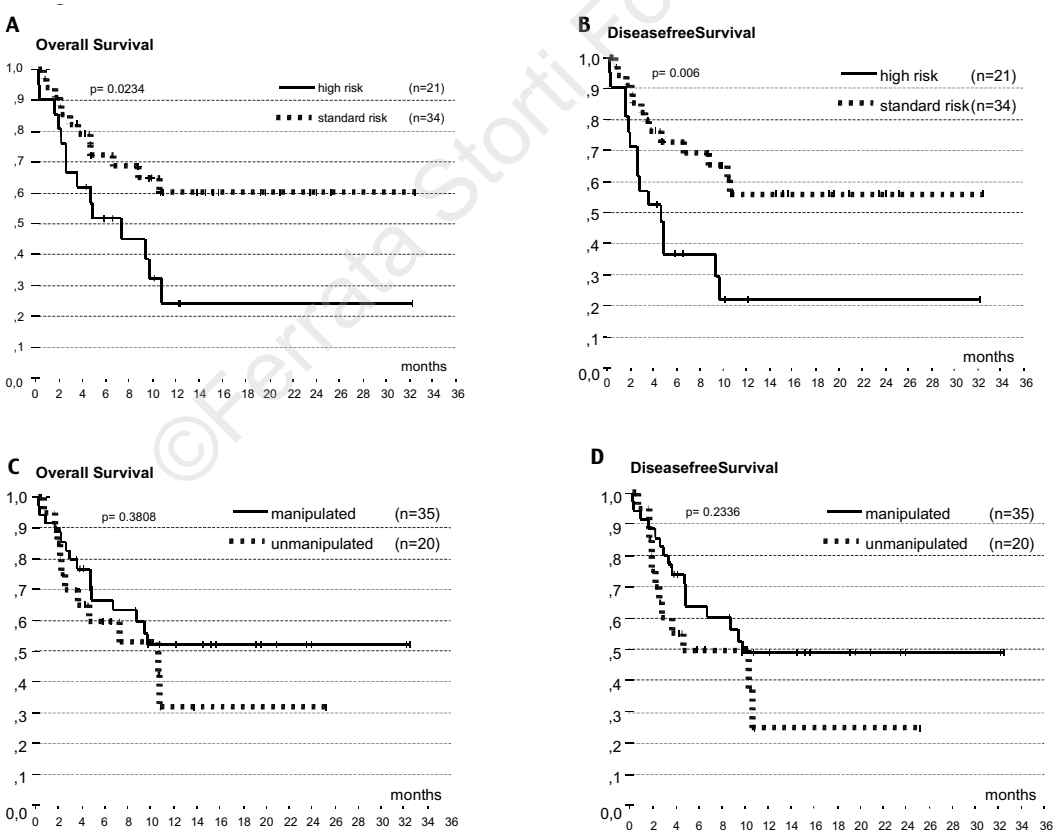

Figure 3. Risk category and graft-manipulation. The graphs A and B summarize the survival data according to risk category for patients receiving their first transplant. High-risk patients had a significantly worse outcome. Graphs C and D provide the Kaplan-Meier plots for overall survival and probability of relapse according to graft-manipulation.

Table 6. Complications and causes of death.

	All	TCD	UM	p
Complications				
Bacteremia	9	4	5	0.29
Invasive fungi	11	8	3	0.52
Veno-occlusive disease	10	4	6	0.17
Pneumonia	17	9	8	1.0
CMV reactivation	17	13	4	0.26
CMV disease	4	2	2	0.65
Causes of death				
Relapse	6	3	3	0.89
Organ failure	3	0	3	0.1
Pneumonia	5	3	2	1
Infection	5	3	2	1
Sepsis	2	1	1	1
Lung fibrosis	1	1	/	1
Acute GvHD	5	2	3	0.36

Table 7. Multivariable analysis of disease-free survival for patients with first transplants.

Variable	Disease-free survival (months)	p
Age		0.93
Risk group		
High-risk	10.1	0.02
Standard-risk	20.4	
CMV serostatus		
Pos	16.4	0.79
Neg	15.5	
TBI		
Yes	11.1	0.32
No	17.3	
ATG		
Yes	19.1	0.03
No	5.9	
UM/TCD		
UM	10	0.26
TCD	18.1	
CD34 cell dose		0.61
CD3 cell dose		0.66

UM : unmanipulated; TCD: T-cell depleted.

subsequent CR, CML 1st CP, PNH, n=34) to those at high risk (MDS, refractory or relapsing acute leukemia, CML other than 1st CP, n=21). Patients with standard risk receiving first transplants had a significantly better overall (60.4% vs. 24%, p=0.02) and disease-free survival (57.2% vs. 22.3%, p=0.006) compared to the high risk group. Only a few patients of the high risk group survived more than 12 months.

The two lower graphs across represent the overall survival (left) and probability of relapse (right) for the patients according to graft-manipulation. Although a trend towards a better survival-rate was observed after TCD transplantation (52.2%) than after an UM graft (38.1%), this difference was not statistically significant. The probability of relapse was significantly higher in patients after UM transplants (38.8% vs. 8.4%).

Multivariable analysis

Risk category (p=0.02) and ATG administration (p=0.03) were shown to have a significant influence on DFS in multivariate analysis for patients receiving first transplants. Table 7 shows that age, CMV serostatus, use of TBI, graft-manipulation, and CD34 or CD3 cell dose had no significant impact on outcome. When all 79 patients were analyzed for the impact of CD34 and CD3 cell dose, GvHD prophlyaxis, graft manipulation, risk category and age on the end-points of acute and chronic GvHD and neutrophil and platelet recovery, no single variable was shown to have a significant impact.

Discussion

This study gives an overview of the clinical course of patients with different malignant and non-malignant diseases receiving G-CSF mobilized PBSC from unrelated volunteer donors. Since our analysis is retrospective and the number of patients in the subgroups is rather small, statistical comparisons must be regarded with caution. Some transplant centers preferred to infuse T-cell depleted PBSC instead of the unmanipulated leukapheresis products. The reasons or inclusion criteria for patients to receive TCD grafts varied between the different centers. This makes statistical comparison somewhat difficult. Nevertheless, we believe the data obtained can be used to summarize the first experience with PBSC from unrelated donors in terms of safety, engraftment and short-term outcome.

Although the rate of acute GvHD observed after allogeneic PBSC transplantation from HLA identical siblings has been reported to be similar to that after BMT,[8] there have been retrospective analyses showing a very high rate of chronic GvHD after PBSC transplantation.[6] The draw-backs of T-cell depletion have been known for years, especially in patients with CML, in whom the rate of relapse had increased substantially in series exploring T-cell depletion in related BMT.[20] Nevertheless, the high rate of GvHD after allogeneic BMT from unrelated donors[14] has prompted some investigators to explore depletion of cytotoxic $CD8^+$ cells[21] or $CD6^+$ T-cells[22] to diminish the rate of acute GvHD while preserving the graft-versus-leukemia effects.

The dose of CD34 positive cells infused has been shown to be an independent prognostic factor, especially after TCD BMT.[23] As shown for BMT in other reports, 20% of patients in the TCD group of this study had primary graft-failure. Although regrafting was possible in some of them, these data suggest that even the higher number of CD34 positive cells transplanted compared to BMT might not be enough to compensate for the loss of T-cells which are needed for supporting engraftment. A delayed add-back of T-cells seems to be one way to address this problem, even though the timing and dose of $CD3^+$ cells needed may be different from that determined by the BMT experience.[22] Of course there are other differences between BM and PBSC progenitors which may explain why a significantly smaller number of $CD34^+$ BM progenitors can lead to the same rate of stable engraftment.[24] Nevertheless, the survival data for patients receiving TCD PBSC for non-malignant diseases seem to be

comparable to those achieved by BMT.

Another problem has been the increased rate of post-transplant lymphoproliferative diseases arising after allogeneic T-cell depleted BMT.[25,26] The positive selection for CD34 positive progenitors leads to an effective depletion of T- and B-cells. Therefore, EBV lymphomas, which arise from infected donor B-cells in most cases, should not develop in these patients. No EBV lymphoma was reported in the whole group.

On the other hand, the depletion of T-cells prevents cytokine activation of donor T-cells which are infused immediately after high-dose radiochemotherapy. A significant release of TNFα has been reported during total body irradiation and high-dose chemotherapy.[27,28] This so-called *cytokine storm* not only activates effector cells of acute GvHD but might also play a role in severe organ damage. The higher rate of deaths associated with GvHD and organ failure in the UM PBSC group is in concordance with this hypothesis. Nevertheless, the higher rate of relapse in the UM group can be explained by the higher percentage of high-risk patients.

After TCD PBSCT most patients received no GvHD prophylaxis or only CsA. This probably significantly reduced toxicity in these patients compared to in patients receiving methotrexate (MTX). The frequency of G-CSF administration was not different between the two groups. Since toxicity and GvHD are the main determinants of recovery, patients receiving TCD PBSC could be discharged significantly earlier. Like the use of G-CSF after allogeneic PBSC, this might be important from an economic point of view.[29]

The differences in the rate of transplant-related mortality might be explained by the higher percentage of children in the TCD group (p=0.07). Transplant-related mortality is known to be lower in this age group. On the other hand, there was also a considerable number of patients over the age of 40 in the TCD group. These patients might particularly benefit from the faster neutrophil and platelet engraftment reached by the use of PBSC.[30]

There have been reports on the faster cellular immunologic recovery obtained with PBSC compared to BM in transplants from related donors.[31] Although the same might be true in the unrelated setting, ATG containing GvHD prophylaxis and the impaired cellular immunity induced by acute and chronic GvHD and subsequent intensification of immunosuppression might outweigh this advantage. Late infections can occur in patients with extensive GvHD which we were not able to include in this report.[18] As expected, we found a higher rate of CMV antigenemia in patients receiving TCD grafts; preemptive treatment strategies might have led to the few cases of CMV disease observed so far.[32]

Although these results of allogeneic unrelated PBSC transplantation seem to be encouraging, some points of caution must be raised: we think it is too early to recommend PBSC transplantation from unrelated donors for standard risk patients with CML in first chronic phase. If the rate of chronic GvHD observed after related PBSC transplantation is extrapolated into the unrelated setting, it seems difficult to imagine that the favorable results of unrelated BMT reported in younger patients can be reached with this approach.[33] The relatively low rate of chronic GvHD in this study must be regarded with caution because there are still several patients at risk of this complication.

On the other hand, the use of unrelated PBSC might offer more antileukemic effects in patients with advanced or refractory diseases.[7,34] We found no survival advantage for patients with high-risk disease receiving UM compared to TCD PBSC. Whether the reduced toxicity obtained with TCD PBSC can result in even better overall and disease-free survival needs to be studied prospectively. The risk of relapse might become smaller when prophylactic donor leukocyte infusions are employed. The optimal timing and cell dose of such infusions must be determined in future trials. We believe that most interventions should be guided by sequential analysis of donor chimerism in cell subsets and residual disease in the patient.[35]

This study in 12 different centers has shown the feasibility and safety of allogeneic PBSC transplantation from unrelated volunteer donors in malignant and non-malignant diseases. Since the patient population is heterogeneous, definitive conclusions cannot be drawn. Nevertheless, engraftment with either UM and TCD PBSC seems to be faster than after BMT. The rate of acute GvHD seen in these 79 patients was in the same range reported for unrelated BMT with and without TCD. A prospective comparison of UM and $CD34^+$ selected PBSC transplantation from unrelated donors is needed in comparable patient populations to show whether the advantages of TCD in terms of treatment-related mortality and GvHD can outweigh the disadvantages of graft failure and increased relapse rate.

Contributions and Acknowledgments

All co-authors collected their data. MB and GE were the principal investigators and were responsible for the contents of the questionaires send to each center and the interpretation of the data. SS and CT were involved in the editing and design of the questionaire as well as the statistical analysis. The manuscript was critically reviewed by each author. Each co-author approved the final version, and the order of authorship, which was determined according to either the role in the conception of the study or the number of patients included in the survey. We thank the following clinicians who also participated in the study: RH, ML, RT and LK.

Disclosures

Conflict of interest: none.

Redundant publications: yes, <50%. In the paper by Professor Ringden (Blood 1999, 94:455-64) 17 patients from Dresden and 14 patients from Idar-Oberstein, had been included with a short follow-up. The major goal of this paper had been to compare results of unrelated BMT with unrelated PBSCT. We have extended the follow-up for these patients and have added 49 patients from various centers including our own, who were not included in Prof. Ringdens manuscript. All donors are registred in the DKMS (German Bone Marrow Donor Center). A larger patient group was analyzed in our study without retrospective comparison to the BMT experience.

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Potential implications for clinical practice

- The implications for clinical practice are that PBSC from unrelated donors lead to rapid engraftment with GvHD rates comparable to the BM experience. This might become especially relevant for patients with prior infectious complications and high-risk leukemia. T-cell depletion is possible with CD34 positive selection effectively minimizing the risk of acute GvHD.

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