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Marrow versus Blood-Derived Stem Cell Grafts for Allogeneic Transplantation from Unrelated Donors in Patients with Active Myeloid Leukemia or Myelodysplasia

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Peripheral blood stem cells (PBSCs) are increasingly used as the graft source in allogeneic hematopoietic cell transplantation. We compared long-term outcome after unrelated donor transplantation of 85 consecutive patients with acute myelogenous leukemia or myelodysplastic syndrome regarding disease status (early disease [CR1, refractory anemia); n = 25 and advanced/active disease [>CR1, >refractory anemia]; n = 60) who were treated with conventional conditioning regimens followed by bone marrow (BM) or PBSC grafts. Graft-versus-host disease prophylaxis consisted mainly of cyclosporine A, short-course methotrexate, and anti-T-lymphocyte globulin. After a median follow-up of 118 months (68-174), the 10-year event-free survival rate after peripheral blood stem cell transplantation (PBSCT) was 54.8% (95% confidence interval [CI], 39.7%-69.8%), and after bone marrow transplantation (BMT), it was 27.9% (14.5%-41.3%; $P < .004$). In the advanced/active disease group, the 10-year event-free survival rate after PBSCT was 50% (30.8%-69.2%), and after BMT, it was 23.5% (9.3%-37.8%; $P < .007$). Non relapse mortality was less after PBSCT than BMT (14.3% vs 30.2%), respectively. In multivariate Cox regression analysis, PBSCT showed a better overall survival (OS; hazard ratio [HR], 0.43; 95% CI, 0.23-0.79; $P = .007$) compared to BMT; unfavorable/unknown prognostic impact cytogenetic abnormalities were an adverse factor for all patients (HR, 2.202; 95% CI, 1.19-4.06; $P = .011$). In patients with advanced disease, the use of PBSCs showed a significant favorable outcome via multivariate analysis (HR, 0.49; 95% CI, 0.24-0.99; $P = .046$). Outcome of acute myelogenous leukemia/myelodysplastic syndrome after unrelated hematopoietic cell transplantation is adversely affected by cytogenetic abnormalities and state of remission at hematopoietic cell transplantation. PBSC as a graft source has a significant favorable influence on survival.

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INTRODUCTION

Over the last decade, peripheral blood stem cells (PBSCs) have increasingly been used as the graft source in allogeneic hematopoietic cell transplantation (HCT) compared to bone marrow (BM). Reasons are faster engraftment, [1-3] harvesting without general anesthesia, higher counts of stem cells, and improved disease control by enhanced graft-versus-leukemia (GVL) effect. This is accompanied by more frequent and extensive chronic graft-versus-host disease (cGVHD) [1,4,5]. These data have been primarily collected after sibling transplantation. In a meta-analysis involving nine randomized trials and 1111 patients with sibling transplantation comparing PBSC and BM as graft sources, patients with advanced disease benefited from peripheral blood stem cell transplantation (PBSCT) with improved disease-free survival (DFS) and overall survival (OS) [6]. On the

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other hand, retrospective registry data obtained in children suggested a worse outcome after transplantation from a sibling donor when PBSC was compared to BM [7,8]. Recipient and donor factors such as gender, [8] cytomegalovirus (CMV) serology, [9] and donor age, [10,11] as well as the transplanted cell dose may have contributed to the different outcome in addition to the actual graft source. At least in BM transplantation, a higher marrow-cell dose is an important factor to improve survival rates [12-14]. This association is less clear when PBSC grafts were used [15].

Few data are available comparing bone marrow transplantation (BMT) and PBSCT after volunteer unrelated donor (URD) transplantation. Transplantation with PBSC as a graft source from HLA identical URD revealed improved DFS compared to BMT in patients with chronic myelogenous leukemia (CML) in the first chronic phase (CP1), [16] or no difference in OS or DFS, but more cGVHD after PBSCT in patients with various other hematological malignancies [17-19]. A randomized trial showed the safety of URD transplantation using anti-T-lymphocyte globulin (ATG-F) as graft-versus-host disease (GVHD) prophylaxis after PBSCT [20].

We retrospectively analyzed the outcome after matched and mismatched URD transplantation with respect to disease status (early vs advanced/active disease) and graft source (BM vs PBSC) in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). All patients received their first allogeneic hematopoietic cell transplantation (alloHCT) after standard high-dose conditioning. Regarding OS and event-free survival (EFS), the importance of disease-related factors like cytogenetics, CMV status or GVHD prophylaxis are shown. The presented data have an exceptionally long follow-up of 10 years.

METHODS

Patient Characteristics

For this survey, we used prospectively collected data from our University of Freiburg alloHCT database and identified 85 patients; their characteristics are listed in Table 1. Diagnoses were de novo AML (n = 55), therapy-related AML (n = 4), secondary AML (n = 20), or MDS (refractory anemia [RA], refractory anemia with excess blast [RAEB II], and chronic myelomonocytic leukemia [CMML]; n = 6). Median duration of disease until transplantation was 222 days (range, 54-8876 days). The 42 female and 43 male patients had a median age of 40.1 years (range, 17-58 years). At transplantation, 11 patients were untreated, 31 were in complete remission (CR) at transplantation (CR1 [n = 23] or CR2/3 [n = 8]) after chemotherapy, while 19 patients were refractory to induction/reinduction chemotherapy and never in CR, and 24 patients had relapsed from CR in median after 6 months (range, 2-39 months). Reasons for URD transplantation in patients with early disease were induction failure (n = 3), treatment-related acute myelogenous leukemia ([tAML] n = 1), life-threatening cytopenias (n = 2), myelomonoblastic leukemia (n = 1), or cytogenetic abnormalities (n = 18). Overall, 46 patients had known cytogenetic abnormalities with 19 patients presenting with >1 abnormality. Cytogenetic abnormalities involved chromosomes 7

Table 1. Patient Characteristics

	BMT (n = 43)				PBSCT (n = 42)			
Age in median	36.2 years (17-55)				43.5 years (18-58)			
Male:female	22:21				20:22			
	CR1/RA		Advanced		CR1/RA		Advanced	
Number	No.	%	No.	%	No.	%	No.	%
	9	(21)	34	(79)	16	(38)	26	(62)
Diagnosis								
de novo AML	6	(14)	23	(58)	13	(31)	13	(31)
t+s+ts AML	1	(2)	9	(21)	2	(5)	10	(24)
MDS RA	1	(2)			1	(2)		
MDS >RA	1	(2)	2	(4)			3	(8)
Cytogenetics								
Favorable			1	(2)			1	(2)
Intermediate	4	(12)	12	(35)	3	(31)	14	(32)
Unfavorable	1	(2)	10	(23)	6	(14)	9	(21)
Unknown dignity	3	(7)	5	(12)	7	(16)		
Unknown	1	(2)	6	(21)			2	(5)
Remission at TX								
CR 1	8	(19)			15	(36)		
Untreated	1	(2)	4	(9)	1	(2)	5	(5)
CR 2/3			5	(12)			3	(8)
REL >1			16	(37)			8	(20)
PIF			9	(21)			10	(24)
Conditioning								
BU/CY containing	9	(21)	30	(70)	16	(38)	26	(62)
TBI/CY + VP16			4	(9)				
GVHD prophylaxis CSA +								
Mini-MTX	1		16	(37)	1	(2)	22	(52)
MTX/+PRED	2/6		6/9		14/1		3	(7)
Other			3	(7)	1	(2)		
ATG-F <60 mg/kg			7	(16)	1	(2)	24	(57)
ATG-F ≥60 mg/kg	9	(21)	27	(63)	15	(36)	2	(4)
CMV serology								
Donor (D) pos	2	(4)	3	(7)			2	(5)
Recipient (R) pos	4	(9)	14	(32)	10	(24)	11	(26)
Both pos	2	(4)	10	(23)	1	(2)	6	(14)
Negative R&D	1	(2)	7	(16)	4	(10)	7	(17)
Blood group								
No mismatch	2	(4)	8	(19)	5	(12)	8	(19)
Minor mismatch	1	(2)	14	(32)	5	(12)	10	(24)
Major mismatch	6	(14)	12	(28)	6	(14)	8	(20)
Rh-G-CSF post-TX	9	(21)	32	(74)	11	(26)	22	(52)

BMT indicates bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; AML, acute myeloblastic leukemia; t, therapy associated; s, secondary; ts, therapy-associated secondary; MDS, myelodysplastic syndrome; RA, refractory anemia; TX, transplantation; CR, complete remission; REL, relapse; PIF, persistent induction failure; BU/CY, busulphane/cyclophosphamide; TBI, total body irradiation; VP16, etoposide; GVHD, graft-versus-host disease; CSA, cyclosporine; MTX, methotrexate; PRED, prednisolone; ATG-F, antithymocyteglobuline-fresenius; CMV, cytomegalovirus; R&D, recipient and donor; Rh-G-CSF post-TX, granulocyte colony-stimulating factor posttransplantation.

(n = 12), 3 (n = 3), 5 (n = 1), 9 (n = 2), 4 (n = 2), t(15;17), t(9;22), -18, inv 16 (n = 1 each), del 11 (n = 1), +8 solely (n = 3), and complex karyotype in three patients. The karyotype was unknown in nine and normal in 29 patients. According to the Cancer and Leukemia Group B (CALGB) criteria, [21] cytogenetics were classified as favorable (n = 2), intermediate (n = 33), unfavorable (n = 26), or unknown prognostic impact (n = 15). No patient had undergone previous transplantation. Pretransplantation CMV serology was positive in 19 patient/donor pairs, in seven cases in donors only, and in 39 cases in patients only. Blood group mismatch transplantation was performed in 62 cases (n = 30 minor, n = 32 major).

Conditioning Regimens and GVHD Prophylaxis

All patients received oral busulphan (16 mg/kg body weight [bw]) in combination with cyclophosphamide (120 mg/kg; n = 81) or fractionated total body irradiation (TBI; 12 Gy) plus cyclophosphamide 60 mg/kg plus etoposide VP 16 60 mg/kg bw (n = 4). GVHD prophylaxis consisted of intravenous cyclosporine A (CsA) starting at day -3 at a dose of 2.5 mg/kg b.i.d (trough level, 250-350 ng/mL) in combination with methotrexate ([MTX] 15 mg/m^2 day +1, 10 mg/m^2 day +3, day +6) (n = 25) and in 16 patients who additionally received prednisolone, or mini-MTX (5 mg/m^2 day +1, day +3, day +6) (n = 40). CsA was substituted by tacrolimus in one patient. CsA or tacrolimus were given orally as soon as the patient was able to swallow. In addition, all patients received ATG 20-90 mg/kg bw (ATG-F, Fresenius; Graefelfing; Germany) [20,22]. Standard supportive care and, in case of CMV reactivation, pre-emptive ganciclovir or foscarnet therapy was given as described previously [23]. RhG-CSF (Filgrastim, Amgen, Munich, Germany) was given to 64 of 85 patients (75%) usually starting on day +7 until neutrophil recovery >1 × 10^9/L. The transplantation protocols were approved by the Freiburg University Medical Center institutional review board, and all patients gave written informed consent for treatment and prospective data collection in accordance with the Declaration of Helsinki.

Donors and Grafts

In 24 of 85 transplantations (28%), the donor was a mismatched URD (n = 3 >1 mismatch) (Table 2). HLA class-I antigens (A and B) were serotyped (two digits), and class II (DRB1 and DQB1) were analyzed by DNA high-resolution typing (four digits) [23]. BM was grafted in 43 of 85 patients (50%) and unmanipulated PBSC in 42 of 85 patients (50%). The median donor age was 34 years (range, 20-55 years). A woman donated to a male recipient in 18 transplantations.

During the first half of the time period (1995-1999), the majority of patients underwent transplantation with BM (n = 37 of 42), and from 2000 to 2004, preferentially with PBSC (n = 38 of 43).

The median number of white blood cells (WBCs) transfused was 3 × 10^8/kg (range, 1.2-13.9) per recipient bw in BMT and 11 × 10^8/kg bw (range, 1.6-21.4) in PBSCT; the median values for CD34+ and CD3+ were 2.9 (range, 0.15-7.1) and 29 × 10^6/kg bw (range, 1.8-270) in BMT and 5.9 (range, 1.5-17) and 305 × 10^6/kg bw (range, 110-2000) in PBSCT, respectively.

Evaluation and Statistical Analysis

Acute GVHD (aGVHD) and cGVHDs were assessed using the criteria of Przepiorka and Shulman [24,25]. Data were evaluated as of March 1, 2010, and follow-up of patients was complete except for one patient (UPN 020626). OS was defined as the time from HCT to death of any cause, and EFS was defined as the time from HCT to relapse or death of any cause. Observation times were censored at the date the patient was last seen alive in case the event of interest was not observed. OS and EFS rates were estimated and displayed using the Kaplan-Meier method. We analyzed the influence of the following parameters on OS in all patients and in the subgroup of patients who underwent transplantation and had advanced-stage disease: graft (BMT vs PBSC), sex, female donor in male recipient, age at HCT (</≥40 years), cytogenetics (favorable/intermediate vs unfavorable/unknown prognostic impact), CMV positive serology in donor and recipient, remission at HCT (early vs advanced), match vs mismatched donor, chronic GVHD (yes or no as a time-dependent variable), time of transplantation (1995-1999 vs 2000-2004) and ATG-F dose (</≥60 mg/kg). This cut-off was used because it is the dose of the large randomized trial. [20] Statistical analysis of OS was carried out using univariate and multivariate Cox proportional hazard models with SAS software version 9 (SAS Institute, Cary, NC). Univariate analyses were regarded as a preliminary step. In the multivariate model, a backward elimination procedure was performed until only prognostic factors with $P < .20$ were retained. Results are presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and Wald χ^2 test P values.

Group comparisons (BMT vs PBSCT) for binary prognostic factors observed at the time of transplantation were conducted by applying the Fisher exact test.

Probabilities for the occurrence of cGVHD were estimated using cumulative incidence rates, where death without cGVHD was considered as a competing risk. Similarly, relapse mortality (RM) and nonrelapse mortality (NRM) were regarded as competing risks, and the respective RM and NRM probabilities were estimated as cumulative incidence rates.

Table 2. Donor and Graft Characteristics

	BMT (n = 43)		PBSCT (n = 42)	
	CR1/RA (n = 9)	Advanced (n = 34)	CR1/RA (n = 16)	Advanced (n = 26)
Mismatch TX	1	14	3	6
A, B		4		1
DR mismatch		8	1	3
DQ mismatch	1	1	2	2
>1 mismatch		2		1
Age of donor (range)	34.5 (26-45)	35.5 (21-55)	34.5 (25-41)	30.5 (20-51)
Female donor/male recipient	3	7	4	4
Graft size				
WBC $\times 10^8$/kg bw (range)	2.8 (1.2-13.9)	3 (1.6-8.8)	9.6 (1.6-8.8)	13.1 (2.5-1.4)
CD 34 $\times$ 10^6/kg bw (range)	1.6 (0.15-5.3)	3.2 (0.25-7.1)	4.3 (1.8-17)	6.9 (1.5-16)
CD 3 $\times$ 10^7/kg bw (range)	2.9 (1.2-11)	2.85 (0.18-27)	29.5 (11-52)	33.5 (15-200)

BMT indicates bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CR, complete response; RA, refractory anemia; TX, transplantation; WBC, white blood cell; bw, body weight; A, HLA-A; B, HLA-B; DR, HLA-DRB1; DQ, HLA-DQB1.
Note: Not all parameters are in all patients available.

Neutrophil and platelet recovery were analyzed and compared using the unpaired *t*-test with GraphPad-Prism software (Graph Pad Software, La Jolla, Ca). Furthermore, we compared the median size of the graft according to WBC, CD34+ cells, and CD3+ cells/kg recipient bw in each graft source group.

RESULTS

Engraftment

All patients achieved engraftment with WBC counts $\geq 1 \times 10^9$/L by median day +17 (range, 12-28 days) after BMT and by median day +14 (range, 10-30 days) after PBSCT ($P < .05$), except for one patient with AML after primary induction failure who died on day +12 of pulmonary hemorrhage before engraftment after BMT. No primary or secondary graft failure occurred. Stable platelet counts $\geq 20 \times 10^9$/L and $\geq 50 \times 10^9$/L after BMT were reached by median day +27 (range, 14-100 days; n = 36) and median day +34 (range, 22-204 days; n = 34), respectively. The values after PBSCT were median day +17 (range, 9-79 days; n = 41; $P < .001$) and day +23 (range, 15-97 days; n = 35; $P = .0005$), for engrafting patients only. Eight patients died before stable platelet engraftment (Table 3).

Response

At day +30, CR was achieved by standard diagnostic procedures in 78 of 85 evaluable patients (92%) and partial remission (PR) in two of 85 patients (2%). One patient was refractory, and four patients died before day +30. No difference in response was observed regarding the graft source BM (CR, 38 of 43 patients; 88%) vs PBSC (CR, 40 of 42 patients; 95%).

Graft-versus-Host Disease

Clinically relevant aGVHD II to IV developed in 19 of 84 patients (27%) and GVHD III to IV in seven of 84 evaluable patients (8%) after engraftment. One patient, who died before engraftment, was excluded. Limited cGVHD was observed in 12 patients and extensive cGVHD in 25 patients. Cumulative incidence rates for cGVHD after 12 months were estimated as 32.6% (95% CI, 21.2%-50.1%) for BMT and 52.4% (95% CI, 39.3%-69.9%) for PBSCT ($P = .11$).

Outcome According to Graft Source

As of March 1, 2010, 41 of 85 patients (48%) were alive with a median follow-up of nearly 10 years (118 months; range, 68-174 months). For all patients, 10-year OS rates estimated by the Kaplan-Meier method are 30.2% (95% CI, 16.5%-44%) for BMT, and 59.5% (95% CI, 44.7%-74.4%; $P = .0029$) for PBSCT (Figure 1). The cumulative 10-year EFS rate after PBSCT was estimated to be 54.8% (95% CI, 39.7%-69.8%) and after BMT 27.9% (95% CI, 14.5%-41.3%; $P < .004$) (Figure 2).

Thirty patients relapsed. Second transplantation was performed in nine patients; two of them achieved sustained CR. Multiple donor lymphocyte transfusions were given to 12 patients; only one patient (8%) responded with a long-lasting CR.

Relapse was the leading cause of death in 25 of 85 patients (29%), followed by infection in eight of 85 patients (9%) and multiorgan failure or acute respiratory distress syndrome in six of 85 patients (7%). One patient died from aGVHD (1%), and five of 85 patients (6%) died from cGvHD. Other causes were diffuse hemorrhage and secondary malignancy in one patient each.

The cumulative incidence rate of NRM at 5 years was 14.3% (95% CI, 7%-30%) in the PBSCT group and 30.2% (95% CI, 19%-48%) in the BMT group. Relapse was the cause of death in 15 of 43 in the BMT group and eight of 42 in the PBSCT group with a cumulative incidence at 5 years of 32.6% (95% CI, 21%-50%) and 23.8% (95% CI, 14%-41%), respectively (Figure 3A and B).

Table 3. Results and Outcome

	BMT (n = 43)		PBSCT (n = 42)	
	CR1/RA	Advanced	CR1/RA	Advanced
Number	9	34	16	26
Engraftment (day+)				
WBC (range)				
>0.5 × 10^9/L	15 (13-21)	17 (10-24)	14.5 (11-24)	12 (9-17)
>1 × 10^9/L	16 (14-22)	17 (12-28)	16.5 (12-30)	12.5 (10-19)
Platelets				
>20 × 10^9/L	30 (16-63)	25 (14-100)	18 (14-30)	16 (9-79)
>50 × 10^9/L	86 (22-172)	33.5 (22-204)	23 (17-48)	24 (15-9)
CMV reactivation	6	20	9	16
Best response				
CR	9	29	16	24
PR		1		1
Refractory		1		
Not evaluable		3		
aGVHD (n)	9	33	16	26
0-I	8 (89%)	25 (75%)	15 (94%)	17 (65%)
II-IV	1 (11%)	8 (25%)	1 (6%)	9 (35%)
III-IV		1 (3%)		6 (23%)
Not evaluable				1
cGVHD (n)				
No	3 (33%)	15 (63%)	11 (29%)	8 (33%)
Limited	1 (11%)	3 (13%)	3 (19%)	4 (17%)
Extensive	5 (55%)	6 (25%)	2 (13%)	12 (50%)
Not evaluable		10		2
Follow-up 1.3.2010				
Alive (n)	4/9	9/34	11/16	14/26
Months (in median)	147	145	81	111
Range	(126-169)	(109-174)	(69-132)	(68-129)
Causes of death (n)				
Relapse	4	11	5	5
aGVHD				1
cGVHD	1	1		3
MOF/ARDS		3/3		
Infection		5		3
Hemorrhage		1		
Secondary malignancy		1		

BMT indicates bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; WBC, white blood cell; CMV, cytomegalovirus; CR, complete response; PR, partial response; aGVHD, acute graft-versus-host disease; n, evaluable patients; cGVHD, chronic graft-versus-host disease; MOF, multiorgan failure; ARDS, acute respiratory distress syndrome.
Note: Not all parameters are available in all patients, and not all patients reached ≥20 × 10^9/L platelets.

Univariate and Multivariate Analysis of all Patients

Univariate regression analysis with Cox proportional hazard models for OS in all patients (n = 85) revealed a significant influence of the graft source in favor of PBSC (HR, 0.42; 95% CI, 0.23-0.75; P = .004) and showed a disadvantage for disease status at HCT >CR1 (HR, 2.18; 95% CI, 1.08-4.38; P = .03) and for ≥1 cytogenetic unfavorable/unknown prognostic impact abnormalities (HR, 1.74; 95% CI, 0.93-3.27; P = .08). No other significant differences could be shown regarding sex, female donor in male recipient, age at HCT (<40 years vs ≥40 years), ATG-F dose (≥60 mg/kg bw vs <60 mg/kg bw), and CMV serology of donor/patient and cGVHD. We noted a statistical trend for a better OS with an HLA-mismatched donor and negative CMV serology in the patient (Table 4A).

Within each group (BM vs PBSC), we did not observe any statistically significant difference concerning the transplanted median WBC, $CD3^+$, or $CD34^+$ cell doses/kg bw.

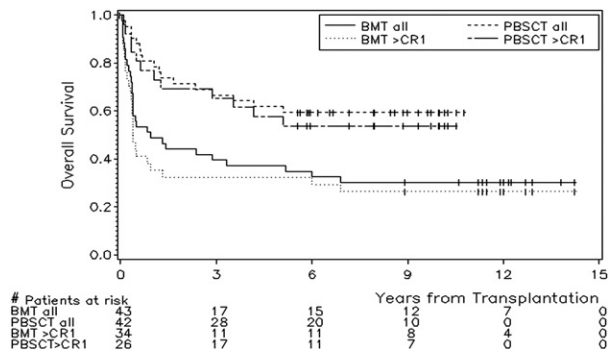

Figure 1. Overall survival comparing all patients (n = 85) and patients with >CR1 (n = 60) according to graft source (bone marrow [BM] vs peripheral blood stem cell transplantation [PBSCT]).

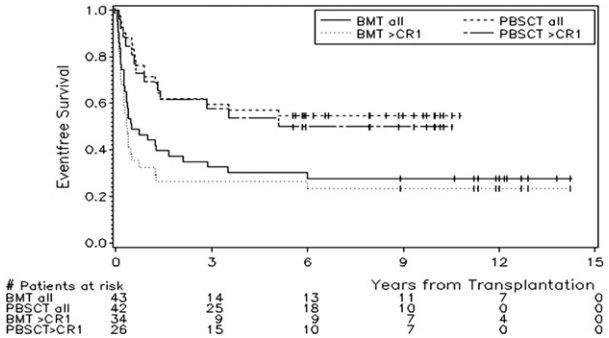

Figure 2. Event-free survival comparing all patients (n = 85) and patients with >CR1 (n = 60) according to graft source (bone marrow [BM] vs peripheral blood stem cell transplantation [PBSCT]).

In the multivariate analysis, PBSC (HR, 0.43; 95% CI, 0.24-0.8; P = .007) remained as a positive prognostic factor. The strongest negative influence on outcome was active/advanced disease at HCT (HR, 2.37; 95% CI, 1.16-4.86; P = .018) and the presence of unfavorable/unknown prognostic impact cytogenetic abnormalities (HR, 2.2; 95% CI, 1.19-4.06; P = .012). Additionally, and in line with published risk factors, patients with positive CMV serology had a trend to decreased survival (HR, 1.85; 95% CI, 0.93-3.66; P = .078) (Table 4B).

Univariate and Multivariate Analysis in Patients with Advanced/Active Disease

In the active/advanced disease group (n = 60), univariate analysis revealed a significant advantage for PBSCT (HR, 0.42; 95% CI, 0.21-0.84; P = .015) (Figure 1). OS was significantly decreased with unfavorable/unknown prognostic impact cytogenetic abnormalities (HR, 3.13; 95% CI, 1.51-6.49; P = .0021). All other analyzed parameters revealed no significant effect (Table 5A).

This statistical effect of the graft source was weaker in the multivariate analysis but still remained significant (HR, 0.491; 95% CI, 0.24-0.99; P = .0461). Again, abnormal cytogenetics at diagnosis continued to provide the strongest statistical significance for survival impairment (HR, 2.68; 95% CI, 1.33-5.40; P = .0057) (Table 5B). Survival in the CR1 group showed no difference according to the graft source (data not shown).

DISCUSSION

Our retrospective analysis of 85 consecutive patients with AML and MDS after conventional, myeloablative conditioning and URD transplantation in early or active/advanced disease indicated a significant benefit for the use of PBSC compared to BM. This is in contrast to a Spanish database survey for sibling alloHCT, which showed no difference according to OS [26] but is in line with a meta-analysis in

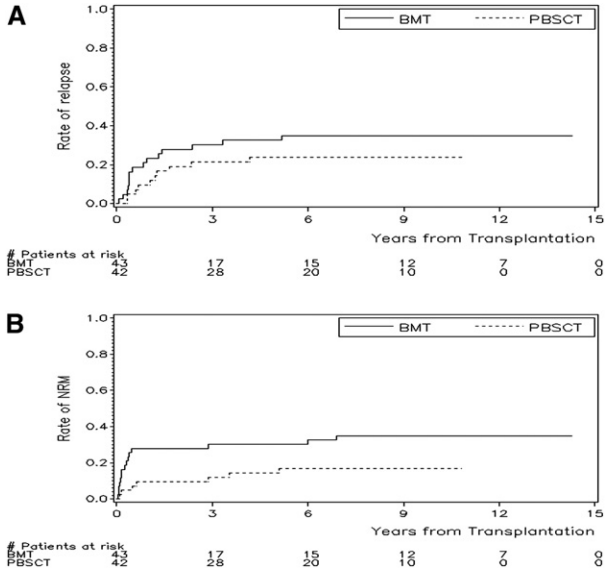

Figure 3. Cumulative relapse (A) and nonrelapse mortality (B) incidence comparing all patients (n = 85) according to graft source (bone marrow [BM] vs peripheral blood stem cell transplantation [PBSCT]).

sibling HCT [6] and with a validated Markov model analysis, which shows an advantage for PBSC in patients with an increased risk of relapse [27]. Furthermore, we also demonstrated a faster engraftment in URD transplantation after PBSC for neutrophils and platelets [2,28]. Such an analysis in a uniformly treated patient collective after URD has not been performed before with such long patient follow-up of almost 10 years. The data contradict published investigations in sibling transplantations in randomized trials [6,29,30] and recently published registry data for URD transplantation [19] for various hematologic malignancies, which showed no difference between the graft sources for OS and EFS. Higher incidence of NRM is seen by the Japanese Society for HCT Registry in a recent published analysis for standard-risk patients after sibling donor HCT but not for high-risk patients [31]. Chronic GVHD has been suspected to cause the higher rate of late NRM [19]. In our patients, cGVHD was the cause of only one late death in the last 5 years (2006-2010) associated with NRM.

Moreover, we could confirm the prognostic importance of cytogenetic aberration evaluation in myeloid diseases at diagnosis of AML/MDS to designate patients at risk for poor outcome [32-34].

We performed univariate and multivariate Cox regression analysis with known prognostic factors for OS, but except for remission at alloHCT and cytogenetic abnormalities, no other parameters proved to be statistically significant in our analysis. Interestingly, in contrast to published sibling-transplantation data, we observed no statistically significant effects for the incidence of cGVHD, [4,8] positive-CMV serology of the patient, [9] female donor and male recipient,

Table 4. Univariate (A) and Multivariate (B) Analysis of Prognostic Factors for OS in All Patients (n = 85)

A				
	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Remission at TX				
Advanced vs early	2.176	1.080	4.383	.0296
Cytogenetics				
Unfavorable/unknown dignity	1.742	0.929	3.267	.0834
HLA mismatch				
Yes vs no	1.613	0.888	2.929	.1164
CMV serology				
Patient positive vs negative	1.651	0.840	3.246	.1461
Gender patient				
Male	1.286	0.725	2.282	.3895
CMV serology				
Donor positive	1.181	0.646	2.159	.5894
Age at TX				
≥40 years	1.021	0.576	1.810	.9422
Sex mismatch				
Patient male, donor female	1.019	0.518	2.002	.9572
Time period				
2000-2004 vs 1995-1999	0.646	0.363	1.150	.1375
Chronic GVHD				
Yes, time dependent	0.897	0.440	1.829	.7657
Graft				
PBSC vs BM	0.415	0.228	0.754	.0039

B				
	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Remission at TX				
Advanced vs early	2.372	1.158	4.858	.0182
Cytogenetics				
Unfavorable/unknown dignity	2.202	1.194	4.061	.0115
CMV serology				
Patient CMV positive	1.850	0.934	3.663	.0776
Graft				
PBSC vs BM	0.433	0.236	0.796	.0070

OS indicates overall survival; CI, confidence interval; TX, transplantation; CMV, cytomegalovirus; GVHD, graft-versus-host disease; PBSC, peripheral blood stem cell; BM, bone marrow.
Only variables with significant or trend differences listed.

Table 5. Univariate (A) and Multivariate (B) Analysis of Prognostic Factors for OS in Advanced Disease Patients (n = 60)

A				
	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Cytogenetics				
Unfavorable/unknown dignity	3.134	1.513	6.492	.0021
CMV serology				
Patient positive	1.443	0.698	2.983	.3226
Patient gender				
Male	1.362	0.712	2.602	.3502
HLA mismatch				
Yes	1.353	0.701	2.612	.3678
Age at TX				
≥40 years	1.168	0.612	2.228	.6381
CMV serology				
Donor positive	1.045	0.532	2.053	.8975
Chronic GVHD				
Yes, time dependent	1.031	0.450	2.361	.9424
Sex mismatch				
Patient male, donor female	0.900	0.395	2.050	.8012
Time period				
2000-2004 vs 1995-1999	0.629	0.323	1.224	.1723
Graft				
PBSC vs BM	0.421	0.211	0.842	.0145

B				
	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Cytogenetics				
Unfavorable/unknown dignity	2.683	1.333	5.401	.0057
Graft				
PBSC vs BM	0.491	0.244	0.988	.0461

OS indicates overall survival; CI, confidence interval; CMV, cytomegalovirus; TX, transplantation; GVHD, graft-versus-host disease; PBSC, peripheral blood stem cell; BM, bone marrow.
Only variables with significant or trend differences are listed.

[8] or graft size within each graft group (</> median cell dose) [10-13]. Regarding the graft source, a clear statistical advantage for improved survival in favor for PBSC could be observed.

All patients received ATG-F for GVHD prophylaxis, which in our opinion, is responsible for our low incidence of aGVHD and the low NRM rate due to GVHD [20] compared to the mentioned registry evaluation [19]. This has been shown in a large randomized study comparing ATG-F vs no ATG-F [20] and in two recently published surveys of the Center for International Blood and Marrow Transplant Research (CIBMTR) [28] and the French Transplant Group [35]. Our prophylaxis led to equal results in matched and mismatched transplantations [22]. Additionally, it is notable that the transplantations were performed only with antigen-matched HLA class I typing (two-digit) in contrast to the current high-resolution testing (four-digit allele). The comparison of different doses of ATG-F showed no difference; hence, lower doses (<60 mg/kg) may suffice to prevent aGVHD.

Lower NRM and relapse rates are responsible for the better OS observed in patients with active/advanced disease undergoing PBSCT. We assume that the higher dose of transplanted T cells in patients in the PBSC group led to a higher cumulative incidence of cGVHD at 12 months (32.6% vs 52.4%), indicating a statistical trend in our analyses; this trend has been published in URDs before [16,17]. Why the patients receiving PBSC had a lower NRM is unclear.

Of note, when comparing our data with study results involving sibling donors, our patients present a particularly negative selection when one considers their adverse cytogenetics (52%), those with persistent induction failure (22%), and those in relapse before HCT (28%). Therefore, we do not agree with a review [36] where palliative care only is suggested for these patients. In contrast, despite these poor prognostic factors in our patients, we achieve long-term CR.

In fact, our long-term survival results concur with data raised in matched sibling transplantations in patients <56 years with similar cytogenetic risks and a DFS of 52% after 5 years [21].

We have conducted a retrospective analysis of nonrandomized patients, and we are aware that this may result in possibly biased effect estimation. Besides the prognostic factors considered in our investigations, time of transplantation differed between graft sources and may thus have added to a possible bias, because better supportive care was available. However, the application of multivariate regression methods may alleviate these shortcomings. Furthermore, our data have a notably long observation time with a median follow-up of nearly 10 years. Therefore, our investigation contributes important information to the choice of the graft source.

We thus conclude that an early search at initial diagnosis should be performed for a URD in each patient with myeloid malignancy. Furthermore, PBSC should be the graft of choice in URD transplantation in patients with active, advanced myeloid disease, receiving ATG-F as part of their GVHD prophylaxis.

We are waiting for the results of a large randomized trial comparing BM and PBSC in URD transplantation (BMT CTN 0201). The enrollment was completed in September 2009 [37].

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