Marrow versus peripheral blood for geno-identical allogeneic stem cell transplantation in acute myelocytic leukemia: influence of dose and stem cell source shows better outcome with rich marrow

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Several studies have compared bone marrow (BM) and peripheral blood (PB) as stem cell sources in patients receiving allografts, but the cell doses infused have not been considered, especially for BM. Using the ALWP/EBMT registry, we retrospectively studied 881 adult patients with acute myelocytic leukemia (AML), who received a non–T-depleted allogeneic BM (n = 515) or mobilized PB (n = 366) standard transplant, in first remission (CR1), from an HLA-identical sibling, over a 5-year period from January 1994. The BM cell dose ranged from 0.17 to 29 × 10^8/kg with a median of 2.7 × 10^8/kg. The PB cell dose ranged from 0.02 to 77 × 10^8/kg with a median of 9.3 × 10^8/kg. The median dose for patients receiving BM (2.7 × 10^8/kg) gave the greatest discrimination. In multivariate analyses, high-dose BM compared to PB was associated with lower transplant-related mortality (RR = 0.61; 95% CI, 0.39-0.98; *P* = .04), better leukemia-free survival (RR = 0.65; 95% CI, 0.46-0.91; *P* = .013), and better overall survival (RR = 0.64; 95% CI, 0.44-0.92; *P* = .016). The present study in patients with AML receiving allografts in first remission indicates a better outcome with BM as compared to PB, when the dose of BM infused is rich. (Blood. 2003;102:3043-3051)

Introduction

In the past decade, the use of peripheral blood (PB) as a source of hematopoietic stem cells for allogeneic transplantation has increased considerably. A large number of retrospective studies,[1-6] several prospective and randomized,[7-10] have compared the outcome of patients receiving allografts with bone marrow (BM) versus PB, using a family identical sibling; in all studies PB has resulted in faster engraftment and shorter hospital stay. In most studies, with the notable exception of the EBMT study,[9] the incidence and severity of acute graft-versus-host disease (aGVHD) has been similar with PB and BM; PB on the other hand has been associated with more chronic GVHD (cGVHD). Finally, the outcome with PB, in terms of leukemia-free survival (LFS) and overall survival (OS), has been identical to BM and sometimes superior.[11] All things considered, for practicality reasons, PB has therefore become a first choice for many transplantation teams. It has been postulated that the benefit brought by PB was at least in part due to the higher cell dose infused to the recipient when compared to BM.[12]

In the same period, other studies on BM and PB transplantations have drawn attention to the importance of the dose of stem cells infused; a lower transplant-related mortality (TRM) and also in some studies a lower relapse rate after transplantation have been observed in patients undergoing allografting[13,14] or autografting[15-19] with higher BM cell doses.

In the present retrospective study based on the ALWP/EBMT registry, we compared the outcome of patients with acute myelocytic leukemia (AML) receiving allografts in first remission (CR1) using BM or PB as a source of stem cells, focusing on the dose of stem cells infused. We found a significantly better outcome in patients receiving higher BM cell doses (rich marrow), when compared to the others, that is, patients receiving low-dose BM or high- or low-dose PB.

Patients and methods

Data collection and patient selection

The European Blood and Marrow Transplant (EBMT) Registry is a voluntary working group of more than 500 transplantation centers. Participants are required once a year to report all consecutive transplantations and follow-up. The Acute Leukemia Working Party (ALWP) of the EBMT is in charge of validating and checking submitted data to ensure data quality.

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A complete list of EBMT members contributing to the ALWP appears in the "Appendix."

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This study included 881 patients with AML, older than 16 years of age, who received a non–T-depleted allogeneic BM (n = 515) or mobilized PB (n = 366) standard transplant, in CR1, from an HLA-identical sibling, over a 5-year period from January 1994 (date of the first allogeneic PB transplantation) to January 2001. The dose of cells infused with the graft was in nucleated cells per kilogram. The study was approved by the EBMT review board.

End points of the study

Hematopoietic recovery. Neutrophil and platelet recoveries were analyzed separately and defined by a neutrophil count equal to or more than 0.5×10^9/L for 3 consecutive days and a platelet count equal to or more than 50×10^9/L for 7 consecutive days with no platelet support, respectively. The median time to recovery was calculated using the product limit method.

Mortality and relapse. Transplant-related mortality (TRM) was defined as nonleukemic deaths. Relapse incidence (RI) was defined on the basis of morphologic evidence of leukemia in BM or other extramedullary sites. To evaluate the probability of relapse, patients dying either from direct toxicity of the procedure or from any other cause not related to leukemia were censored. Leukemia-free survival (LFS) was defined as the time interval from transplantation to the first event (either relapse or death in complete remission).

GVHD. Acute GVHD (aGVHD) was diagnosed and graded at each transplantation center according to Seattle criteria.[20] Only patients with grade II or superior were considered as having aGHVD. For chronic GVHD (cGVHD), only patients surviving without relapse for more than 100 days after transplantation with sustained donor engraftment were considered as evaluable; cGVHD was defined according to standard criteria (limited and extensive).

Statistical analyses

All analyses were performed with the SPSS statistical analysis program (SPSS, Chicago, IL). Values reported for quantitative variables were median and range. The following patient or graft characteristics were analyzed for their potential prognostic value on each of the outcomes: patient's and donor's characteristics (age, sex, and sex matching), disease factors (white blood cell count at diagnosis, French-American-British [FAB] classification, interval from diagnosis to CR1, interval from CR1 to transplantation), and transplant-related factors (source of stem cells, nucleated cell dose infused per kilogram, year of transplantation, nature of the conditioning regimen including or not total body irradiation [TBI]). For these prognostic analyses, continuous variables were categorized according to the median value. To compare the distribution between the subgroups of patients we used the χ^2 test for categorical variables and the nonparametric Mann-Whitney *U* test for continuous variables.

Patients were censored at the time of relapse or the last follow-up. Probability of LFS, RI, TRM, and OS were estimated by the product-limit method.[21] The significance of differences between curves was estimated by the log-rank test (Mantel-Cox).[22] All variables associated with outcome with a *P* value of less than .1 in univariate analyses and characteristics statistically different ($P < .05$) between subgroups of patients were included in a multivariate analysis. Because a center effect had been observed in a previous EBMT[23] study in patients receiving a BM transplant for AML in CR1, all further multivariate analyses were adjusted on center.

Table 1. Distribution of patients by source and dose of nucleated cells/kg infused

	BM			*P*	
	NC less than 2.7 × 10^8/kg, n = 258	NC more than 2.7 × 10^8/kg, n = 257	PB, n = 366	BM more than 2.7 vs BM less than 2.7 × 10^8/kg	PB vs BM less than 2.7 × 10^8/kg
Year of BMT (range)	1996 (1994-2000)	1996 (1994-2000)	1998 (1994-2001)	.03	< .0001
Age, y (range)					
Patients	36 (16-58)	37 (16-57)	37 (16-66)	.25	.04
Donors	35 (5-65)	35 (10-59)	37 (14-67)	.81	.008
Patient sex (%)					
Male	138 (53)	126 (49)	189 (52)		
Female	120 (46)	130 (51)	174 (48)	.33	.73
Donor sex (%)					
Male	128 (51)	146 (58)	203 (56)		
Female	124 (49)	104 (42)	162 (44)	.08	.24
Female donor to male recipient, %	27	18	24	.02	.43
White blood cell count at diagnosis, × 10^9/L	11 (0.2-420)	10.6 (0.7-500)	13.5 (0.7-710)	.57	.49
FAB classification (%)					
M0	3 (1)	1 (0.4)	3 (1)		
M1	46 (20)	53 (23)	52 (16)		
M2	67 (29)	84 (36)	111 (34)		
M3	13 (5)	9 (4)	11 (3)	.23	.66
M4	58 (25)	46 (20)	81 (25)		
M5	37 (16)	29 (12)	52 (16)		
M6	6 (2)	10 (4)	13 (4)		
M7	4 (2)	1 (0.4)	4 (1)		
Cytogenetics, n (%)	n = 125	n = 115	n = 126	—	—
Good	21 (17)	15 (13)	21 (17)	—	—
Intermediate	95 (76)	93 (81)	96 (76)	—	—
Poor	9 (7)	7 (6)	9 (7)	.65	1
Interval diagnosis-CR1, d (range)	40 (12-305)	43 (17-480)	41 (17-432)	.34	.96
Interval CR1-transplantation, d (range)	99 (13-369)	94 (11-2375)	97 (12-594)	.29	.37
TBI, %	45	57	37	.005	.06
NCs infused, × 10^8/kg (range)	2 (0.17-2.7)	3.68 (2.7-29)	9.3 (2.2-77)	—	—
aGVHD grades II-IV, %	38	35	36	.5	.61
aGVHD grades III-IV, %	13	9	12	.18	.64
Follow-up, mo (range)	33 (1-79)	35 (1-81)	16 (1-72)	—	—

NC indicates nucleated cells; —, not applicable.

Results

Patient populations in relation to hematopoietic stem cell doses infused and univariate analyses

The outcome was identical when comparing BM and PB transplantations: At 2 years, the TRM with BM and PB was 22% ± 2% and 22% ± 2% ($P = .98$), the RI 19% ± 2% and 22% ± 3% ($P = .61$), the LFS 63% ± 2% and 61% ± 3% ($P = .72$), and the OS 66% ± 2% and 66 ± 3% ($P = .82$), respectively.

The BM cell dose ranged from 0.17 to 29 × 10^8/kg recipient weight with a median of 2.7 × 10^8/kg. The PB cell dose ranged from 2.2 to 20 × 10^8/kg with a median of 9.3 × 10^8/kg.

There was no difference for outcome when taking the median dose of PB cells infused as a cutoff within the PB group: The 3-year LFS was 64% ± 6% in patients receiving doses below the median and 59% ± 7% for those receiving doses above the median ($P = .76$). For patients receiving BM, the median dose (2.7 × 10^8/kg) gave the greatest discrimination for all end points studied.

We therefore studied 3 populations of patients: those receiving higher doses (above median) of marrow (n = 257), those receiving lower (below median) doses of marrow (n = 258), and those receiving PB whatever the dose (n = 366).

Table 1 gives the distribution of the 3 groups for disease and transplantation characteristics; the only differences concerned the year of transplantation, which was more recent for PB, and more TBI and a trend for fewer female donor–to–male recipient combinations in the group receiving higher doses of BM.

The distribution was even for patient age and sex, white blood cell count at diagnosis, FAB classification, and pretransplantation intervals.

Information on cytogenetics was available for 366 patients. In keeping with our previous work,[24] 57 patients were in the good-risk category (t(15;17), t(8;21) and inv16), 25 in the poor-risk category (abnormality 5 or 7, 11q−), and 284 in the intermediate-risk category. The number of missing values was too high to include cytogenetics in the multivariate analysis. However, the distribution by cytogenetics over the 3 groups of patients was even.

Recovery of polymorphonuclear cells (PMNs) to 500/mm^3 with high-dose BM, low-dose BM, and PB occurred at days 18 (range, days 10-39), 19 (range, days 10-53), and 14 (range, days 10-42), respectively. The differences were statistically significant between rich and poor BM ($P = .009$) and PB and poor BM or rich BM ($P < 10^{-4}$ for both). Recovery of platelets to 50 000/mm^3 with high-dose BM, low-dose BM, and PB occurred at days 24 (range, days 12-385), 27 (range, days 12-263), and 17 (range, days 7-343), respectively. The differences were statistically significant between rich and poor BM ($P = .02$), PB and poor BM ($P = .0002$) or rich BM ($P < 10^{-4}$).

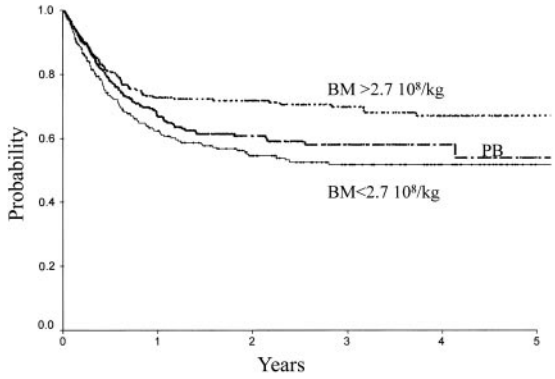

Figure 1. LFS of patients receiving transplants with high-dose BM, low-dose BM, or PB.

Table 2 indicates the outcome at 2 years in these 3 groups of patients. The LFS was 72% ± 3% with the high BM dose versus 54% ± 3% with the low BM dose ($P = .0007$) and 61% ± 3% with PB ($P = .04$; Figure 1). The TRM (Figure 2) and the RI (Figure 3) were lower with the high BM dose compared to the low BM dose (TRM, 17% ± 2% versus 27% ± 3%, $P = .02$; RI, 14% ± 2% versus 25% ± 3%, $P = .02$). The incidence of aGVHD was similar in the 3 groups. Patients receiving PB had the highest incidence of cGVHD evaluated at 1 year (50% ± 4%) over low-dose BM (43% ± 5%, $P = .002$) and high-dose BM (40% ± 5%; $P = .0006$).

Table 3 lists prognostic factors other than cell dose influencing outcome. Not surprisingly, a younger age for the patient and for the donor, a short interval from diagnosis to CR1 (rapid remitters), and a short interval from CR1 to transplantation were all significantly associated with a lower TRM. A female donor–to–male recipient combination resulted in a higher TRM. aGVHD (score II and over) resulted in higher TRM, lower RI, and lower LFS and OS. Of particular interest was the confirmation of the existence of a center effect affecting TRM, LFS, and OS, but not RI, as we previously reported.[23]

Table 4 gives the causes of death.

Multivariate analyses

There was no difference between PB and low-dose BM in terms of TRM, RI, LFS, and OS. In contrast, high-dose BM compared to PB was associated with lower TRM (Figure 2; RR = 0.61; 95% CI, 0.39-0.98; $P = .04$), better LFS (Figure 1; RR = 0.65; 95% CI, 0.46-0.91; $P = .013$), and better OS (Figure 4; RR = 0.64; 95% CI, 0.44-0.92; $P = .016$). No significant association was found for RI (Figure 4). Marrow at low and high dose induced less cGVHD than PB (low-dose BM versus PB, $P = .006$; high-dose BM versus PB, $P = .003$).

Table 2. Outcome of patients by source and dose of nucleated cells/kg infused

	BM, %*			*P*	
	NC less than 2.7 × 10^8/kg	NC more than 2.7 × 10^8/kg	PB, %*	PB vs BM less than 2.7 × 10^8/kg	PB vs BM more than 2.7 × 10^8/kg
2-y outcome					
LFS	54 ± 3	72 ± 3	61 ± 3	.17	.04
RI	25 ± 3	14 ± 2	22 ± 3	.23	.17
TRM	27 ± 3	17 ± 2	22 ± 2	.23	.17
OS	58 ± 3	74 ± 3	66 ± 3	.08	.14
1-y cGVHD	43 ± 5	40 ± 5	50 ± 4	.002	.0006

*Values given as mean ± SD.

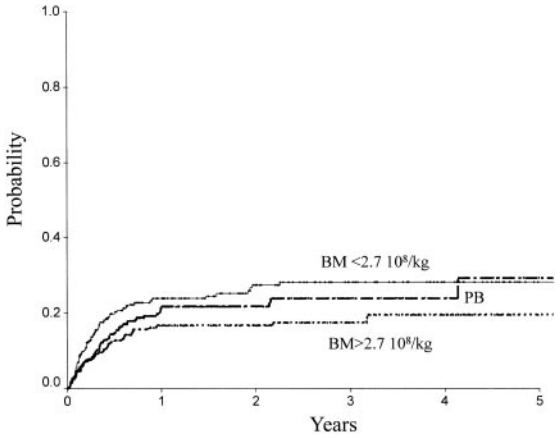

Figure 2. TRM of patients receiving transplants with high-dose BM, low-dose BM, or PB.

None of the other studied factors (patient and donor age and sex, female donor to male recipient, year of transplantation, and use of TBI) influenced any component of the outcome.

Discussion

In the past 5 years several prospective randomized studies have compared BM and PB as alternative sources of stem cells for allogeneic stem cell transplantation using HLA-identical siblings.[7-10] Conclusions from these studies have been that PB is associated with faster engraftment, similar or greater incidence of aGVHD, and higher incidence of cGVHD. LFS and OS have been found identical or even better with PB.[11] All these studies have combined transplantations for several hematologic malignancies. A more limited number of retrospective studies have suggested poorer results with PB in more risky situations, such as with mismatched related donors,[25] unrelated donors,[26] or more advanced diseases. Also, it has been recently suggested that results may vary for different diseases, with the observation in transplantations using unrelated donors of similar outcome with BM and PB in AML contrasting with a worse outcome with PB in acute lymphocytic leukemia (ALL).[26]

The minimum doses of cells to ensure safe engraftment have been established very early with the development of BM and then PB transplantation. For allogeneic stem cell transplantation, it is generally accepted that a BM graft should contain more than 2×10^8 nucleated cells/kg and a PB graft (as initially defined in the setting of autologous PB stem cell transplantation) more than 2 or even better 5×10^6 $CD34^+$ cells/kg. These thresholds have been established from observations on the kinetics of engraftment and, with PB, infusion of doses more than 5×10^6 $CD34^+$ cells/kg has been shown not to further reduce the duration of aplasia. Only recently, however, has attention focused on the possibility that increasing the doses of stem cells above these thresholds might not only reduce the TRM but also and more unexpectedly reduce the relapse/progression rate of the underlying disease. In the field of AML specifically, in the context of autologous BM transplantation with BM purged by mafosfamide, the dose of stem cells infused has been identified as an important prognostic factor for outcome.[15-19] Modeling of prognostic groups for LFS generated 3 groups of patients.[18] The best one consisted of patients who received a stem cell dose evaluated before purging in granulocyte-macrophage colony-forming units (CFU-GMs)/kg (agar cultures with placenta conditioned medium and no cytokines) over the median ($> 5.46 \times 10^4$/kg) and an actual residual CFU-GM dose evaluated after mafosfamide purging below the median ($< 0.02 \times 104$/kg); in this group the LFS at 12 years was 70% with a 2% TRM. More recently, with PB autologous transplantation in AML, the EORTC-GIMEMA group (AML 10 study) reported on an increase in relapse incidence following autografting with PB, linked to higher doses of $CD34^+$ cells infused[27] but in a subsequent paper[28] linked this observation to the presence in the graft of large amounts of leukemic $CD34^+$ cells. In patients over 60 years of age, receiving autografts for AML in CR1, high-dose PB and BM infusion were associated with a lower RI than low-dose PB.[19] Following allogeneic BM transplantation with an HLA-identical twin or sibling[29,30]

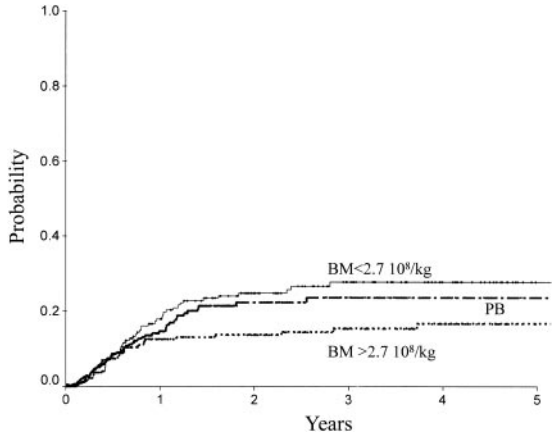

Figure 3. RI of patients receiving transplants with high-dose BM, low-dose BM, or PB.

Table 3. Prognostic factors other than cell dose influencing outcome, *P* (log-rank test)

	LFS	RI	TRM	OS
Patient sex	.91	.89	.78	.53
Donor sex	.86	.1	.09	.68
Female to male	.54	.1	.02†	.15
FAB M5 versus other	.88	.83	.98	.7
TBI	.72	.79	.48	.57
Patient age	.06	.86	.007†	.02†
Donor age	.009†	.28	.01†	.012†
Year of transplantation (before 1997 versus after 1997)	.26	.16	.79	.92
Interval diagnosis-CR1, d	.08	.88	.03†	.02†
Interval CR1-transplantation, d	.16	.52	.02†	.14
White blood cell count at diagnosis	.94	.82	.77	.51
Center*	.02†	.22	.03	.01†

*One class grouping all centers performing fewer than 10 transplantations during the period.

†Significant difference.

Table 4. Causes of death

	BM		
	NC less than 2.7×10^8/kg, %	NC more than 2.7×10^8/kg, %	PB, %
Failure/rejection	2	0	2
Infection	21	16	14
Interstitial pneumonitis	2	13	7
GVHD	28	21	31
Leukemia	43	45	40
Other	4	5	6

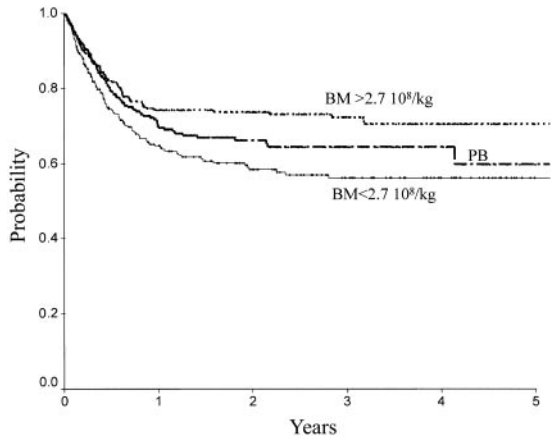

Figure 4. OS of patients receiving transplants with high-dose BM, low-dose BM, or PB.

for various hematologic malignancies, a greater dose of nucleated or progenitor $CD34^+$ cells has been shown to reduce fungal infections and TRM and to result in a better OS. As an example in 212 patients who received a transplant of an unmanipulated graft from an HLA-identical sibling donor,[30] 5-year survival and 180-day TRM were, respectively, 64% and 19% for patients receiving a $CD34^+$ cell dose of 3×10^6/kg or more and 40% and 37% for the other. EBMT similarly has recently reported on the impact of the dose of BM on the outcome of patients receiving allotransplants for AML with a geno-identical family donor; higher doses of cells infused expressed in nucleated cells/kg (above median value) not only were associated with a lower TRM but also with a reduced RI, with no effect on GVHD.[14] In high-risk patients, the Seattle group, studying transplantation with unrelated donors, made similar observations,[13] that is, an increase in LFS with higher stem cell doses due mainly to a reduction in TRM but also at least in part to an enhanced graft-versus-leukemia (GVL) effect. To explain the reduced RI in relation to the higher dose of cells infused, 2 mechanisms have been proposed, a stem cell competition effect whereby an expanded normal stem cell pool might have a growth advantage over the minimal residual tumor population, and higher numbers of lymphocytes infused with the richer stem cell graft inducing more GVL, both effects possibly combining.

PB grafts contain 5 to 10 times more nucleated cells and about 10 times more T lymphocytes than BM grafts.[12] PB following mobilization with granulocyte colony-stimulating factor (G-CSF) has more T polarized cells (Th2) with anti-inflammatory cytokines (hence supposedly the absence of more GVHD, as initially feared),[31] and more $CD14^+$ cells. In contrast, mesenchymal cells are present only in BM (approximately $1/10^4$ BM cells/kg) and virtually absent in mobilized PB.[32] Richer marrows may contain higher doses of mesenchymal stem cells. Other types of accessory cells also may be differently distributed in the 2 products and there may be so far unforeseen advantages in using BM, or even combining BM and blood. Allografting with PB is associated not only with better kinetics of engraftment but also more rapid immune reconstitution.[12] Despite an increase in cGVHD and a questionable increase in aGVHD with PB, which would favor the use of BM, PB tends presently to be preferred by many teams, but the general assumption is that most of its benefit comes from the higher stem cell dose infused. However, in all studies comparing PB to BM the dose of BM infused never has been considered. In addition, in all studies comparing PB to BM, the median number of BM nucleated cells infused was lower than in the present study. In this respect this study may be of importance because it draws attention to the fact that infusion of rich BM during allogeneic stem cell transplantation from an HLA-identical sibling gives a better outcome than PB, whereas low-dose BM and PB are equivalent. Previous studies comparing PB to BM not only have not taken into account the doses for BM, but also have mixed several diseases and disease status. Because the present study is homogeneous in that it concerns only patients with AML in CR1, the present finding may not necessarily apply to other hematologic malignancies or more advanced stages of AML.

Appendix

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