Filgrastim-mobilized peripheral blood progenitor cells versus bone marrow transplantation for treating leukemia: 3-year results from the EBMT randomized trial

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Background and Objectives. Allogeneic peripheral blood progenitor cells (PBPC) are now widely used as the source of hematopoietic stem cells for transplantation. However, it is still not clear which patients should receive mobilized PBPC or bone marrow cells to reconstitute hematopoiesis after myeloablative conditioning. The aim of this study is to present 3-year-follow-up data on outcome (incidence and severity of chronic graft-versus-host disease (GVHD), overall survival (OS) and leukemia-free survival (LFS) after a PBPC transplant (PBPCT) or a bone marrow transplant (BMT).

Design and Methods. Data on 350 patients with leukemia were collected in a multicenter, randomized study initiated by the EBMT. The patients were randomized to receive filgrastim-mobilized PBSCT or BMT from an HLA-identical donor.

Results. At a median follow–up of 3 years, significantly more patients transplanted with PBPC than with bone marrow developed chronic GVHD (73% vs 55%, p=0.003) and extensive chronic GvHD (36% vs 19%, p=0.002). The higher incidence and greater severity of chronic GvHD had little impact on the patient's performance status or survival. OS was 58% for PBPCT recipients versus 65% among those undergoing BMT. LFS was 56% for PBPCT recipients versus 60% for BMT recipients.

Interpretation and Conclusions. Patients transplanted with PBPC from an HLA-identical sibling develop more chronic GvHD than those transplanted with bone marrow, but the final impact of this difference is unclear. Longer follow-up is necessary to characterize the impact of chronic GvHD on quality of life, leukemia-free survival and overall survival.

Key words: allogeneic transplantation, leukemia, PBPCT, BMT.

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Approximately half of all allogeneic transplants from HLA-identical family donors worldwide were accomplished using hematopoietic stem cells harvested from peripheral blood (PB), even before the results of the large randomized trials comparing this new source of allogeneic hematopoietic stem cells with bone marrow (BM) became available.[1] Randomized studies from the US, Canada, France, and the European Group for Blood and Marrow Transplantation (EBMT)[2-5] showed that peripheral blood progenitor cell transplantation (PBPCT) resulted in significantly faster hematopoietic recovery than that following bone marrow transplantation (BMT), but results of other important endpoints differed. The incidence and severity of acute graft-versus-host disease (GvHD) were found to be virtually identical after transplantation of blood or marrow in all except the EBMT study, which reported significantly more GvHD in recipients of PB cells. Chronic GvHD was more severe and occurred significantly more often after PBPCT in the EBMT and French studies, while no apparent differences were seen in patients treated in the US and Canada. Overall survival after PBPCT or BMT did not significantly differ in either the EBMT or the French study. However, the US study showed a trend (p= 0.06) in favor of PBPCT and the Canadian study reported a significant improvement of survival when PB cells were used as the source of hematopoietic stem cells. With such divergent results, it is still not clear which patients should receive mobilized blood or bone marrow cells to reconstitute hematopoiesis after myeloablative conditioning. We report the 3-year follow-up of the largest published study, describing the evolution of chronic GvHD and other important outcome parameters.

Design and Methods

Study design

This was a multicenter, prospective, randomized study initiated by the EBMT, with 350 patients randomized between 13 February 1995 and 2 September 1999. Details of the design and the first analysis of the study results have been published previ-

ously.[5] Here we present the results of a planned follow-up study performed at a median of 3 years after transplantation. The study was approved by the institutional review board or ethics committee of each of the participating institutions and all donors and patients gave written informed consent.

Patients

Patients eligible for enrollment were women and men aged 18 to 55 years with a diagnosis of *de novo* acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) in first or second remission, or first untreated relapse with a blast marrow count <30%; chronic myeloid leukemia (CML) in first chronic or accelerated phase, or myelodysplastic syndromes (MDS), excluding patients with refractory anemia with excess of blasts in transformation. Ninety-eight percent of patients transplanted were classified as good-risk patients (defined as patients with CML in first chronic phase; AML in first or second remission; ALL in first or second remission; or MDS). The remaining patients, who had accelerated CML, were classified as poor risk. Each patient had an HLA-identical sibling donor aged 16 to 60 years and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Patients were not eligible for the study if they had inadequate organ function, were HIV-positive, had a history of splenectomy or splenic irradiation, or had previously undergone PBPCT or BMT.

Conditioning therapy for patients consisted of total body irradiation (TBI) and standard doses of cyclophosphamide, melphalan, or etoposide. Transplant centers without access to irradiation facilities or which preferred a regimen not based on TBI were allowed to use the combination of busulfan (16 mg/kg) and cyclophosphamide (200 mg/kg). Patients received filgrastim (5 μg/kg/day) post-transplant until their absolute neutrophil count (ANC) was 10×10^9/L on a single day or 1.0×10^9/L for 3 consecutive days. Filgrastim was stopped at day 28 regardless of ANC.

Diagnosis, prophylaxis, and treatment of GvHD

Acute and chronic GvHD were diagnosed according to the criteria proposed by Glucksberg[6] and Shulman.[7] Prophylaxis for acute GvHD consisted of cyclosporine starting on day -1 and continuing until day +180 (monitored by measurement of blood levels) and intravenous methotrexate on days +1, +3, and +6. The study protocol stipulated intravenous or oral methylprednisolone for treatment of acute GvHD grades 2 to 4. No other recommendations were made.

Collection of hematopoietic stem cells from normal donors

Donor requirements and collection procedures have been reported elsewhere in detail.[8] Briefly, normal donors in the PBPC group received subcutaneous injections of filgrastim (10 μg/kg/day) for 4 or 5 consecutive mornings to mobilize PBPC. During leukapheresis, 10 L of blood were passed through an automated continuous-flow, blood-cell separator to collect a target of 4×10^6 $CD34^+$ cells/kg. The leukapheresis product was kept overnight at 4°C and infused into the patient the next morning, together with a second harvest if necessary. Normal donors in the BMT group had marrow harvested from both posterior iliac crests under general anesthesia, according to standard institutional procedures. At least 2×10^8 nucleated cells/kg were required from each harvest. The unmanipulated marrow was immediately infused into the patient through a central venous catheter.

End-points considered at the 3-year follow-up

The end-points considered at 3 years were the incidence and severity of chronic GvHD, overall survival (OS), and leukemia-free survival (LFS). Each patient's status with regards to chronic GvHD was recorded at day 100 and at months 6, 12, 24 and 36. OS was calculated as the number of months from transplant to death and LFS was calculated as the number of months from transplant to the earlier of either leukemia recurrence or death. Patients who remained alive at the study censor date (31 August 2002) were censored at this time.

We investigated whether any of the patient's characteristics or type of treatment predicted survival and we explored the relationships among these predictors.

Statistical methods

The Kaplan-Meier estimate of the percentage of patients with chronic GvHD at 3 years, and extensive chronic GvHD at 3 years was calculated for each treatment group from the patients who survived beyond 100 days after the transplant. The time to chronic GvHD and extensive chronic GvHD were compared between the treatment groups using the log-rank test at a significance level of 0.05. In addition, the cumulative incidence of chronic GvHD was estimated in a competing risks context in which death was included as the competing risk.

The estimates of OS and LFS at 3 years were also calculated using Kaplan-Meier methods from patients who received a transplant. These were compared between the treatment groups by using the log-rank test and by estimating the hazard ratio and 95% confidence interval (CI). Cox proportional hazards regression analysis was used to identify predictors of overall survival. A multivariate model was constructed using baseline predictors that were significantly associated with overall survival in a univariate analysis. Entry to the multivariate model was allowed when the univariate analysis for a predictor showed a significance of < 0.05. This model was verified by using a forward and

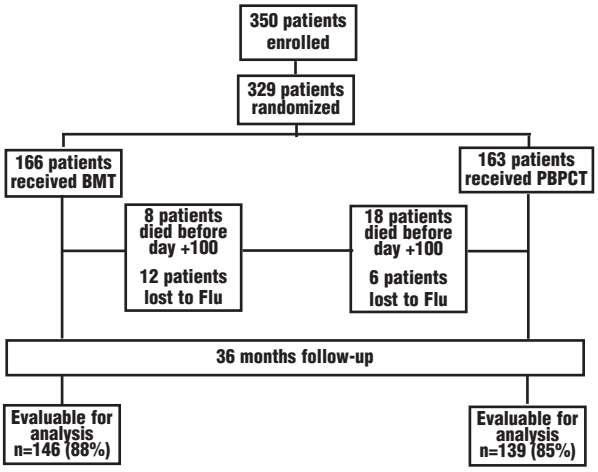

Figure 1. Patient accountability.

backward selection procedure. Interactions between significant predictors of overall survival and treatment group were explored and were considered significant at the α=0.1 level.

Results

Patients

Of the 329 patients who actually received a transplant (PBPCT in 163 patients, BMT in 166 patients), 18 patients (5%) were lost to follow-up (6 PBPCT, 12 BMT); that is, they were last reported alive less than 33 months after their transplant. Among those remaining, 285 patients (87% of all 329 patients) survived beyond 100 days after transplantation (139 PBPCT, 146 BMT) and were evaluable for this analysis. The duration and pattern of follow-up were similar for the patients receiving PBPCT and those receiving BMT (Figure 1).

Chronic graft-versus-host disease

Significantly more patients in the PBPCT group than in the BMT group had any chronic GvHD at some point during the 3-year follow-up: 73% (95% CI: 65%-81%) versus 55% (95% CI: 46%-63%) (p=0.003) (Figure 2). Extensive chronic GvHD at 3 years was also significantly more common in the PBPCT group than in the BMT group: 36% (95% CI: 28%-45%) versus 19% (95% CI: 12%-25%) (p=0.002) (Figure 3). An estimate of the cumulative incidence of chronic GvHD at 36 months in the competing risks context also showed that this incidence was higher among the PBPC recipients than in the BMT group (60% versus 46%). Progressive, quiescent, and *de novo* chronic GvHD were found at similar rates at 3 years in patients transplanted with blood and those transplanted with bone marrow (Table 1). ECOG performance status and the most recent platelet counts were also similar between the two groups (Table 1).

Table 1. Performance status, platelet count, and chronic GvHD at the 36-month follow-up.

	PBPC	*BMT*
Number of patients	163	166
Alive at follow-up	94 (58%)	108(65%)
ECOG Performance Status		
0	60 (64%)	67 (62%)
1	23 (24%)	25 (23%)
2	6 (6%)	2 (2%)
3	1 (1%)	3 (3%)
Missing	4 (4%)	11 (10%)
Platelet count ($\times 10^9$/L)		
N	78	91
Median	228	207
Range	21.9, 563	3.4, 461
Plt < 100×10^9/L	3 (4%)	5 (5%)
Plt < 50×10^9/L	1 (1%)	2 (2%)
Chronic GvHD		
Any type	97	75
de novo	22 (23%)	14 (19%)
Quiescent	32 (33%)	29 (39%)
Progressive	43 (44%)	32 (43%)

Causes of death

Overall, 127 (39%) of the 329 patients initially enrolled have died; 58 patients (35%) in the BMT group and 69 patients (42%) in the PBPCT group. The primary causes of death were similar in both groups (p=0.33) (Table 2). Thirty-seven patients were reported as having died from relapse; 23 patients (33%) after PBPCT and 14 patients (24%) after BMT. We retrospectively looked at the karyotypes of patients with AML and ALL, because 21 patients (AML, n=12; ALL, n=9) in the PBPCT group but only 10 patients (AML and ALL, 5 patients each) in the BMT had relapsed. Karyotypes were available for 136 of 172 patients (79%) with acute leukemias. One of us (*BS*) classified patients with abnormal karyotypes into good, intermediate, or poor-risk.[9-11] No obvious differences were found to explain the higher number of relapses seen after PBPCT.

Overall survival and leukemia-free survival

There were no significant differences in OS or LFS between the PBPCT and BMT groups. At 3 years, 202 patients were alive, of whom 108 patients in the BMT group and 94 patients in the PBPCT group. The 3-year OS rate was 58% (95% CI: 50% - 66%) for patients in the PBPCT group and 65% (95% CI: 57% - 72%) for patients in the BMT group (Figure 4). The estimated hazard of death for patients in the PBPCT group was 1.26 times that for patients in the BMT group (95% CI:

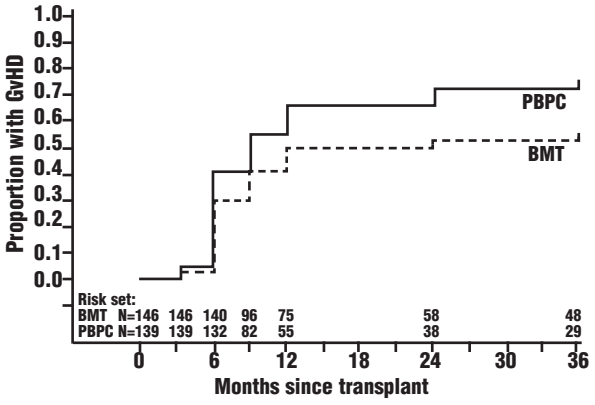

Figure 2. Time from transplant to onset of chronic GvHD among patients treated with filgrastim-mobilized peripheral blood progenitor cells (n = 102) or bone marrow (n=80). Hazard ratio = 1.69 (95% CI:1.20, 2.38).

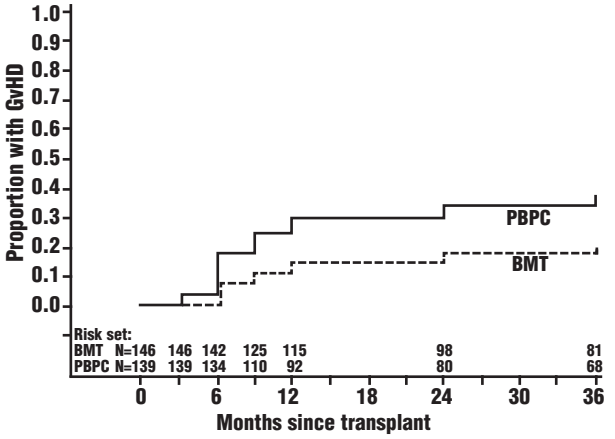

Figure 3. Time from transplant to onset of extensive chronic GvHD among patients treated with filgrastim-mobilized peripheral blood progenitor cells (n = 50) or bone marrow (n = 28). Hazard ratio = 2.22 (95% CI:1.34, 3.65).

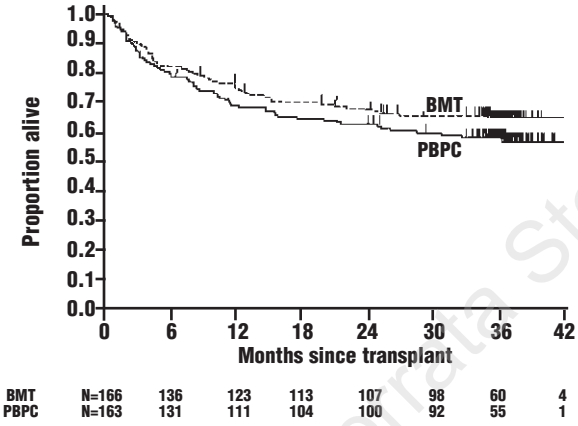

Figure 4. Three-year overall survival among patients treated with filgrastim-mobilized peripheral blood progenitor cells (n = 163) or bone marrow (n = 166; intent-to-treat population).

Table 2. Causes of death.

	PBPC	*BMT*
Number of Patients	163	166
Dead	69 (42%)	58 (35%)
Cause of Death		
Infection/Sepsis	22 (32%)	16 (28%)
Relapse	23 (33%)	14 (24%)
GvHD	14 (20%)	11 (19%)
Organ Failure	7 (10%)	8 (14%)
Hemorrhage	2 (3%)	7 (12%)
Other	1 (1%)	2 (3%)

0.89, 1.79; p=0.19).

Patients in the PBPCT group had a 3-year LFS rate of 56% (95% CI: 49-64%), compared to 60% (95% CI: 52-67%) for patients in the BMT group (Figure 5). The estimated hazard of leukemia or death for patients in the PBPCT group was 1.17 times that for patients in the BMT group (95% CI: 0.84 to 1.63; p=0.36).

Patients' characteristics as predictors of survival

Of the characteristics analyzed, only diagnosis (p=0.0001) and the patient's age (p=0.03) were found to be independent predictors for overall survival in a univariate analysis. After fitting terms for diagnosis and patient's age into a multivariate model, these predictors remained significant (p=0.0001 and p=0.01, respectively). No other variables were found to predict survival in either a forward or backward selection procedure. In particular, no significant difference in survival was related to the type of transplant received (p=0.11), and no interactions between these predictors and type of transplant were identified. OS and LFS differed significantly among patients with different diagnoses, but not for risk status. Both survival rates were highest for patients with CML, followed by patients with AML, MDS, and ALL (Tables 3 and 4). No statistically significant differences in OS or LFS were seen between patients with good-risk or poor-risk disease. The estimated hazard of death for good-risk patients was 1.26 times that for poor-risk patients (95%CI:0.61, 2.61; p=0.53), and the estimated hazard of leukemia or death in good-risk patients was 1.19 times that in poor-risk patients (95%CI: 0.58, 2.45; p=0.64). However, only 19 patients were classified as poor-risk patients compared to 245 patients who were classified as good-risk (*data*

Table 3. Overall survival by diagnosis.

	ALL	MDS	AML	CML
Number of patients	55	10	117	147
Percent (95% CI) alive*				
1 year	52 (39, 66)	50 (19, 81)	73 (65, 81)	80 (73, 86)
3 years	37 (24, 50)	38 (6, 69)	63 (54, 72)	71 (63, 78)
Significance°		p=0.0001		
Hazard Ratio	2.68	2.75	1.29	1.0
95% CI	(1.71, 4.19)	(1.17, 6.47)	(0.85, 1.97)	

Kaplan-Meier estimate; °assessed using a Cox proportional hazards model.

Table 4. Leukemia-free survival by diagnosis.

	ALL	MDS	AML	CML
Number of subjects	55	10	117	147
Percent (95% CI) Alive*				
1 year	51 (38, 64)	50 (19, 81)	69 (61, 78)	77 (70, 84)
3 years	32 (20, 45)	40 (10, 70)	60 (51, 68)	68 (60, 75)
Significance°		p=0.0001		
Hazard Ratio	2.69	2.46	1.33	1.0
95% CI	(1.75, 4.14)	(1.05, 5.75)	(0.89, 1.99)	

Kaplan-Meier estimate; °assessed using a Cox proportional hazards model.

not shown). Patient's age was also a predictor of OS. Patients aged 40 years or older had a 3-year survival of 37%, compared to 71% for patients younger than 40 years. The estimated hazard of death for patients age 40 years or more was 1.47 times higher than for patients aged younger than 40 years (95% CI: 1.04-2.08).

The severity of acute GvHD was inversely related to survival. The 3-year survival was 56% for patients with more severe acute GvHD (grade 2 or higher) and 65% for patients with acute GvHD of less than grade 2. The estimated hazard of death for patients with acute GvHD grade 2 or higher was 1.48 times higher than for patients with lower grades of acute GvHD (95% CI: 1.05 - 2.10).

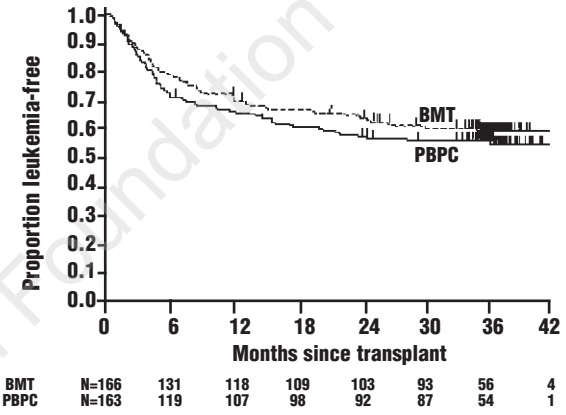

Figure 5. Three-year leukemia-free survival among patients treated with filgrastim-mobilized peripheral blood progenitor cells (n = 163) or bone (n = 166; intent-to-treat population).

Discussion

Leukemia patients who receive a PBPC transplant from an HLA-identical sibling donor developed significantly more chronic GvHD than recipients of BM transplants in this study, regardless of whether the overall incidence of GvHD or only extensive disease is considered. This finding is consistent with our previous report[5] and a recent follow-up of the French randomized study.[12] It also confirms a trend observed by other recent studies.[3,13,14] Nonetheless, the higher rate of GvHD does not predict lower survival. This study, as well as follow-up studies from the randomized US, French, and Norwegian studies, showed no significant differences in overall and leukemia-free survival of patients transplanted with PBPC or BM.[12,13,15]

Interestingly, neither the US and French studies[12,15] nor the EBMT study[5] found significant differences in the mode of onset of chronic GvHD, the pattern of organ involvement, or the performance status of patients at last follow-up, which might be considered indicators of the quality of life after transplantation. It is also remarkable that the higher incidence and increased severity of chronic GvHD after PBPCT did not result in an obvious increase of severe and fatal infections. All three available follow-up reports of the large randomized studies report very similar numbers of deaths overall[5,12] or in patients with extensive chronic GvHD[15] after PBPCT or BMT. There is no indication that the numbers of fatal infections or any other cause of death was significantly increased after PBPCT. However, the US authors[15] observed that chronic GvHD occurring after PBPCT may run a more protracted clinical course and be less responsive to current treatments than chronic GvHD occurring after BMT. Of course, it remains to be seen whether chronic GvHD will adversely affect long-term survival and quality of life or whether the higher incidence and severity of chronic GvHD will finally be associated with lower relapse rates after PBPCT. Surprisingly, follow-up reports of this and other randomized trials do not support the latter expectations, raised by experimental data[16] and smaller randomized[13,17] and non-randomized studies.[18] In our study, in which predominantly good-risk patients were enrolled, much longer observation periods may be necessary before any differences become evident. To date, how-

ever, not even a trend in this direction appears in our data. Studies which involve more patients with poor-risk characteristics may be more suitable for resolving this aspect.

We conclude that transplantation of PBPC instead of BM into HLA-identical siblings results in more chronic GvHD. To date, this has not reduced the incidence of relapses seen after PBPCT, but neither has it adversely affected OS or LFS. A recent meta-analysis including updated information from all 9 randomized trials performed with unmanipulated PBPC or BM cells (*unpublished data*) confirms these conclusions. Further follow-up of all randomized trials is mandatory in order to compare the impact of allogeneic PBPCT and BMT. Late effects, some of which have been correlated with the occurrence of chronic GvHD after transplantation, may not become evident until many years after grafting.[19] It is also important to note that the patients enrolled into the randomized trials were all transplanted from HLA-identical sibling donors and, with few exceptions, suffered from acute leukemia or CML. As results of PBPCT and BMT may give different results in different diseases,[20,21] randomized trials should also be performed in patients with alternative donors and other diagnoses, such as lymphoma, myeloma, or aplastic syndromes.

NS, JA, EG, AG were actively involved in the planning, conduct and analysis of the study. MB, AnB, TR, AN, NR, JS, KB, AgB enrolled patients in the study, helped with analysis of the data, contributed to and approved the manuscript. BS did the classification of cytogenetic data attributing patients to good, intermediate, or high-risk cytogenetic categories. JM was the responsible statistician for the study.This study was sponsored by Amgen, Thousand Oaks, California, and by F Hoffmann La Roche, Basle, Switzerland.

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