Chronic graft-versus-host disease after allogeneic blood stem cell transplantation: long-term results of a randomized study

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The use of peripheral blood stem cells (PBSCs) is rapidly growing in the allogeneic transplantation setting as an alternative to bone marrow (BM). We previously reported a higher incidence of chronic graft-versus-host disease (cGVHD) associated with allogeneic PBSC transplantation in a randomized trial. In this follow-up report, we analyzed the evolution of cGVHD in the patients (n = 101) enrolled on this study. At a median follow-up of 45 months (range, 31-57 months), we found that the 3-year cumulative incidence of cGVHD was 65% (95% confidence interval [CI] 51%-78%) in the PBSC group and 36% (95% CI 23%-49%) in the BM group (*P* = .004). We also found that extensive cGVHD was more frequent in the PBSC group (44% [95% CI 30%-58%] vs 17% [95% CI 7%-27%]; *P* = .004). The prevalence of cGVHD was always higher in the PBSC arm. Ocular involvement was more frequent in PBSC recipients (*P* = .02). Cutaneous and liver involvement was similar among BM and PBSC recipients. Chronic GVHD required multiple courses of immunosuppressive therapy in addition to cyclosporine and corticosteroids during longer periods (*P* = .03). Altogether, this translated into longer periods of hospitalization after transplantation in the PBSC group (*P* = .04). Finally, we also confirm that cGVHD after PBSC transplantation is associated with an antileukemic effect that is at least as potent as after BM. However, to date, this has not translated into a survival difference, possibly due to the early-stage leukemic status of these patients or to the relatively small size of the study population. (Blood. 2002;100: 3128-3134)

Introduction

Peripheral blood stem cells (PBSCs) have become the preferred source for autologous transplantation due to the ease of collection, faster hematopoietic recovery, and economic advantages.[1,2] Based on similar positive initial findings, the use of PBSCs as an alternative to bone marrow (BM) has rapidly grown in the allogeneic setting.[3-14] However, the use of PBSCs for allogeneic transplantation is still not universally accepted. This is in part due to unresolved concerns about the long-term effects of growth factor treatment in healthy volunteers and uncertainty about whether this stem cell source is associated with more acute and chronic graft-versus-host disease (aGVHD and cGVHD, respectively). Compared with BM, PBSC grafts contain significantly more total blood cells and more $CD34^+$ cells. However, the most striking difference is the 10-fold higher number of T cells in the PBSC graft. Other differences include a higher number of monocytes[13] and the absence of mesenchymal stem cells.[15]

In 1996, the centers affiliated with the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) conducted a prospective randomized trial comparing allogeneic PBSCs with BM. It showed that there was faster platelet and neutrophil recovery in the PBSC arm but also an increased incidence of cGVHD.[13] Since this report, 5 other similar prospective comparisons have been published.[10-12,14,16] They all confirm that the use of PBSCs is associated with faster hematologic recovery but have yielded differing results regarding the incidence of aGVHD and cGVHD. All but one[17] found no difference in the incidence of acute graft-versus-host disease (aGVHD). The issue of chronic GVHD also was unclear. A number of reports, including randomized studies, have reported a higher incidence of cGVHD among recipients of allogeneic PBSCs.[11,13,16,18] However, follow-up has been relatively short in the studies reported to date, and cGVHD was a not a primary end point of any of the reported trials. Thus, the issue of whether the use of PBSCs instead of BM resulted in a different occurrence of cGVHD remains unresolved. In this study, representing a long follow-up cohort, we report an analysis of factors associated with cGVHD in patients included in our randomized study and evaluable for cGVHD.

Patients and methods

Study design

Details of the study design, patient eligibility, preparative regimen, stem cell collection and reinfusion, supportive care, primary study end points,

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and economic evaluation have been previously reported.[13] Written informed consent was obtained from each patient and donor, and the study was approved by the scientific committee of the SFGM-TC and the local ethical committee of Marseille II (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale—CCPPRB). Stratification by center occurred at randomization to ensure a balanced treatment of all aspects of transplantation and, notably, GVHD management in both groups. The comparison of cGVHD was one of the secondary end points of the original randomized trial. Briefly, in the PBSC group, mobilization consisted of daily subcutaneous administration of lenograstim at a dose of 10 μg/kg. According to current practice in France at the time of this study, prophylactic granulocyte colony-stimulating factor (G-CSF) after transplantation was not allowed per protocol in either of the 2 groups. The study was a multicenter, randomized, comparative trial performed between September 1996 and October 1998 in 17 centers affiliated with the SFGM-TC. By October 1998, 111 patients had been randomized, with 101 patients proceeding to transplantation.

GVHD prophylaxis

All patients received cyclosporine and methotrexate (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3 and 6) as GVHD prophylaxis.[19] Within each center, a uniform protocol for methotrexate dose reduction was applied in both arms for mucositis, hyperbilirubinemia, renal insufficiency, or effusions. Cyclosporine was started intravenously on day −1, usually at the dosage of 2 to 3 mg/kg, and switched to oral formulation as soon as the patient was able to take medication after engraftment. The dosage was adjusted to blood levels and renal function according to each center's practice. Acute GVHD (aGVHD) was graded as previously described.[20]

Chronic GVHD assessment

Medical charts from each participating center were reviewed in detail, and clinical and biologic data were collected by a specifically trained clinical research technician. The technician screened every medical chart of study patients (in addition to case report forms) and reported on a detailed questionnaire biologic (peripheral blood counts), clinical, and therapeutic parameters for each patient at 3-month intervals and whenever changes in these parameters occurred. These elements were chosen based on the published description of cGVHD.[21-23] To ensure data uniformity, this technician was blinded as to the patient's treatment assignment. After collection, all data were systematically reviewed again by 2 hematologists experienced in the management of cGVHD from the Marseille Center team (D.B. and M. Mohty).

Study definitions. The diagnosis of cGVHD was made based on both clinical and/or histology criteria of skin and other affected sites as previously described.[24,25] Chronic GVHD was defined as any GVHD present after day 100. Date of diagnosis of clinical cGVHD was determined as the time when a specific immunosuppressive therapy was started for cGVHD. Chronic GVHD had a progressive onset if it followed as a direct extension of aGVHD. Quiescent-onset cGVHD developed after the resolution of aGVHD, while de novo cGVHD was not preceded by aGVHD.[26] Extensive cGVHD was defined according to standard criteria.[27] Chronic GVHD–associated specific organ involvement criteria were predefined at the beginning of data collection. Assessment of specific organ involvement was performed according to standard procedures of each center and was expected to be the same in the 2 different groups for a given center.

Skin and fascia involvement. Skin and fascia involvement was defined as erythema, dryness, itching, pigment changes, mottling, plaques, papules, exfoliation and, in later stages, induration and contractures. Based on these features, 2 different forms could be distinguished: lichenoid changes similar to lichen planus or sclerodermatous changes similar to scleroderma.

Mouth involvement. Mouth involvement was defined as clinical and/or histologic documentation of oral GVHD with or without ulcers associated with different clinical symptoms. Symptoms included dryness, loss or change in taste, burning, and difficulty in swallowing. Later changes most often included dry atrophic mucosal surfaces and difficulty in fully opening the mouth and/or need for pain medication.[28]

Ocular involvement. Ocular involvement was defined as dry eyes with abnormal or absent tear production as assessed by Schirmer test. Other symptoms consisted of ocular sicca with pain, blurring, burning, grittiness, xerophthalmia, photophobia, conjunctivitis, and keratitis.[29]

Vaginal involvement. Vaginal involvement was defined as dryness of the vagina with stricture formation or stenosis.[30]

Liver involvement. Liver involvement was defined as elevated liver function tests (predominantly alkaline phosphatase, and serum bilirubin) not explained by medication or other illnesses.

Lung involvement. Lung involvement was defined as a new obstructive defect with significant deterioration of spirometry parameters not due to infections or other etiologies.[31]

Other organs. Gastrointestinal and muscle involvement were defined according to previously described criteria.[32,33]

Performance status. The Karnofsky performance score (KPS) was used as previously described.[34]

Immunosuppressive therapy. Upon diagnosis of cGVHD, the treatment decision in regard to management was made by the transplantation team of each participating center. Decisions for topical or systemic measures and for antimicrobial prophylaxis during immunosuppressive therapy for cGVHD were made according to standard procedures of each participating center and were expected to be the same in the 2 study groups for a given center. All patients were primarily treated with cyclosporine and an immunosuppressive corticosteroid-based regimen. Patients were considered off immunosuppressive therapy when having had no immunosuppressive therapy for at least 15 days. Restart of immunosuppressive therapy was defined as the reinitiation of immunosuppressive therapy at full dose more than 15 days after discontinuation because of recurrence of symptoms of cGVHD during this time period. Second-line immunosuppressive regimen was defined as the initiation of secondary systemic immunosuppressive treatment replacing or being in addition to primary first-line systemic therapy because of refractory or clinically worsening cGVHD. Patients received various second-line therapies such as azathioprine, thalidomide, mycophenolic acid mofetil (MMF), tacrolimus, psoralen ultraviolet A phototherapy (PUVA), extracorporeal photochemotherapy, and total lymphoid irradiation. If corticosteroids were started again after completion of a course of steroid therapy, this was not considered second-line therapy.

Statistics

All data were computed using SPSS for Windows (SPSS, Chicago, IL). The Mann-Whitney test was used for comparison of continuous variables. Categoric variables were compared using the χ^2 test corrected with the Yates method if necessary.[35] The probability of developing cGVHD was depicted by calculating the cumulative incidence[36] and prevalence[37] with relapse and death without relapse or cGVHD as competing risks.[22] Disease-free survival (DFS) was defined as survival in continuous complete remission; relapse and death in remission were events; and patients surviving in continuous complete remission were censored at last contact. DFS and duration of immunosuppressive therapy in each treatment group were analyzed using the Kaplan-Meier product-limit estimates.[38,39] Differences between groups were tested using the log-rank test when Kaplan-Meier analysis was performed.[40] Because the risk of chronic GVHD begins by day 100 following transplantation, we also measured DFS in each treatment group from a prespecified "landmark" time of 100 days after transplantation in a landmark analysis.[41]

Results

Patient characteristics and early transplantation-related events

Of the 101 patients who proceeded to transplantation, data on follow-up (relapse or death), cGVHD onset and extent (limited vs extensive), and overall duration of immunosuppressive treatments are shown in Table 1. The baseline characteristics and GVHD risk factors (recipient and donor age, sex, diagnosis, disease status, ABO mismatch, cytomegalovirus (CMV) status, conditioning

Table 1. Features of cGVHD according to transplantation type

	PBSC (n = 48)	BM (n = 53)	*P*
Patients evaluable for cGVHD (%)	42 (87)	44 (83)	NS
Patients developing cGVHD (%)*	31 (74)	19 (43)	.004
Patients developing extensive cGVHD (%)*	21 (50)	9 (20)	.004
Patients developing limited cGVHD (%)*	10 (24)	10 (23)	NS
Time to onset of cGVHD, mo			
Median	6.0	4.1	NS
Range	3.3-17.4	3.1-12.9	
Mode of onset of cGVHD (%)			
De novo	9 (29)	2 (10)	NS
Quiescent	7 (23)	10 (53)	
Progressive	15 (48)	7 (37)	
Duration of immunosuppressive therapy, mo			
Median	27.0	18.0	.03
Range	6.0-50.9	5.3-53.1	

*Percentage of assessable patients. NS indicates not significant.

regimens) of these 101 patients have been reported previously and were found balanced in both treatment arms.[13] All donors were HLA-A–, HLA-B–, and HLA-DR–matched siblings. A total of 94% of the patients included in this study were in first complete remission (acute leukemia) or in first chronic phase (chronic myeloid leukemia), and this was balanced between the 2 arms. As expected, PBSC collection led to the infusion of a higher number of $CD34^+$ hematopoietic progenitors (median [range], PBSCs, 6.6×10^6/kg [1.5×10^6/kg-19.2×10^6/kg]; BM, 2.4×10^6/kg [0.5×10^6/kg-8.6×10^6/kg]; $P < 10^{-6}$) and $CD3^+$ T cells (median [range], PBSCs, 356×10^6/kg [131×10^6/kg-754×10^6/kg]; BM, 26×10^6/kg [7×10^6/kg-92×10^6/kg]; $P < 10^{-6}$). Patients in the PBSC arm reached platelet count of 25×10^9/L 8 days earlier than did patients in the BM arm ($P < 10^{-4}$). The time to reach neutrophil counts of 0.5×10^9/L was 6 days shorter in the PBSC group than in the BM group ($P < 10^{-5}$). Forty-three patients developed at least grade 2 acute GVHD with no difference between the 2 groups (PBSCs, 44%; BM, 42%; P = NS).

Incidence of cGVHD

At time of this analysis (median follow-up 45 months [range, 31-57 months]), the 3-year cumulative incidence of cGVHD was 65% (95% confidence interval [CI] 51%-78%) in the PBSC group and 36% (95% CI 23%-49%) in the BM group (P = .004) (Figure 1A). Furthermore, among patients evaluable for cGVHD, extensive cGVHD was more frequent in the PBSC group (PBSCs, n = 21 [44%, 95% CI 30%-58%]; BM, n = 9 [17%, 95% CI 7%-27%]; P = .004) (Table 1). The prevalence of cGVHD was higher among patients in the PBSC arm at all time points of analysis (Figure 1B). In addition, the proportion of patients with cGVHD who received systemic immunosuppressive therapy was higher in the PBSC arm at all time points of analysis (P = .03) (Figure 2). Eleven patients experienced de novo cGVHD, whereas 39 patients had progressive or quiescent cGVHD, with no difference in the type of cGVHD onset between the 2 groups (Table 1).

Chronic GVHD characteristics

Chronic GVHD organ-specific involvement and immunosuppressive treatments were assessed in all 101 patients included in this study. While the baseline characteristics of these patients have been described elsewhere,[13] for the purpose of this analysis we have reexamined in detail the parameters that may be predictive of the likelihood of developing cGVHD. Table 2 summarizes these characteristics. There were no significant differences between the 2 groups with respect to the preparative regimen they received and for known risk factors associated with cGVHD. Among the 50 patients who experienced cGVHD, 13 patients had recurrence of cGVHD following cessation of all immunosuppressive therapy, statistically more significant in the PBSC group (39%) than the BM group (5%) (P = .02). In these patients, systemic immunosuppressive therapy had to be restarted after a median time of 3.8 months (range, 2-11 months). Moreover, 16 patients in the PBSC group needed a second-line immunosuppressive regimen, compared with only 4 patients in the BM arm (P = .03) (Table 3). To assess the functional impact of cGVHD, a detailed evaluation of the Karnofsky performance status could be obtained in 37 patients among the 50 patients who experienced cGVHD. The median time to reach a Karnofsky score of 90% (symptomatic but able to perform normal activity) was 12 months (range, 3-48 months) in the PBSC group compared with 6 months (range, 3-30 months) in the BM group (P = .08). This altered quality of survival could also be measured by the higher number of days of inpatient hospitalization experienced by cGVHD patients from the PBSC group, following day 100 after transplantation (PBSCs, mean 9.6 days [range, 0-70 days]; BM, mean 0.5 days [range, 0-5 days]; P = .04).

The most relevant clinical features encountered in patients developing cGVHD from both groups are summarized in Table 3. Based on the type of cutaneous lesions, we did not find a significant difference in the number of patients with lichenoid lesions between the 2 groups, while there was a trend, although not statistically significant, to more sclerodermatous cGVHD in the PBSC group (PBSC, n = 9; BM, n = 4), suggesting more generalized cGVHD cutaneous manifestations associated with the use of PBSCs. Oral involvement was similar in both groups and was associated with

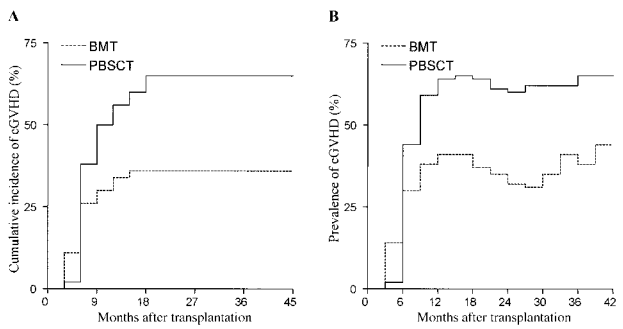

Figure 1. Incidence and prevalence of cGVHD. Comparison of (A) cumulative incidence and (B) prevalence of cGVHD following allogeneic transplantation of peripheral blood stem cells (PBSCT) or bone marrow (BMT).

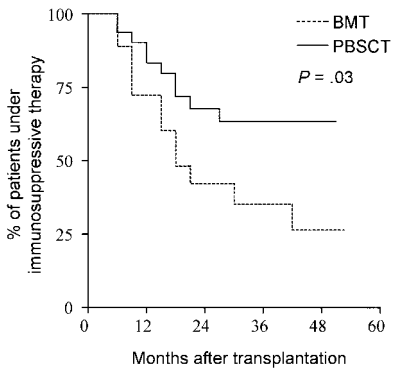

Figure 2. Immunosuppressive therapy. Comparison of percentage of patients receiving immunosuppressive therapy in the cGVHD population following allogeneic transplantation of peripheral blood stem cells (PBSCT) or bone marrow (BMT).

Table 2. Chronic GVHD risk factors of the study population

	PBSC (n = 48)	BM (n = 53)	*P*
Sex, no. (%)			
Male with male donor	11 (23)	14 (26)	NS
Male with female donor	15 (31)	13 (25)	
Female with female donor	11 (23)	9 (17)	
Female with male donor	11 (23)	17 (32)	
Diagnosis, no. (%)			
Acute myeloid leukemia	25 (52)	20 (38)	NS
Acute lymphoblastic leukemia	6 (13)	13 (24)	
Chronic myeloid leukemia	17 (35)	20 (38)	
Disease status, no. (%)			
Chronic phase or first complete remission	45 (94)	50 (94)	NS
Advanced disease	3 (6)	3 (6)	
Cytomegalovirus status, no. (%)			
Seronegative with seronegative donor	18 (38)	18 (34)	NS
Other combinations	30 (62)	35 (66)	
Patient/donor ABO mismatch, no. (%)	13 (27)	11 (21)	NS
Conditioning regimen, no. (%)			
Cytoxan + total-body irradiation	34 (71)	39 (74)	NS
Cytoxan + busulfan	9 (19)	6 (11)	
Other	5 (10)	8 (15)	
Acute GVHD (%)			
No. assessable for aGVHD (%)	47 (98)	52 (98)	NS
Grade			
0	14 (30)	19 (37)	
I	12 (25)	11 (21)	
II-IV	21 (45)	22 (42)	

NS indicates not significant.

both types of cutaneous cGVHD. A higher incidence of ocular symptoms was seen in the PBSC group ($P = .02$). There was no difference between the 2 groups for hepatic involvement (PBSC, n = 20; BM, n = 8; P = NS), but a longer time to normalization of hepatic abnormalities, especially serum bilirubin, was observed in the PBSC group (PBSC, 22 months; BM, 14 months; $P = .08$). Three patients had pulmonary symptoms, and 5 patients had symptoms involving organs other than those cited above (3 musculoskeletal and 2 gastrointestinal tract), all in the PBSC group. Vaginal involvement was comparable in both groups. When assessed in terms of number of organs involved, cGVHD patients from the PBSC arm had a significantly higher number of organs involved (PBSC, median 4 organs [range, 1-6 organs]; BM, median 2 organs [range, 1-4 organs]; $P = .01$). In addition, the number of patients experiencing cGHVD and having more than 3 organs involved was significantly higher in the PBSC group (PBSC, n = 16; BM, n = 3; $P = .01$).

Table 3. Clinical features of cGVHD according to transplantation type

	PBSC (n = 31)	BM (n = 19)	*P*
Immunosuppression withdrawal/restarting (%)*	12 (39)	1 (5)	.02
Median time between immunosuppression withdrawal/restarting, mo (range)*	3.8 (2-11)	24	
Second-line immunosuppressive regimen (%)	16 (52)	4 (21)	.03
Skin (%)			
Lichenoid lesions	22 (71)	15 (79)	NS
Sclerodermatous lesions	9 (29)	4 (21)	
Mouth (%)	29 (93)	15 (79)	NS
Eyes (%)	22 (71)	7 (37)	.02
Liver (%)	20 (64)	8 (42)	
Median time to normalization of serum bilirubin, mo (range)	22 (6-49)	14 (8-36)	.08
Pulmonary (%)	3 (10)	0	
Vaginal (%)	3 (10)	2 (13)	NS
Other (%)	5 (16)	0	

*These patients had recrudescence of cGVHD following total withdrawal of the immunosuppressive therapy, thus leading to the restarting of immunosuppressive therapy.

NS indicates not significant.

Lymphocyte repopulation

At present, there is evidence that GHVD (both acute and chronic) is mediated by alloreactive T lymphocytes derived from the donor inoculum.[42] In an attempt to establish a correlation between lymphocyte counts and incidence of cGVHD, we found that at all time points after day 100 following transplantation, and during the first 3 years of follow-up, the mean absolute peripheral blood lymphocyte counts were higher among PBSC recipients compared with BM recipients (Figure 3).

Rates of death, relapse, and survival

Of the 48 patients who received PBSCs, 15 (31%) died during the follow-up period, as compared with 19 (36%) of the 53 in the BM group (Table 4). The causes of death in both arms are shown in Table 4. Four deaths in the PBSC group were directly attributed to cGVHD, as compared with only 1 patient in the BM group (P = NS). Fatal infections were comparable in both groups. The median follow-up time of surviving patients was also comparable in both groups (Table 4). Over this long period of follow-up, only 2 patients (4%) relapsed among the 50 who experienced cGVHD, as compared with 9 of the 36 (25%) without ($P = .009$), suggesting that cGVHD may reduce the risk of relapse. The data also supported that cGVHD after PBSCs is associated with an antileukemic effect that is at least as potent as after BM (1 relapse in 31 [3%] PBSC patients with cGVHD, 1 relapse in 19 [5%] BM patients with cGVHD; P = NS). However, when we considered the whole population, the use of PBSCs was not associated with a survival advantage, and the rate of disease-free survival was not significantly different between the 2 groups (P = NS) (Figure 4A). Moreover, because the risk of chronic GVHD begins by day 100 following transplantation, we also attempted to detect a survival difference exclusively among patients who survived beyond day 100. Thus, we measured DFS in each treatment group using a landmark analysis.[41] Among patients surviving beyond day 100 and evaluable for cGVHD, we could not show an association

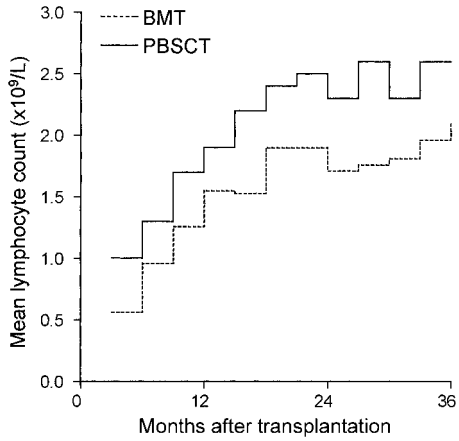

Figure 3. Lymphocyte count. Comparison of mean peripheral blood lymphocyte counts following allogeneic transplantation of peripheral blood stem cells (PBSCT) or bone marrow (BMT).

Table 4. Outcome according to transplantation type

	PBSC (n = 48)	BM (n = 53)	*P*
Median follow-up of surviving patients, mo	47 (32-57)	45 (31-57)	NS
No. of deaths (%)	15 (31)	19 (36)	NS
Causes of death			
Relapse	3	8	NS
aGVHD	3	7	
cGVHD	4	1	
Infectious	3	2	
VOD	1	1	
Other	1	0	

VOD indicates veno-occlusive disease; NS, not significant.

between disease-free survival and the use of PBSCs (P = NS) (Figure 4B), possibly due to the early-stage leukemic status of these patients or to the relatively small size of the study population.

Discussion

We recently reported the results of a randomized study comparing allogeneic BM transplantation with PBSC transplantation, in which PBSC transplantation was associated with a higher incidence of cGVHD.[13] In the present report, we performed a more detailed analysis of factors potentially associated with cGVHD in the 2 groups over a longer time. Our results show a significant effect of stem cell source on the incidence, prevalence, presentation, and therapy of cGVHD. Six randomized studies, including this study, have compared the use of allogeneic PBSC with BM.[10-14,16] These studies showed discrepancies regarding the incidence of cGVHD following PBSC transplantation. Differences such as the length of follow-up, the number and type of patients, the type of GVHD prophylaxis, the regimen of G-CSF used for the mobilization of PBSCs, and the use of postgraft G-CSF have been suggested to explain these different results.

Our study provides the longest follow-up to date. In our study, methotrexate was omitted on day 11. Although the omission of the dose of methotrexate on day 11 can increase the risk of aGVHD,[43] which predisposes patients to the development of cGVHD, this was not the case in our study. Acute GVHD alone cannot explain the higher incidence of cGVHD encountered by patients receiving PBSCs, because our data, although not statistically significant, show a higher rate of de novo cGVHD independent of aGVHD. In a study including 173 high-risk patients who received day 11 methotrexate prophylaxis, Bensinger et al concluded that the risk of aGVHD and cGVHD was not increased by the use of PBSCs.[14] However, the 95% confidence intervals for the hazard ratio for cGVHD in that study was reported to be 0.71 to 1.90 for the PBSC group as compared with the BM group, which does not exclude the possibility that the use of allogeneic PBSCs might nearly double the risk of cGVHD. More importantly, this study did not report on patients in whom limited cGVHD developed, perhaps because limited cGVHD was thought not to be clinically significant.[44] However, the latter may be only partially true, because cGVHD even in its limited form may impact patients' quality of life and long-term well-being. Our study also differs from other trials[10,14] by not administrating G-CSF after grafting. There are data suggesting that G-CSF can affect immune functions,[45-47] leading to down-regulation of the inflammatory response involved in GVHD.[48,49] However, whether this influences clinical GVHD remains to be demonstrated.

Another main determinant for the development of cGVHD is the presence of high numbers of circulating alloreactive lymphocytes.[42,50] Our study demonstrated that patients receiving PBSCs maintained a higher level of circulating blood lymphocytes, as compared with patients receiving BM. A sustained high level of donor circulating and potentially alloreactive lymphocytes could explain the initiation and maintenance of less responsiveness to therapy and more severe cGVHD.

In our study, cGVHD was associated with a potent antileukemic effect similar in both groups.[51] One could propose that an increased incidence of cGVHD may be an acceptable trade-off because of a possible increased antileukemic effect. However, for this to be meaningful, it should be associated with a better survival. This was not shown in our study, where patients developed more severe symptoms of cGVHD without an additional benefit from a graft-versus-leukemia effect.

Time to discontinuation of immunosuppressive treatment is another end point in cGVHD management. In our study, PBSC-associated cGVHD needed to be treated for a longer period with more highly immunosuppressive regimens. This in turn has been shown in previous studies to increase the risk of secondary tumors.[52] Therefore, the incidence of secondary tumors might be expected to rise in long-term surviving patients[53] who received PBSCs. Our study suggests caution in using allogeneic PBSCs over BM in patients with early-stage leukemic disease. Nevertheless, survival and relapse were not the primary end points of this study. Thus, one cannot exclude that the lack of difference in relapse and survival might be due to the relatively small number of patients included. Because some studies support that allogeneic PBSCs may benefit poor-risk patients,[14,21] additional studies will be necessary, specifically addressing disease recurrence and the regimens used in GVHD prophylaxis. These issues must be carefully assessed to determine the patient subgroup for whom an overall benefit is associated with allogeneic PBSCs. Our study supports that PBSCs and BM do not appear to be simply interchangeable sources of hematopoietic grafts. A shorter initial hospital stay, a quicker hematopoietic recovery, or less pronounced donor discomfort should not be the only factors considered in the choice of stem cell source. The possible survival benefit due to fewer relapses and the potential morbidity associated with cGVHD, adjusted for quality of life, may be crucial determinants for the ultimate outcome.

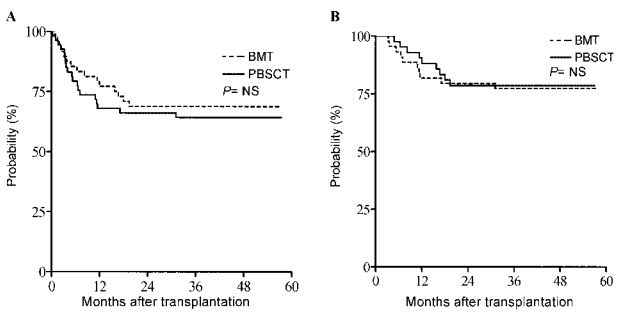

Figure 4. Disease-free survival. (A) Comparison of disease-free survival following allogeneic transplantation of peripheral blood stem cells (PBSCT) or bone marrow (BMT). (B) Comparison of disease-free survival using landmark analysis among patients surviving beyond day 100.

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