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Allogeneic bone marrow transplantation *vs* filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation

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Summary:

In a multicentre trial involving 20 transplant centres from 10 countries haematopoietic stem cells were obtained either from the bone marrow of 33 sibling donors or from the peripheral blood of 33 such donors after administration of filgrastim (10 μg/kg/day). The haematopoietic stem cells were infused into their HLA-identical recipients suffering from acute leukaemias in remission or chronic myeloid leukaemia in chronic phase. PBPC donors tolerated filgrastim administration and leukapheresis well with the most frequent side-effects being musculoskeletal pain, headache, and mild increases of LDH, AP, Gamma-GT or SGPT. Pain and haematoma at the harvest site and mild anaemia were the most frequent complaints of BM donors. Severe or life-threatening complications were not seen with any type of harvest procedure. Time to platelet recovery greater than 20×10^9/l was 15 days (95% confidence interval (CI) 13–16 days) in the PBPCT group and 19 days (CI 16–25) in the BMT group. Time to neutrophil recovery greater than 0.5×10^9/l was 14 days (CI 12–15 days) in the PBPCT group as compared to 15 days (CI 15–16 days) in the BMT group. The numbers of platelet transfusions administered to PBPCT and BMT patients were 12 (range: 1–28) and 10 (range: 3–39), respectively. Sixteen patients (48%) transplanted with bone marrow and 18 patients (54%) transplanted with PBPC developed acute GVHD of grades II–IV; acute GVHD of grades III or IV developed in six (18%) and seven (21%) patients, respectively. Kaplan–Meier plots for transplant-related mortality until day 100 and leukaemia-free survival at a median of 400 days after BMT or PBPCT showed no significant differences. Administration of filgrastim and leukapheresis in normal donors were feasible and well tolerated. The number of days with restricted activity and of nights spent in hospital was lower in donors of PBPC. Transplantation of PBPC to HLA-identical siblings with early leukaemia resulted in earlier platelet engraftment. The incidence of moderate to severe acute GVHD, transplant-related mortality, and leukaemia-free survival did not show striking differences. Further investigation of allogeneic PBPCT as a substitute for allogeneic BMT is warranted.

Keywords: allogeneic bone marrow transplantation; allogeneic peripheral blood progenitor cell transplantation

The first small series of patients transplanted with allogeneic granulocyte colony-stimulating factor (G-CSF)-mobilised peripheral blood progenitor cells (PBPC) were published in 1995.[1–4] These studies have led to a surge of allogeneic PBPC transplants (PBPCT) comparable to that seen some years earlier when autologous PBPCT started to replace autologous bone marrow transplantation (BMT). In 1995, 571 allogeneic PBPCT were reported to the European Group for Blood and Marrow Transplantation (EBMT)[5] and in 1996, over 1100 transplants (representing close to a quarter of all allogeneic transplants performed in Europe) used PBPC as the source of hematopoietic stem cells (A Gratwohl, data on file). This massive switch from marrow to blood contrasts with the scarcity of reliable information supporting this change: besides a number of uncontrolled single institution studies only a single small and retrospective matched pair analysis comparing allogeneic PBPCT with BMT has been reported.[6] Randomised trials have not been published.

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We report the results of the first prospective randomised trial evaluating the feasibility and safety of allogeneic PBPCT in comparison to BMT in patients with early leukaemias.

Patients and methods

Study design

This was a randomised, multicentre trial designed to investigate the feasibility, safety, and outcome of allogeneic PBPCT compared with BMT. Seventy recipients and their HLA-identical sibling donors were enrolled at 20 institutions from 10 countries. The study was approved by the ethics committee of each participating centre and written informed consent was obtained from all donors and recipients. Patients were centrally randomised at the International Institute for Drug Development (id^2), Brussels, Belgium, where inclusion and exclusion criteria were checked prior to randomisation. The minimisation method was used to allocate donor and recipient to the BMT or PBPCT arm of the study. This method stratifies randomisation and in this case took into account if the diagnosis was chronic myelogenous leukaemia (CML) or acute leukaemia and if the donor was female and had ever been pregnant. The morphologic subtypes of acute leukaemias and other prognostic factors (ie karyotype, initial WBC, duration of remission for patients grafted in CR2) were not considered for stratification.

Patients

Patients between 18 and 50 years of age and an ECOG performance status of 0–2 were eligible to participate in the study if they had a diagnosis of *de novo* acute myelogenous leukaemia (AML) or acute lymphoblastic leukaemia (ALL) in first or second remission, or CML in first chronic phase. Patients with inadequate organ function (serum creatinine >10% above normal, abnormal left ventricular size or function, DLCO <50%, bilirubin >2 mg/dl), HIV positivity, and/or a history of splenectomy or splenic irradiation were excluded as were patients who previously had received a BM or PBPC transplant.

Donors

The sibling donors were between 18 and 60 years of age and HLA-identical to the recipient. Exclusion criteria were any of the following: inability to undergo general anaesthesia and bone marrow or PBPC harvest, peripheral venous access deemed impossible at initial examination, positive serology for HIV, hepatitis C or B, or a history of malignant disease or concurrent malignancy.

Harvest procedures

Donors randomised to donate BM had their marrow harvested from both posterior iliac crests under general anaesthesia. A minimum of 2×10^8 nucleated cells/kg recipient weight was required for transplantation. Donors randomised to undergo PBPC collection were treated with filgrastim (r-metHuG-CSF) (Amgen, Thousand Oaks, CA, USA) at a dose of 10 μg/kg/day subcutaneously for 4 or 5 consecutive days depending on the yield of the first leukapheresis. Leukapheresis was started on day 5 of filgrastim administration using an automated continuous-flow blood cell separator. A minimum of 4×10^6 $CD34^+$ cells/kg recipient weight was to be collected. If this goal was met with one leukapheresis the harvest product was stored at 4°C overnight and infused into the patient on the following day (defined as day 0 for the recipient). If the first leukapheresis gave less than 4×10^6 $CD34^+$ cells/kg the donor received another filgrastim injection, the first leukapheresis product was stored as described but was infused with a second leukapheresis product collected on the following day (day 0). BM harvests and PBPC collection products were characterised in an identical manner at each participating institution: the total number of nucleated cells (NC), $CD34^+$ cells (using the HPCA-2-PE antibody; Becton Dickinson, Heidelberg, Germany), T lymphocytes (UCHT-1-FITC antibody, DAKO, Hamburg, Germany), natural killer (NK) cells (Leu-19-PE antibody; Becton Dickinson) as well as the number of colony-forming units-granulocyte/macrophage (CFU-GM) were counted. If there was AB0 incompatibility between recipient and donor the red blood cells and/or plasma were separated from the graft prior to transplantation. Other manipulations of the graft (ie cryopreservation, $CD34^+$ selection) were not allowed.

Conditioning

Conditioning therapy had to be identical for all patients treated at each of the participating institutions and could consist of either total body irradiation (TBI) administered as a single dose ≥7.5 Gy or fractionated with a total dose ≥10 Gy in conjunction with cyclophosphamide or etoposide or combinations thereof. Alternatively, busulphan (total dose 16 mg/kg) and cyclophosphamide (200 mg/kg) could be used as a non-TBI containing regimen. BM or PBPC cells were infused via a central venous catheter on day 0 (defined as the day bone marrow would ordinarily have been given).

Prophylaxis and treatment of graft-versus-host disease (GVHD)

GVHD prophylaxis consisted of cyclosporin A (CsA) and methotrexate (MTX). CsA was started on day −1 and stopped on day +180 unless active GVHD required continuation of the drug. CsA was given intravenously until oral administration became feasible; dosing of CsA followed local practice but was monitored by regular measurements of CsA plasma levels. MTX was injected on day +1 (15 mg/m^2) and days +3 and +6 (10 mg/m^2 each). If acute GVHD developed intravenous methylprednisolone or oral prednisolone was administered. Further treatment – if necessary – was left to the discretion of the responsible physician. Acute GVHD was graded daily for inpatients and twice weekly thereafter until day +100 according to

the Glucksberg criteria;[7] chronic GVHD was classified as described by Shulman *et al*.[8]

Supportive care and clinical monitoring

All patients received intravenous or subcutaneous filgrastim at a dose of 5 μg/kg/day starting 24 h after transplantation of BM or PBPC until absolute neutrophil counts (ANC) of either 1.0×10^9/l for 3 consecutive days or 10×10^9/l for 1 day were reached. Filgrastim was stopped at day 28 regardless of the ANC. Prophylaxis and treatment of infections were left to the discretion of the investigator but needed to follow a standardised plan at each participating centre. Prophylactic administration of gancyclovir was not allowed. Platelet and red blood cell (RBC) transfusions were given according to centre policy.

The patients' history, performance status, vital signs, complete blood count (CBC), and biochemistry were recorded pre-study, at regular intervals during hospitalisation, and at each follow-up visit but at least at 6, 9, 12, 24 and 36 months after transplantation. Bone marrow aspirates were performed pre-study and on days +28, +100 as well as 12, 24 and 36 months after grafting in order to evaluate the remission status and chimeric state of the patient.

Each donor was asked about his medical history and had a physical examination prior to entering the study. Performance status, CBC, biochemistry, and vital signs were documented pre-study, daily during filgrastim administration and leukapheresis, and 30 days after BM or PBPC harvest. All adverse events (definition see below) were recorded. In addition, patients were asked about their donor's well being 100 days, 6, 9, 12, 24 and 36 months after grafting; telephone interviews with the donors were scheduled at the same time intervals.

Study endpoints and definitions

Experience with the administration of G-CSF to normal individuals is limited. Therefore, in the donors all adverse events defined as any new undesirable medical experience or change of an existing condition which occurred during or after treatment whether or not related to filgrastim or leukapheresis were documented and analysed. Adverse events in the donors which required medical intervention (ie blood transfusion, drug treatment) were considered severe. The route of access and the duration of the leukapheresis procedure, the duration of hospitalisation, and the number of days with restriction of regular activities were also recorded.

The safety of the patients enrolled in the study was monitored by evaluating the incidence of severe toxicities which were defined as engraftment failure, acute GVHD of grades III and IV, organ toxicity of grades 3 and 4 according to the Bearman criteria,[9] or death from any cause. Secondary endpoints for the recipient were the time to an unsupported platelet count of 20 or 50×10^9/l (ie the time from transplantation to the first of 3 consecutive days without a platelet transfusion and a platelet count above 20 or 50×10^9/l), the time to an ANC of 0.5 or 1.0×10^9/l, the duration of fever and hospitalisation, the incidence and severity of acute and chronic GVHD, relapse incidence, leukaemia-free survival, and time to death.

Statistical analysis

The primary objective of this study in both donors and recipients was to demonstrate the feasibility and safety of allogeneic PBPCT in comparison to BMT. Secondary endpoints are summarised in the section 'study endpoints and definitions'. Because the study protocol included the possibility of extending the study to a phase III trial comparing the incidence and severity of acute GVHD as primary endpoint we chose to perform no formal tests on the results reported here. Instead, descriptive statistics and estimates of differences for relevant endpoints together with the respective 95% confidence intervals are given to compare allogeneic PBPCT and BMT. Analyses were based on the intention-to-treat principle as far as relevant data were available.

Results

Donors

The median age, sex, parity, and CMV status of all donors entered into this study are summarised in Table 1. Important differences between donors randomised to bone marrow harvest or PBPC collection were not observed. Thirty-three of 36 PBPC donors and 33 of 34 bone marrow donors proceeded to the harvest procedure. Three donors randomised to PBPC collection and one potential bone marrow donor were not harvested; the reasons why they did not continue on the study protocol are detailed in Figure 1.

Sixteen of 34 bone marrow donors (47%) and 22 of 36 PBPC donors (61%) experienced at least one adverse event of any severity. Table 2 lists all adverse events reported by the donors. One event in a marrow donor was considered severe by the investigator because anaemia detected after the donation (Hgb 10.4 g/dl) necessitated the transfusion of

Table 1 Characteristics of donors and patients according to treatment group

	BMT (n = 34)	*PBPCT (n = 36)*
The donors		
Median age (range)	34 (20–57)	33 (17–59)
Sex (male/female)	16/18	17/19
Nulliparous women	7	8
Donor and recipient		
CMV negative[a]	8	10
The recipients		
Median (range) age	34 (20–48)	34 (19–49)
Sex (male/female)	16/18	17/19
Diagnoses at time of randomisation		
AML first remission	14	14
AML second remission	3	1
ALL first remission	1	3
ALL second remission	2	3
CML first chronic phase	14	15

[a]CMV status unknown in two donor/recipient pairs.

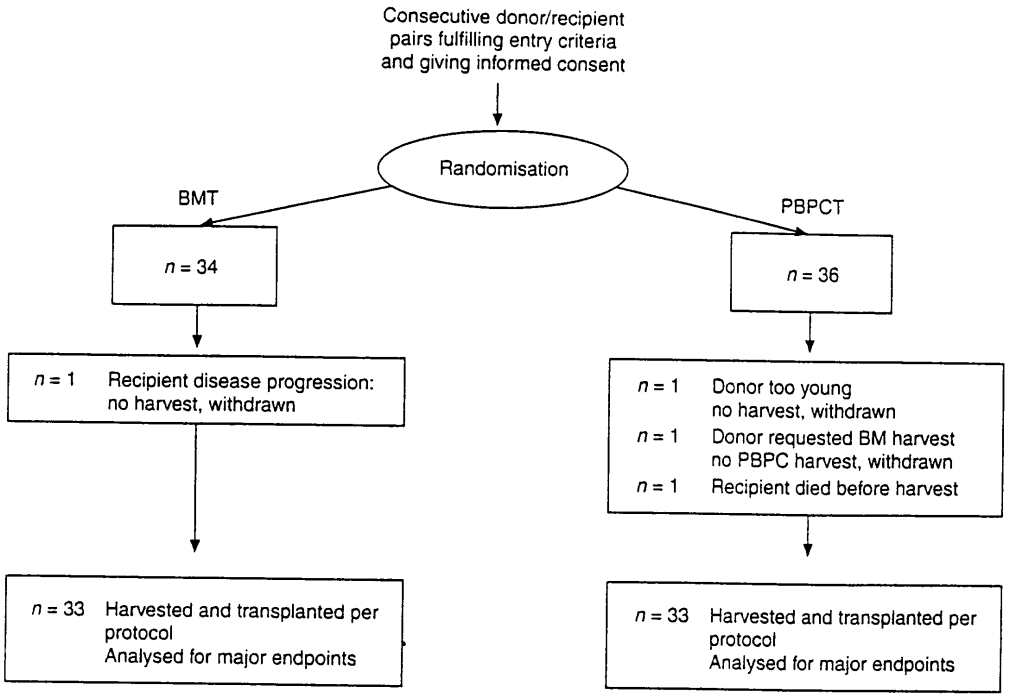

Figure 1 Trial profile.

Table 2 Summary of adverse events in bone marrow and PBPC donors

Adverse event	*No. of donors with adverse events*	
	BM donors n = 33 (%)	*PBPC donors n = 33 (%)*
Musculoskeletal pain[a]	5 (15)	18 (50)
Pain/hematoma at harvest site		
Headache	8 (24)	—
Fever, rigors, hot flushes	1 (3)	5 (14)
Anemia[2]	3 (9)	3 (9)
Thrombocytopenia	6 (18)	—
Increase of liver enzymes or LDH	—	1 (3)
	—	3 (9)
Hypocalcaemia	—	1 (3)
Respiratory tract infection/dyspnea	—	2 (6)
Rash	—	1 (3)
Hysteria	—	1 (3)
Vomiting	1 (3)	—
Circulatory failure	—	1 (3)
Asthenia	1 (3)	1 (3)
Peripheral edema	1 (3)	—

[a]Severe pain in one PBPC donor.
[b]Moderate anaemia (WHO grade 1) in one BM donor.

autologous RBCs. A PBPC donor developed severe skeletal pain which resolved only after filgrastim was discontinued and paracetamol was administered. In general, both types of harvest procedure were tolerated well and no life-threatening or fatal adverse events occurred during the study period and until last follow-up. PBPC donors reported a median of 1 (range: 0–12) as opposed to 6 (range: 0–38) days of restricted activity; the number of nights spent in hospital was 0 (range: 0–8) for PBPC donors and 2 (range: 0–6) for BM donors.

Central venous access was not necessary in any of the donors randomised to PBPC harvesting. Nineteen donors (58%) had one leukapheresis, 12 donors (36%) required two, and two donors (6%) required three leukaphereses in order to collect the target cell number of 4×10^6 $CD34^+$ cells/kg recipient weight. The donors who underwent three apheresis procedures had final yields of 3.8 and $>1.43 \times 10^6$ $CD34^+$ cells/kg ($CD34^+$ cells were not counted in the first of three apheresis products of the latter donor due to technical problems). Both grafts were used for transplantation and the patients engrafted with an ANC $>0.5 \times 10^9$/l reached on days 18 and 17; a platelet count $>20 \times 10^9$/l was reached on days 32 and 31, respectively. The cellular composition of 33 BM and PBPC harvests available for analysis is summarised in Table 3.

Recipients

From January 1995 until May 1996 36 patients were randomised to PBPCT and 34 patients were randomised to

Table 3 Characterisation of bone marrow (BM) and peripheral blood progenitor cell (PBPC) harvests

Cell type		*BM (n = 33)*	*PBPC (n = 33)*
Nucleated cells	median	318	1025
($\times 10^6$/kg)	range	55–508	346–2332
$CD34^+$ cells	median	4.0	6.7
($\times 10^6$/kg)	range	0.4–24.8	1.5–13.2
$CD3^+$ cells	median	62.7	290.8
($\times 10^6$/kg)	range	9.0–360.8	15.6–1451.9
$CD56^+$ $CD3^-$ cells	median	3.4	24.1
($\times 10^6$/kg)	range	0.0–36.4	0.0–194.6
CFU-GM	median	10.9	41.5
(10^4/kg)	range	0.5–129.9	1.8–1278.2

kg = recipient body weight.

BMT. The age, sex, and diagnoses of all 70 patients randomised are given in Table 1. Two of 14 patients with AML in first remission randomised to BMT and two of 14 patients randomised to PBPCT were deemed poor-risk because of an unfavourable karyotype as defined by the MRC AML 10 trial.[10] Two patients randomised to PBPCT actually were in relapse at the time of transplant; one BMT candidate was reported to be in unstable CR with a borderline blast count at the time of transplantation. Two patients with ALL in first remission given PBPC were Philadelphia chromosome positive, the other two ALL patients grafted in CR1 with BM or PBPC had normal karyotypes. All five ALL patients grafted in CR2 were cytogenetically normal. One recipient randomised to BMT and three recipients randomised to PBPCT were not treated according to the study protocol because of disease progression, relapse of the underlying disease, ineligibility of the donor, or because the donor requested a marrow harvest after randomisation to PBPCT. Thirty-three patients proceeded to each of PBPCT or BMT (see Figure 1 for details).

Conditioning therapy: Twenty-nine of 33 patients (88%) transplanted with BM and 27 of 33 patients (82%) transplanted with PBPC received a combination of TBI and chemotherapy. Four patients randomised to BMT (12%) and six patients randomised to PBPCT (18%) were given a combination of busulphan and cyclophosphamide. For further details see Table 4.

Engraftment and hematopoietic recovery: One patient died 14 days after BMT without hematopoietic recovery and six patients had not achieved a platelet count $\geq 50 \times 10^9$/l at day +100 (end of the study) or until death on day +45 (one patient). All other patients who had received a marrow transplant were fully evaluable for neutrophil and platelet recovery. In the PBPCT arm, one patient died on day +25 without hematopoietic recovery; another patient died on day +32 and surpassed a neutrophil count of 0.5×10^9/l on day +21 but failed to achieve an ANC $>1.0 \times 10^9$/l and a platelet count $>20 \times 10^9$/l. One patient each did not reach platelet counts of 20×10^9/l or 50×10^9/l by day +100. All other patients randomised to PBPCT were fully evaluable for hematopoietic recovery. Patients grafted with allogeneic PBPC reached an unsupported platelet count of 20×10^9/l or more after a median of 15 days (95% confidence interval (CI) 13–16 days). Patients transplanted with bone marrow needed a median of 19 (CI 16–25) days to surpass this threshold (Figure 2); an unsupported platelet count of 50×10^9/l or more was reached 21 (CI 18–25) days after PBPCT and 25 (CI 23–29) days after BMT. The median time to recover an ANC greater than 0.5×10^9/l was 14 (CI 12–15) days in the PBPCT group compared to 15 (CI 15–16) days in the BMT group (Figure 3). An ANC of 1.0×10^9/l or higher was reached 14 (CI 13–15) days after PBPCT and 16 days (CI 15–17) after BMT. The numbers of platelet transfusions administered to PBPCT and BMT patients were 12 (range: 1–28) and 10 (range: 3–39), respectively.

Table 4 Conditioning therapy for recipients of bone marrow or PBPC grafts

	BMT (n = 33)	*PBPCT (n = 33)*
FTBI/CYCLO	23	20
FTBI/CYCLO/Etoposide	3	1
STBI/CYCLO	3	6
Busulphan/CYCLO	4	6

FTBI = fractionated total body irradiation; STBI = single-dose TBI; CYCLO = cyclophosphamide.

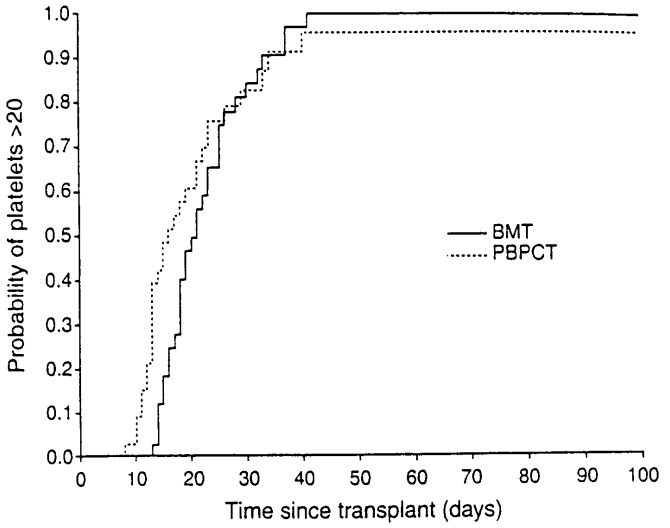

Figure 2 Time to platelet recovery ($>20 \times 10^9$/l) after allogeneic BMT or PBPCT.

Graft-versus-host disease: Twenty-seven of 33 patients in the BMT group (82%) and 31 of 33 patients in the PBPCT group (94%) received all three doses of MTX on days 1, 3 and 6; the remaining patients had only two MTX injections. The median number of days on CsA in the BMT or the PBPCT arm, respectively, was 100 (range: 14–100) and 100 (range: 19–100) days. The number of BM and PBPC recipients who experienced acute GVHD of grades 0–IV is

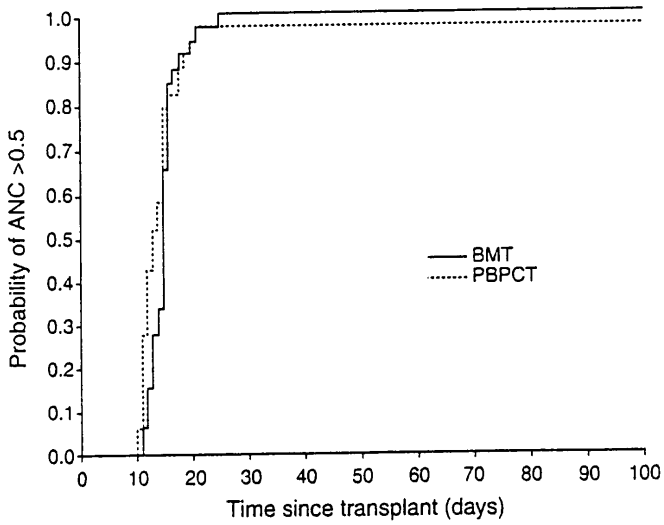

Figure 3 Time to neutrophil recovery ($>0.5 \times 10^9$/l) after allogeneic BMT or PBPCT.

Table 5 Maximum grade of acute graft-versus-host disease according to treatment group

Maximum grade of acute GVHD	*BMT n = 33 (%)*	*PBPCT n = 33 (%)*
0	4 (12)	5 (15)
1	13 (39)	10 (30)
2	10 (30)	11 (33)
3	4 (12)	4 (12)
4	2 (6)	3 (9)

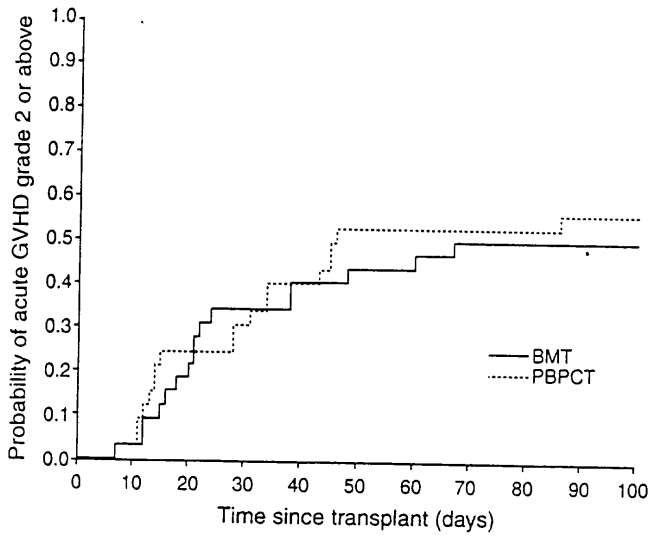

Figure 4 Time to acute GVHD > grade 2 for patients grafted with BM or PBPC.

given in Table 5; the probability of developing grade II–IV GVHD is depicted in Figure 4. There were very few evaluable patients surviving 12 months or more after PBPCT or BMT, respectively. Of six patients grafted with allogeneic PBPC three were reported to suffer from extensive chronic GVHD and three did not. In the BMT arm two patients had developed limited chronic GVHD and four had no chronic GVHD.

Safety: Severe toxicity as defined in the 'study endpoints and definitions' section is given in Table 6. Overall, there were no differences between the treatment groups with respect to the feasibility and safety of BMT or PBPCT. Adverse events seen after both procedures were typical of patients undergoing allogeneic BMT. The median number of days with fever in patients transplanted with PBPC was 8 days (range: 0–55) compared to 13 days (range: 0–31) after BMT. The duration of the first hospital stay was 31 (range: 4–75) days after PBPCT and 35 (range: 2–84) days after BMT. The total number of days spent in hospital until end of study was 52 (range: 24–148) after PBPCT and 45 (range: 26–113) after BMT. Two patients in the BMT group and four patients in the PBPCT group died within 101 days post PBPCT. Transplant-related mortality for both groups of patients is graphically shown in Figure 5.

Table 6 Summary of severe toxicities in patients transplanted with bone marrow or PBPC

	BMT (n = 33)	*PBPCT (n = 33)*
Engraftment failure	0	0
Acute GVHD III or IV	5	8
Severe organ toxicity[a]	3	3
Death until day 100[b]	2	4

[a]Grades 3 or 4 according to Bearman *et al.*[9]
[b]One patient in the PBPCT arm who died on day 101 is included.

Causes of death, relapse incidence, and leukaemia-free survival

As of 1 February 1997, 26 patients in the BMT arm and 24 patients in the PBPCT arm were alive at a median of 400 days (range: 261–740) after BMT and 401 days (range: 246–729) after PBPCT. Of 33 patients grafted with bone marrow, two died prior to day +100 and five additional patients had died by the time of the last follow-up. In the PBPCT group, four patients died before day +101 and five additional patients had died by the follow-up. The causes of death are summarised in Table 7. Six patients relapsed after randomisation to PBPCT, one of them early after randomisation and before any study procedure had occurred. Five of these patients have already died, a patient with CML was alive with relapse at the time of last evaluation. Three of four patients who died of relapse after PBPCT had poor-risk acute leukaemias (see Table 7). One patient randomised to BMT relapsed prior to BMT and died. Two patients with AML or ALL transplanted with BM have relapsed 223 and 261 days after BMT, but were still alive at the time of last follow-up. Another patient grafted with BM cells relapsed 127 days after BMT, was given donor lymphocyte infusions for treatment of relapse and subsequently died of GVHD 322 days after BMT. Leukaemia-free survival for both transplant groups is given in Figure 6.

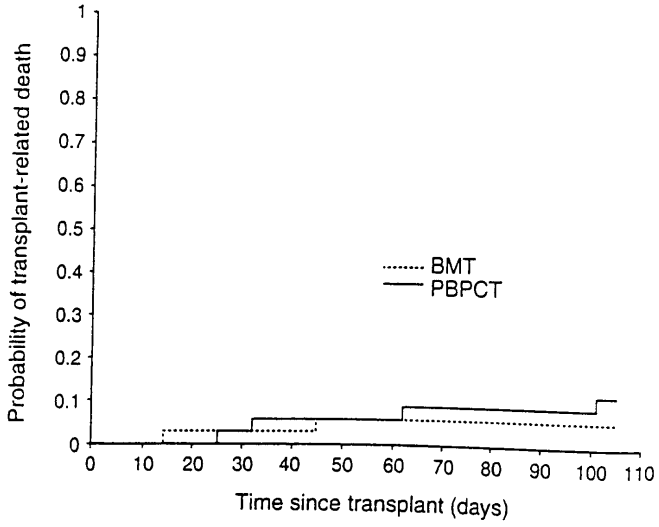

Figure 5 Transplant-related mortality until day +100 of patients grafted with allogeneic BM or PBPC.

Table 7 Causes and time of death after transplantation according to treatment group

BMT		*PBPCT*	
Days post BMT	*Cause of death*	*Days post PBPCT*	*Cause of death*
+14	cerebral haemorrhage	+25	veno-occlusive disease, sepsis
+45	veno-occlusive disease	+32	aspergillus pneumonia
+122	infection (following ATG)	+62	acute GVHD III, g.i. bleeding
+139	acute GVHD IV, infection	+101	acute GVHD IV, infection
+179	infection	+110	relapse (AML CR1, complex aberrations)
+322	acute GVHD following DLI	+149	lung GVHD
+403	obstructive bronchiolitis	+324	relapse (ALL, Ph-positive)
		+351	relapse (ALL, CR2, short CR1)
		+356	relapse (CML)

ATG = anti-thymocyte globulin administered to treat GVHD; DLI = donor lymphocyte infusion following relapse of the underlying disease; g.i. bleeding = gastro-intestinal bleeding; ( ) = diagnosis of patients dying from relapse.

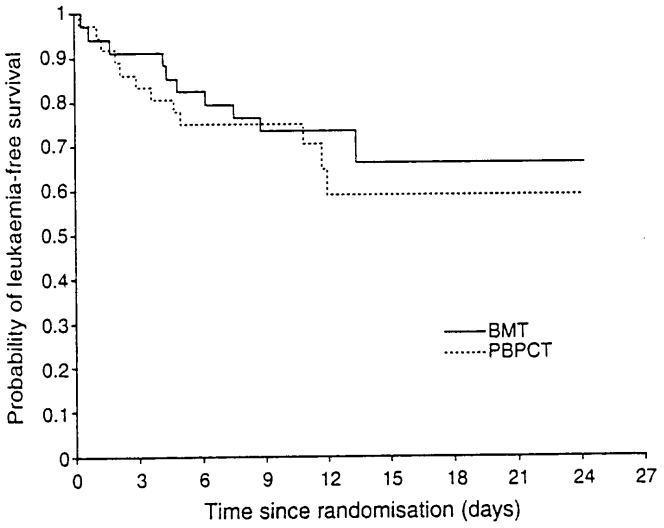

Figure 6 Leukaemia-free survival for patients grafted with BM or PBPC.

Discussion

This study evaluated the feasibility, safety, and clinical consequences of harvesting allogeneic PBPC or BM from normal individuals followed by the transplantation of such cells to HLA-identical siblings with early leukaemia. The acute side-effects of filgrastim administration and leukaphereses in the donors were very similar to that reported previously[11,12] and mainly consisted of musculoskeletal pain, headache, fever or fever-associated symptoms, and increases of hepatic enzymes and lactate dehydrogenase. It was reassuring to note that central venous access was not necessary in any of the donors. This observation demonstrates that clinical judgement is adequate to determine whether a donor's peripheral veins will allow adequate blood flow for the collection of PBPC. All acute side-effects of filgrastim administration and leukaphereses were fully reversible; long-term sequelae have not been reported so far. Clearly, longer follow-up of larger cohorts of donors will be necessary to detect late or rare consequences of these procedures.[13] International co-operation as to how best to achieve this goal is currently under discussion.[14] Although severe or life-threatening immediate side-effects of harvesting PBPC did not occur, the overall frequency (61%) of side-effects may seem relatively high. It needs to be stressed, however, that we prospectively scrutinised all donors for any side-effects possibly related to the harvest procedures. This may at least partly explain why almost two-thirds of the PBPC donors but also half of the BM donors reported side-effects from the collection of haematopoietic cells. In a retrospective analysis of a comparable cohort of 701 BM donors only 22% of the donors experienced complications with the most frequently reported being pain, hypotension, weakness, bleeding and fever.[15] PBPC donors reported fewer days with restricted activities and spent less days in hospital. We realise that different practices at the various institutions participating in the trial may have biased these findings. Nevertheless, this is an important observation which – if confirmed in future studies – could mean better acceptability and major cost savings of PBPC as compared to BM harvesting. Similar observations have been made when the collection of autologous PBPC and BM were compared.[16,17]

The collection of haematopoietic stem cells from peripheral blood yielded higher numbers of nucleated cells, $CD34^+$ cells, CFU-GM, T lymphocytes, and NK cells. The absolute and relative differences between PBPC and BM harvests with respect to the number of $CD34^+$ cells and cells with GVHD- and graft-versus-leukaemia (GVL)-inducing potential (T cells, NK cells) were less pronounced, however, than reported earlier.[18,19] This discrepancy may reflect the effects of the different doses of filgrastim used to mobilise PBPC or the varying blood volumes processed from individual donors; it could also be a consequence of the study protocol which specified that a second leukapheresis was to be performed only if the threshold dose of 4×10^6 $CD34^+$ cells/kg was not met with the first leukapheresis procedure. Higher median cell yields would undoubtedly have been possible if two or more collections would have been performed in all donors. Such a policy, however, would not only have increased the number of $CD34^+$ cells and potentially further accelerated haematopoietic recovery but also would have led to higher numbers of T and NK cells contaminating the grafts. Whether this would have caused a higher incidence of severe GVHD is an open question.

With the numbers of $CD34^+$ cells and CFU-GM infused into the recipients of PBPC or BM studied here the transplantation of PBPC resulted in faster platelet and possibly also neutrophil recovery. Compared with the results of a randomised trial comparing autologous BMT and autologous PBPCT[20] which showed a difference of 7 days for platelet recovery ($>20 \times 10^9$/l) and 3 days for neutrophil recovery (ANC $>0.5 \times 10^9$/l), the differences observed in the allogeneic setting were less marked. This finding was not

totally unexpected as allogeneic transplantation of haematopoietic stem cells is a much more complex biologic process than autologous BMT or PBPCT. Graft rejection and acute GVHD including its prophylaxis with CsA and MTX are unique to the allogeneic setting and together with other complications such as CMV disease, which are much more likely to occur after allotransplantation may all delay engraftment of donor haematopoiesis. Furthermore, the administration of G-CSF to recipients of marrow and PBPCs may have influenced haematopoietic recovery to a various extent in both patient cohorts. Also, in contrast to the autologous situation a beneficial effect of PBPCT on the total number of days spent in hospital or the number of platelet transfusions required by day +100 was not found, although the number of platelet transfusions administered during the first 3 weeks after transplantation was lower in the PBPC arm of the study.

The incidence and severity of acute GVHD observed in patients transplanted with BM or PBPC was very similar. This still is a surprising finding although the dogma that more T cells in the graft will inevitably lead to more frequent or severe GVHD has been questioned by pilot studies from single institutions[1–4] and several retrospective analyses comparing BMT with PBPCT.[21,22] The matched-pair analysis recently reported by the Seattle Group had even shown a lower incidence of acute GVHD after allogeneic PBPCT.[6] On the other hand, several reports have indicated a higher risk for developing chronic GVHD after allogeneic PBPCT as opposed to BMT.[23,24] The very preliminary information obtained from this cohort of patients points in the same direction although the low numbers of patients at risk preclude firm conclusions. Whether the transplantation of allogeneic PBPC will exert a more vigorous GVL effect as recently demonstrated in a mouse model[25] will also need further study. The higher rate of relapses seen in the PBPCT arm of this study may partly be a consequence of the higher numbers of patients with poor-risk leukaemias randomly allocated to PBPCT. Other explanations cannot be excluded at this time.

This study was designed to establish the feasibility and safety of allogeneic PBPCT and to allow a first comparison of the clinical consequences to BMT. The lack of unexpected or serious side-effects of filgrastim administration and leukapheresis in healthy individuals is remarkable and will allow us to further address the question whether the collection of mobilised PBPC from unrelated donors is safe and advantageous for both donor and recipient. With regard to the recipients of PBPC or BM, very similar probabilities for acute GVHD, transplant-related mortality, and leukaemia-free survival were found while an advantage of PBPCT over BMT in terms of the kinetics of platelet and neutrophil recovery seems possible. A thorough evaluation of the clinical consequences of allogeneic PBPCT will surely need longer follow-up of a larger cohort of patients. On the basis of the findings reported here the EBMT has begun a phase III study to compare the clinical consequences of allogeneic PBPCT with allogeneic BMT.

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Appendix

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