

COMPARISONS BETWEEN ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION AND ALLOGENEIC BONE MARROW TRANSPLANTATION IN ADULT HEMATOLOGIC DISEASE: A SINGLE CENTER EXPERIENCE

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This retrospective study compared the outcomes in 32 adult patients with hematologic diseases (acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, myelodysplastic syndrome, severe aplastic anemia) who received allogeneic bone marrow transplantation (BMT, $n = 14$; median age, 28 years) or allogeneic peripheral blood stem cell transplantation (PBSCT, $n = 18$; median age, 29 years) from human leukocyte antigen-identical sibling donors. Median follow-up was 58 months in BMT recipients and 18 months in PBSCT recipients. Neutrophil (median, Day 8 vs Day 13, $p < 0.001$) and platelet engraftment (median, Day 9 vs Day 17, $p < 0.001$) was faster in the PBSCT group than in the BMT group. Patients receiving PBSCT required less platelet transfusion than those receiving BMT (median, 54 units vs 144 units, $p < 0.001$), but there was no significant difference in red cell transfusion. At 100 days, there was no difference in the incidence of acute graft-versus-host disease (GVHD) (42.9% vs 33.3%, $p = 0.72$) or grade II–IV acute GVHD (14.3% vs 5.6%, $p = 0.57$), and there was no difference in the cumulative incidence of chronic GVHD (20% vs 33.3%, $p = 0.67$). No chronic GVHD was noted in any relapsed patients (BMT, 5; PBSCT, 3), and no patients with chronic GVHD during follow-up had a relapse. Relapse was the most frequent cause of death in both groups (BMT, 5/9, 55.6%; PBSCT, 3/4, 75%; $p = 0.25$); all relapses occurred within 1 year after transplantation. Overall survival was significantly better in the PBSCT group (35.7% vs 77.8%, $p = 0.029$), but this difference was lost if only hematologic malignancies were analyzed (30.8% vs 63.6%, $p = 0.20$). Our results are similar to those reported previously, with faster neutrophil and platelet engraftment and less severe acute GVHD and extensive chronic GVHD with PBSCT. Allogeneic PBSCT is a feasible and beneficial alternative to allogeneic BMT in adult hematologic disease.

Key Words: allogeneic, bone marrow transplantation, peripheral blood stem cell transplantation
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Hematopoietic stem cell transplantation is a widely accepted treatment modality for many hematologic diseases, including leukemia, myelodysplasia, lymphoma, myeloma,

and aplastic anemia. Recently, growth-factor mobilized peripheral blood stem cell transplantation (PBSCT) has been performed more frequently than conventional bone marrow transplantation (BMT) [1–3]. Compared with conventional BMT, allogeneic PBSCT is safe, with easy collection of progenitor cells from the donor, rapid neutrophil and platelet engraftment, and reduced transfusion requirements and hospital stay [4–6]. The observation that mobilized peripheral blood grafts contain approximately 10-fold more T-cells than marrow suggests a potential for

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increased graft-versus-host disease (GVHD), but the results remain conflicting [6–12]. Several prospective randomized studies have revealed different results, i.e. some studies revealed an increased incidence of chronic GVHD with PBSCT while others did not, and no increase in the incidence of acute GVHD was noted in these studies [13–17]. We retrospectively analyzed patients who received allogeneic BMT or PBSCT from human leukocyte antigen (HLA)-identical sibling donors at one center, and compared the differences in hematologic recovery, transfusion requirements, acute and chronic GVHD, relapse and disease-free survival, overall survival, and cause of death. We also compared our results with those of other studies [6–17].

MATERIALS AND METHODS

Patients

We retrospectively analyzed data for patients who underwent allogeneic hematopoietic stem cell transplantation at Kaohsiung Medical University Hospital in southern Taiwan between July 1993 and July 2001. Of the 61 patients who received allogeneic hematopoietic stem cell transplantation during this period, 29 were excluded: nine were less than 12 years old, four used matched unrelated donors, 15 used HLA mismatched donors (12 with one-locus mismatch, 3 with two-loci mismatch), and one had insufficient chart information. Thirty-two patients (BMT, 14; PBSCT, 18) included in the analysis fulfilled the following criteria: age between 18 and 50 years, no major organ dysfunction, and Karnofsky scores greater than 80%. The clinical characteristics of patients are detailed in Table 1.

Donors

Donors were genotypically HLA-A-, -B-, and -DR-identical siblings with good performance on physical examination and normal laboratory data results. BMT donors underwent conventional harvest with target nucleated cell yields of 2.0×10^8 /kg recipient body weight. PBSCT donors were treated with granulocyte colony-stimulating factor (G-CSF, filgrastim) 10 µg/kg/day subcutaneously for 5 days and leukapheresis was performed using a COBE Spectra Cell Separator (COBE BCT Inc, Lakewood, CO, USA) until target yields of CD34+ cells exceeded 2.5×10^6 cells/kg on two consecutive days (Days 5 and 6). No T-cell depletion was carried out in either group.

Preparative regimens

All patients received one of the following conditioning

Table 1. Characteristics of patients undergoing allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT)

| | BMT (n = 14) | PBSCT (n = 18) |
|------------------------------|-----------------|-------------------|
| Age | | |
| Median | 28 | 29 |
| Range | 17–47 | 16–46 |
| Sex | | |
| Male | 8 | 7 |
| Female | 6 | 11 |
| Diagnosis | | |
| Acute myeloid leukemia | 7 | 4 |
| Acute lymphoblastic leukemia | 4 | 3 |
| Chronic myeloid leukemia | 1 | 2 |
| Severe aplastic anemia | 1 | 6 |
| Non-Hodgkin’s lymphoma | 1 | 0 |
| Multiple myeloma | 0 | 1 |
| Myelodysplastic syndrome | 0 | 1 |
| Pure red cell aplasia | 0 | 1 |
| Disease status | | |
| Less advanced | 9 | 12 |
| More advanced | 5 | 6 |

Table 2. Conditioning regimens used for allogeneic stem cell transplantation in bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) recipients

| Regimen | BMT (n = 14) | PBSCT (n = 18) |
|-----------|--------------|----------------|
| TBI/CY | 3 | 12 |
| TBI/VP/CY | 6 | 5 |
| BU/CY | 5 | 1 |

TBI = total body irradiation; CY = cyclophosphamide; VP = etoposide; BU = busulfan.

regimens according to usual protocols (Table 2): total body irradiation (TBI) of 1,200 rads followed by cyclophosphamide (CY) 60 mg/kg/day for 2 days; TBI 1,200 rads followed by etoposide 60 mg/kg/day for 1 day and CY 50 mg/kg/day for 2 days; or busulfan 4 mg/kg/day for 4 days and CY 60 mg/kg/day for 2 days. Patients with severe aplastic anemia received TBI 300 rads followed by CY 50 mg/kg/day for 4 days. Acyclovir prophylaxis was given before transplantation. Ciprofloxacin, trimethoprim/sulfamethoxazole and fluconazole were used to decontaminate the gastrointestinal tract and provide antipneumocystis prophylaxis. G-CSF was prescribed at 5 µg/kg/day by subcutaneous injection from trans-

plantation Day 1 until the white blood cell count (WBC) was more than 1,000/ μL , or the absolute neutrophil count (ANC) was more than 500/ μL . Blood component therapy was performed after gamma-irradiation (1,500 rads) according to clinical symptoms and signs to keep the platelet count above 20,000/ μL and the hemoglobin concentration above 8.0 g/dL.

Engraftment

The day of neutrophil engraftment was defined as the first of three consecutive days on which the patient's ANC was above 500/ μL . The day of platelet engraftment was defined as the first of 7 consecutive days on which the platelet count was above 20,000/ μL without the need for transfusion.

GVHD diagnosis and management

Acute GVHD was graded according to standard criteria [18]. GVHD prophylaxis consisted of methotrexate (15 mg/m² on Day 1 and 10 mg/m² on Days 3, 6, and 11) followed by folinic acid (9 mg/m² intravenously, q6h for 8 doses) and cyclosporine (1.5 mg/kg intravenously bid with dose adjustment to maintain serum levels at 200–400 $\mu\text{g}/\text{dL}$, then oral treatment). Acute and chronic GVHD were diagnosed and managed as described previously [18]. Chronic GVHD was defined as GVHD present after Day 100 and was considered to be progressive when it appeared as a continuation of previous acute GVHD. Chronic GVHD was defined as *de novo* when there was no previous acute GVHD, and quiescent when it reappeared after the apparent resolution of previous acute GVHD. Biopsy confirmation of at least one of the affected organs was required.

Statistical methods

Outcome data, such as time to engraftment of neutrophils and platelets, transfusion requirements, development of acute or chronic GVHD, relapse, disease-free survival, overall survival, and causes of death, were analyzed and compared between the two groups. Data that were not normally distributed were analyzed using a nonparametric test (Mann-Whitney test). The probabilities of neutrophil and platelet recovery, acute or chronic GVHD, relapse, disease-free survival, and overall survival were compared using Kaplan-Meier survival analysis with log-rank analysis.

RESULTS

Hematopoietic stem cell harvest

The BMT group received a median of 2.71×10^8 (range,

$2.5\text{--}3.55 \times 10^8$) nucleated cells/kg according to standard procedure. The PBSCT group received a median of 13.35×10^8 (range, $5.48\text{--}29.8 \times 10^8$) nucleated cells/kg and 10.12×10^6 (range, $4.56\text{--}23.6 \times 10^6$) CD34+ cells/kg. G-CSF administration was well tolerated except for mild bone pain, which occurred in most donors.

Engraftment and transfusion requirement

All the recipients in both groups had neutrophil and platelet engraftment, except for one patient in the BMT group who died on Day 55 before the ANC reached 500/ μL . The ANC rose above 500/ μL and the platelet count rose above 20,000/ μL later in the BMT group than in the PBSCT group (both $p < 0.001$) (Table 3). The requirement for platelet transfusion was significantly less in the PBSCT group than in the BMT group ($p < 0.001$), although there was no significant difference in red cell transfusion (Table 3). Figures 1 and 2 show the hematopoietic reconstruction.

Acute and chronic GVHD

There was no difference in the incidence of acute GVHD between patients receiving BMT and those receiving PBSCT ($p = 0.72$), nor in the cumulative incidence of grade II–IV acute GVHD at Day 100 ($p = 0.57$) (Table 4). Grade III–IV acute GVHD occurred in only one patient receiving BMT and in none receiving PBSCT. The cumulative incidence of chronic GVHD for those who survived more than 100 days was 20% (2/10) in the BMT group, compared to 33.3% (6/18) in the PBSCT group ($p = 0.67$). Limited chronic GVHD with skin and mucous involvement was most common, noted in two patients (100%) in the BMT group and four (66.7%) in the PBSCT group. Extensive chronic GVHD was absent in BMT recipients but occurred in two (33.3%) PBSCT recipients ($p = 0.52$); liver and lung presentation was confirmed by biopsy. The most frequent subtype of chronic GVHD was *de novo* GVHD (BMT, 2/2; PBSCT, 4/6). Evidence of chronic GVHD was absent in all relapsed patients (BMT, 5 patients; PBSCT, 3 patients), and there was no relapse among patients with chronic GVHD during follow-up.

Relapse, survival and causes of death

As shown in Table 5, 35.7% of BMT recipients and 16.7% of PBSCT recipients suffered a relapse ($p = 0.25$). All relapse episodes occurred within 1 year of transplantation in both groups, and disease-free survival at 1 year was 35.7% (5/14) in the BMT group and 77.8% (14/18) in the PBSCT group ($p = 0.16$). Overall survival at 1 year was 57.1% (8/14) in the BMT group and 77.8% (14/18) in the PBSCT group ($p = 0.054$), and cumulative overall survival was 35.7% (5/14)

Table 3. Time to engraftment and transfusion requirements in allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) recipients

| | BMT (n = 14) | PBSCT (n = 18) | p |
|---------------------------------|--------------|----------------|---------|
| Time to engraftment (d) | | | |
| ANC > 500/ μ L | | | < 0.001 |
| Median | 13 | 8 | |
| Range | 10–20 | 7–11 | |
| Platelets > 20,000/ μ L | | | < 0.001 |
| Median | 17 | 9 | |
| Range | 10–24 | 7–16 | |
| Transfusion requirement (units) | | | |
| Red cells | | | 0.377 |
| Median | 5 | 4 | |
| Range | 0–22 | 6–12 | |
| Platelets | | | < 0.001 |
| Median | 144 | 54 | |
| Range | 60–546 | 24–144 | |

ANC = absolute neutrophil count.

in the BMT group and 77.8% (14/18) in the PBSCT group ($p = 0.029$) (Figure 3). Relapse was the most common cause of death in both groups, accounting for 55.6% (5/9) of mortality in BMT recipients and 75% (3/4) of mortality in PBSCT recipients. Treatment-related mortality at Day 100 was noted in 28.6% (4/14) of patients in the BMT group and none in the PBSCT group ($p = 0.028$). In addition to relapse,

the causes of death in the BMT group included cytomegalovirus (CMV) interstitial pneumonitis, no engraftment, and bacterial sepsis. One patient in the PBSCT group developed extensive chronic GVHD and died due to Pseudomonas pneumonia with septicemia.

We further compared the survival between the two groups, focusing on malignant hematologic diseases.

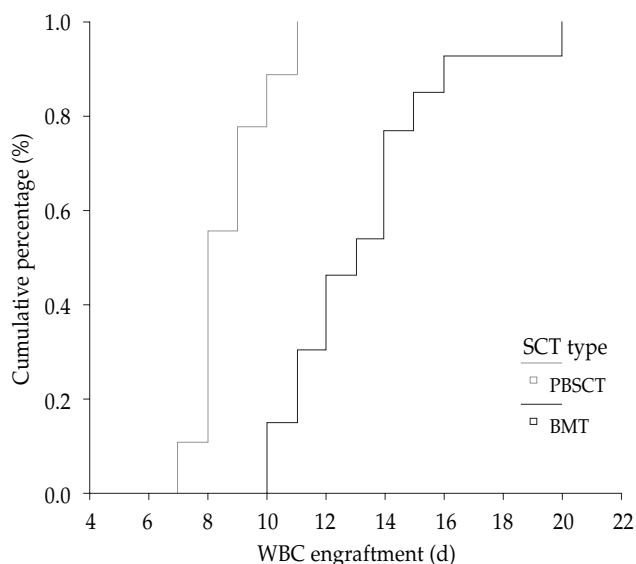


Figure 1. Probability of achieving an absolute neutrophil count (ANC) of more than 500/ μ L after allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) (log rank $p < 0.001$). WBC = white blood cell count; SCT = stem cell transplantation.

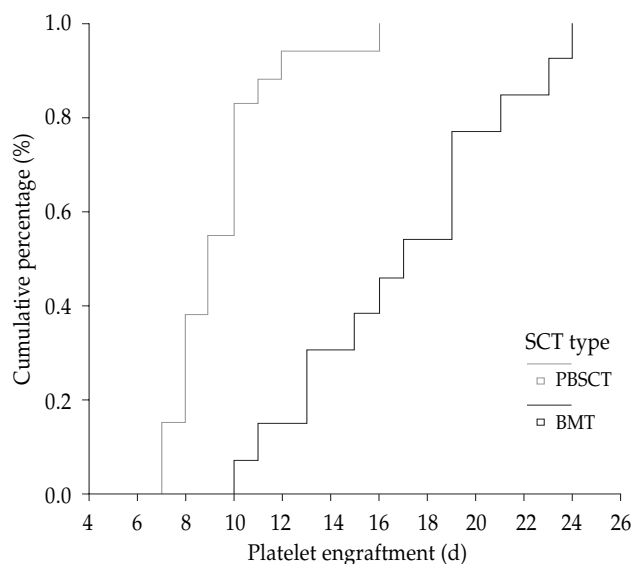


Figure 2. Probability of achieving a platelet count of more than 20,000/ μ L after allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) (log rank $p < 0.001$). SCT = stem cell transplantation.

Table 4. Incidence of acute graft-versus-host disease (GVHD) and chronic GVHD in allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) recipients

| | BMT n = 14 (%) | PBSCT n = 18 (%) | p |
|------------------|-------------------|---------------------|------|
| Acute GVHD | | | |
| All | 6 (42.9) | 6 (33.3) | 0.72 |
| Grades II to IV | 2 (14.3) | 1 (5.6) | 0.57 |
| Grades III to IV | 1 (7.1) | 0 | |
| Chronic GVHD | | | |
| All | 2 | 6 | 0.67 |
| Limited | 2 | 4 | |
| Extensive | 0 | 2 | |

Table 5. Causes of death during follow-up in allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) recipients

| | BMT (n = 14) | PBSCT (n = 18) | p |
|------------------|--------------|----------------|------|
| Number of deaths | 9 | 4 | |
| Relapse | 5 | 3 | 0.25 |
| Bacterial sepsis | 1 | 1 | |
| CMV pneumonitis | 2 | 0 | |
| No engraftment | 1 | 0 | |

CMV = cytomegalovirus.

Disease-free survival at 1 year was 30.8% (4/13) in the BMT group and 63.6% (7/11) in the PBSCT group ($p = 0.20$). Overall survival at 1 year was 46.2% (6/13) in the BMT group and 72.7% (8/11) in the PBSCT group ($p = 0.19$), and cumulative overall survival was 30.8% (4/13) in the BMT group and 63.6% (7/11) in the PBSCT group ($p = 0.20$) (Figure 4). Relapse was still the most common cause of death in both groups: 38.5% (5/13) of BMT recipients and 27.3% (3/11) of PBSCT recipients ($p = 0.55$).

DISCUSSION

This retrospective study compared allogeneic PBSCT with allogeneic BMT from HLA-identical siblings in adult hematologic disease. Allogeneic PBSCT provided significantly faster neutrophil and platelet engraftment than allogeneic BMT and shorter stays in the laminar flow room. In addition, the PBSCT group required significantly

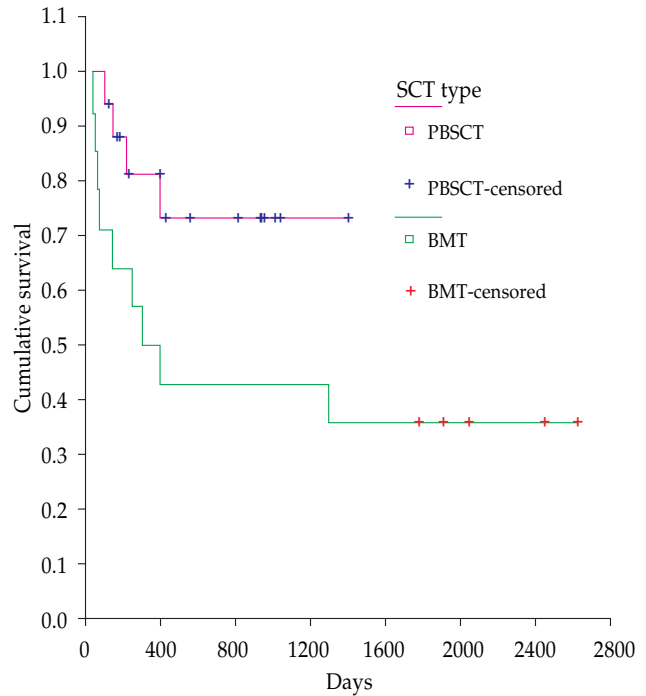


Figure 3. Cumulative overall survival curve in all patients receiving allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) (log rank $p = 0.029$). SCT = stem cell transplantation.

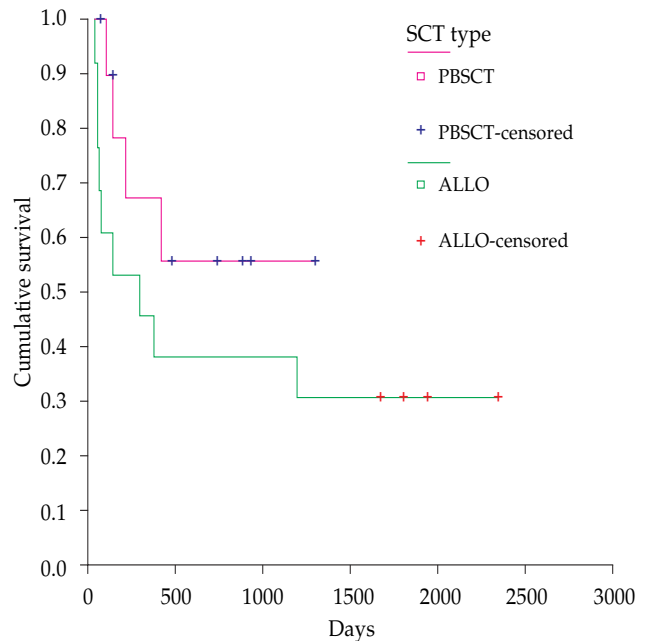


Figure 4. Cumulative overall survival curve for allogeneic bone marrow transplantation (BMT) and allogeneic peripheral blood stem cell transplantation (PBSCT) in hematologic malignancies (log rank $p = 0.20$). SCT = stem cell transplantation.

less platelet transfusion than the BMT group, although red cell transfusion was no different. These results are generally consistent with those of previous reports [4–6,13–17]. Interestingly, we found earlier neutrophil (median, Day 8) and platelet engraftment (median, Day 9) with PBSCT than other studies [4–6,13–17]. This may be due to the higher number of CD34+ stem cells transplanted in our study and prescription of G-CSF after transplantation. The earlier neutrophil engraftment suggests that allogeneic PBSCT might have benefit, compared with conventional allogeneic BMT, in shortening neutropenic periods and in lowering the risk of prolonged neutropenic fever, and this was also evident in other studies [4–6,13–17].

PBSCT recipients did not have a greater incidence of acute GVHD than BMT recipients in our study (for all grades and grades II–IV), which is similar to previous reports [4–6,10–17]. The possible explanations include: G-CSF may induce T-cells to produce interleukin-4 (IL-4) and IL-10, which down-regulate the inflammatory responses involved in GVHD [19]; the presence of large numbers of G-CSF-stimulated monocytes with T-cell suppressor activity in the graft [20]; and greater numbers of dendritic cells that induce a type 2 helper T-cell response [21]. In addition, there was a lower incidence of moderate to severe acute GVHD (grade II or more) in both groups (BMT, 14.3%; PBSCT, 5.6%) in our study compared with other reports.

The incidence of chronic GVHD was not significantly increased in PBSCT recipients (33.3%) compared to BMT recipients (20%) in our study, with a median follow-up of 58 months in BMT recipients and 18 months in PBSCT recipients. Many retrospective studies have debated the greater incidence of chronic GVHD in PBSCT recipients than in BMT recipients, but no definite conclusions have been drawn [7–12]. Several small prospective randomized studies of chronic GVHD report conflicting results [13–16]. A large prospective randomized study by Bensinger et al revealed no increased risk of acute or chronic GVHD with PBSCT [17]. Some studies mention an increased risk for developing chronic GVHD with a previous acute GVHD episode [8,12], but no similar results were found in either group in our study. Only two patients, in our PBSCT group, developed limited chronic GVHD with previous grade I or II acute GVHD episodes; six patients (2 in the BMT group and 4 in the PBSCT group) developed *de novo* chronic GVHD. There was no significant difference in the incidence of extensive chronic GVHD in the two groups ($p = 0.524$), and the incidence was less than that in other studies [7–12, 14–17]. A relationship between chronic GVHD and relapse

was noticed in previous studies, and a lower risk of relapse due to the graft-versus-leukemia effect of allogeneic T-cells was noted, especially in patients with chronic myelogenous leukemia. No evidence of chronic GVHD was noted in our relapsed patients, and no evidence of relapse was found in patients with chronic GVHD during follow-up.

Cumulative overall survival was significantly greater with PBSCT than BMT (35.7% vs 77.8%, $p = 0.029$) and there was borderline significance in favor of PBSCT in 1-year survival (57.1% vs 77.8%, $p = 0.054$). This may have been caused by rapid engraftment and improvement in supportive care in recent years.

There may have been statistical bias between the two groups due to more non-hematologic malignancies in the PBSCT group. When comparing the results in patients with hematologic malignancies, overall survival (30.8% vs 63.6%) and 1-year survival (46.2% vs 72.7%) were better in PBSCT than BMT recipients, although this was not statistically significant ($p = 0.20$ and 0.19 , respectively). There may be a clinical benefit to PBSCT, but the interpretation of survival benefit may be difficult due to limited case numbers in our study; further follow-up and analysis are necessary.

The most important cause of death in both groups was relapse, which accounted for 55.6% of deaths in the BMT group and 75% in the PBSCT group. Treatment-related mortality before Day 100 accounted for 44.6% of deaths, with two suffering from CMV interstitial pneumonitis in the BMT group but none in the PBSCT group. One cause of death in the PBSCT group was extensive chronic GVHD with *Pseudomonas* septicemia. Other causes that have often resulted in mortality after transplantation, such as veno-occlusive disease or hemorrhage, were not observed in our study.

In conclusion, G-CSF-mobilized allogeneic PBSCT provided faster neutrophil and platelet engraftment, decreased requirement for platelet transfusion, and shortened laminar flow room stay and hospitalization compared with conventional allogeneic BMT. There was no significant increase in the incidence of acute GVHD, grade II–IV acute GVHD, or chronic GVHD with PBSCT compared with BMT. Higher overall survival was noted in the PBSCT group, but there was no significant difference when only hematologic malignancies were compared. This implied that the number of cases was limited and that further follow-up is necessary. Relapse constituted the most important cause of death in both groups, and it seemed that there was a lower risk of relapse with chronic GVHD. Our results correlated well with those of previous studies.

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