Original Article

Granulocyte Colony-stimulating Factor-primed Bone Marrow: An Excellent Stem-cell Source for Transplantation in Acute Myelocytic Leukemia and Chronic Myelocytic Leukemia

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Abstract

Background: Steady-state bone marrow (SS-BM) and granulocyte colony-stimulating growth factor-primed BM/peripheral blood stem-cell (G-BM/G-PBSC) are the main stem-cell sources used in allogeneic hematopoietic stem-cell transplantation. Here, we evaluated the treatment effects of SS-BM and G-BM/G-PBSC in human leucocyte antigen (HLA)-identical sibling transplantation.
Methods: A total of 226 patients (acute myelogenous leukemia-complete remission 1, chronic myelogenous leukemia-chronic phase 1) received SS-BM, G-BM, or G-PBSC from an HLA-identical sibling. Clinical outcomes (graft-versus-host disease [GVHD], overall survival, transplant-related mortality [TRM], and leukemia-free survival [LFS]) were analyzed.
Results: When compared to SS-BM, G-BM gave faster recovery time to neutrophil or platelet ($P < 0.05$). Incidence of grade III–IV acute GVHD and extensive chronic GVHD (cGVHD) was lower than seen with SS-BM ($P < 0.05$) and similar to G-PBSC. Although the incidence of cGVHD in the G-BM group was similar to SS-BM, both were lower than G-PBSC ($P < 0.05$). G-BM and G-PBSC exhibited similar survival, LFS, and TRM, but were significantly different from SS-BM ($P < 0.05$). There were no significant differences in leukemia relapse rates among the groups ($P > 0.05$).
Conclusions: G-CSF-primed bone marrow shared the advantages of G-PBSC and SS-BM. We conclude that G-BM is an excellent stem-cell source that may be preferable to G-PBSC or SS-BM in patients receiving HLA-identical sibling hematopoietic stem-cell transplantation.

Key words: Bone Marrow; Granulocyte Colony-stimulating Growth Factor; Human Leucocyte Antigen-identical Sibling Hematopoietic Stem-cell Transplantation; Peripheral Blood Stem-cells

Introduction

Hematopoietic stem-cell transplantation (HSCT) is an important therapeutic option for many malignant and nonmalignant disorders. Since the first report of bone marrow (BM) transplantation, steady-state BM (SS-BM) has been the only stem-cell source for HSCT. In recent years, granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem-cells (G-PBSC) have become an alternative stem-cell source. G-PBSC is even preferred in adults receiving human leucocyte antigen (HLA)-identical sibling transplantation. Although G-PBSC are enriched in progenitor cells as compared to SS-BM, which allows a faster engraftment,[1] the use of G-PBSC will increase the incidence of chronic graft-versus-host disease (cGVHD).[2,3] To take advantage of G-PBSC while decrease the risk of cGVHD, G-CSF-primed BM (G-BM) has been explored. Recently, G-BM has been an attractive option for HLA-haploidentical/mismatched donor transplantation.[4-6] However, G-BM does not seem to be considered an alternative to SS-BM in HLA-identical HSCT due to nonsignificant improvement in survivals,[7-9] although its feasibleness, safety, well-engraftment and limited incidence of GVHD have been demonstrated.[7-16]

The conclusions from previous studies on HLA-identical transplantation with G-BM might be limited due to the number of patients, underlying diseases, disease status at the time of transplantation, G-CSF schedules, conditioning regimens, and GVHD prophylaxis. In this study, we conducted a retrospective nonrandomized controlled study to evaluate the clinical outcomes of G-BM, SS-BM, and G-PBSC in HLA-identical sibling HSCT in our center. The results suggested that G-BM was an excellent stem-cell source in HLA-identical sibling HSCT.

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Methods

Patients

A total of 226 early stage myeloid leukemia patients, including *de novo* acute myelogenous leukemia (AML) (complete remission 1 [CR1]) and chronic myelogenous leukemia (CML) (chronic phase 1 [CP1]), with HLA-identical sibling donor, were enrolled in this study (March 2004–March 2009). Patients who have received second transplants/ reduced-intensity preparative regiments were excluded. The main clinical characteristics of patients at the time of HSCT were listed in Table 1. 43, 60, and 123 patients were enrolled in the G-BM, SS-BM, and G-PBSC groups, respectively.

This study was approved by the Ethics Committee of the affiliated hospital of Academy of Military Medical Sciences. Informed consents were obtained from all patients, donors, or their legal guardians.

Treatment

In the G-PBSC group, donors received G-CSF at 8.0 μg kg^{-1} d^{-1} divided in two subcutaneous injections for 5 consecutive days (day −3 to day +1), and PBSC was harvested on day 0 and day +1. In the G-BM group, donors received G-CSF at 5.0 μg kg^{-1} d^{-1} by a single subcutaneous injection for 3 consecutive days (day −3 to day −1), and G-BM was harvested on day 0. In the SS-BM group, BM was harvested at day 0. BMs was harvested from donors based on a target volume of 20 ml/kg.The stem-cells were infused on the same day they were collected. The median total nucleated cells infused into recipients were 4.2×10^8/kg (G-BM, range: 2.2×10^8– 8.1×10^8/kg), 7.7×10^8/kg (G-PBSC, range: 1.8×10^8– 22.7×10^8/kg), and 2.5×10^8/kg (SS-BM, range: 1.8×10^8–4.4×10^8/kg) of recipient weight, respectively. Plasma or red cell depletion of the grafts was performed if any ABO incompatibility was presented before infusions.

Table 1: Patient characteristics

Items	G - BM	SS - BM	G - PBSC	*P*
Number of patients	43	60	123	
Sex (male/female)				
Recipients (male/female)	29/14	35/25	80/43	0.576
Donors (male/female)	21/22	29/31	61/62	0.986
Age (years)				
Recipients	36 (12 - 52)	28 (15 - 45)	35 (14 - 56)	
Donors	35 (14 - 60)	28 (12 v 42)	35 (12 - 67)	
Female donor/male recipient (%)	39.5	33.3	33.3	0.744
Diagnosis				
AML	27	32	55	0.109
CML	16	28	68	
Conditioning regimen				
Cy/fractionated TBI (%)	100	100	100	

SS-BM: Steady-state bone marrow; G-PBSC: G-peripheral blood stem cell; G-BM: G-CSF-primed bone marrow; AML: Acute myelocytic leukemia; CML: Chronic myelocytic leukemia; TBI: Total body irradiation.

All recipients received the standard preparative regimen involving cyclophosphamide (60 mg·kg^{-1}·d^{-1} × 2, day −4, day −3) and total body irradiation (TBI) (5 Gy/day × 2, day −2, day −1). The GVHD prophylaxis included cyclosporin A (CSA) and the short-term methotrexate (MTX).

Evaluations and definitions

Neutrophil recovery was defined as having occurred after the first of 3 days with an absolute neutrophil count >500/μl after the post-transplant nadir. Platelet recovery was defined as the first of 7 consecutive days with a platelet count >50,000/μl without platelet transfusions. Acute and cGVHD (aGVHD) were graded by the Seattle criteria.[17,18] Transplant-related mortality (TRM) was defined as death from any cause except relapse. Leukemia-free survival (LFS) was defined as the time interval from transplantation to the first event (either relapse or death). Overall survival (OS) was calculated from the time of transplantation to death.

Statistic analysis

The cumulative incidence curves of GVHD, TRM, LFS, and OS were plotted using the Kaplan–Meier method, and the long-rank test was used for independence comparison between variables. For all analysis, $P < 0.05$ was considered as statistically significant. All statistical analysis was performed with the SPSS statistics 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Hematopoietic reconstitution

The median time to neutrophil recovery was 15 days (range, 11–26), 17 days (range, 13–31), and 25 days (range, 15–63) in the G-PBSC group, the G-BM group, and the SS-BM group, respectively [Figure 1a]. The median time to platelet recovery were 22 days (range, 12–176), 32 days (range, 15–365), and 47 days (range, 21–200) in the G-PBSC group, the G-BM group, and the SS-BM group, respectively [Figure 1b]. The time to neutrophils and platelet engraftment was significantly different among all groups (G-PBSC vs. G-BM, G-PBSC vs. SS-BM, G-BM vs. SS-BM) ($P < 0.05$).

G-CSF-primed bone marrow reduced the risk of graft-versus-host disease

The cumulative incidences of grade II–IV aGVHD were (30.4 ± 7.0)%, (26.7 ± 5.9)%, and (36.2 ± 4.4)% in the

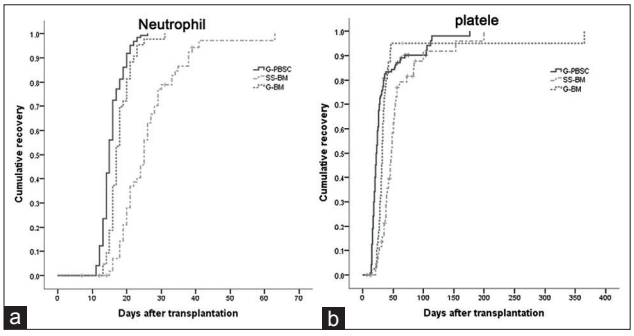

Figure 1: Engraftment. (a) Time to absolute neutrophil count recovery above 0.5×10^9/L. (b) Time to platelets recovery above 50×10^9/L.

G-BM, SS-BM, and G-PBSC group, respectively [Figure 2a]. There was no significant difference on incidence of aGVHD among these groups ($P > 0.05$). The cumulative incidence of grade III–IV aGVHD in the G-BM group ([4.7 ± 3.2]%) was significantly lower than that in the SS-BM group ([17.5 ± 5.0]%, $P < 0.05$). There was a tendency of lower frequency of grade III–IV aGVHD in the G-PBSC group compared to SS-BM, although it was not statistically significant ([16.4 ± 3.4]% vs. [17.5 ± 5.0]%, $P = 0.058$) [Figure 2b].

For cGVHD, the cumulative incidence in the G-BM group was similar to that in the SS-BM group ([28.4 ± 7.8]% vs. [34.0 ± 6.9]%, $P > 0.01$), while there was significant differences between the G-BM and G-PBSC group ([28.4 ± 7.80]% vs. [64.4 ± 5.1]%, $P < 0.05$), and between the SS-BM and G-PBSC group ([34.0 ± 6.9]% vs. [64.4 ± 5.1]%, $P < 0.05$) [Figure 2c]. Similar patterns were observed when the cumulative incidences of extensive cGVHD were analyzed (G-BM vs. G-PBSC: [11.8 ± 5.6]% vs. [42.7 ± 5.1]%, $P < 0.05$; G-BM vs. SS-BM: [11.8 ± 5.6]% vs. [21.7 ± 6.1]%, $P < 0.05$) [Figure 2d].

G-CSF-primed bone marrow increased the survival rates

The OS rate in the G-BM group and the G-PBSC group were (76.3 ± 6.6)% and (70.3 ± 4.6)%, respectively. Both were significantly higher than the SS-BM group ([45.1 ± 6.6]%, $P < 0.05$) [Figure 3a]. The incidences of LFS in the G-BM and G-PBSC were (68.7 ± 7.2)% and (68.9 ± 4.7)%, both were significantly higher than that in the SS-BM group ([45.3 ± 6.6]%, $P < 0.05$) [Figure 3b]. The cumulative incidence of TRM in the SS-BM group was (41.2 ± 6.7)%, which was significantly higher than that in the G-PBSC and the G-BM groups ([19.0 ± 3.9]%, $P < 0.05$; [12.0 ± 5.0]%, $P < 0.05$) [Figure 3c]. However, there were no significant differences in leukemia relapse rates between any two groups (G-BM, [23.9 ± 7.0]%; G-PBSC, [20.3 ± 4.4]%; SS-BM, [24.0 ± 7.0]%) ($P > 0.1$) [Figure 3d].

Table 2 shows the causes of death in each group. A total of 33 of 60 patients (55%) died due to a variety of factors (leukemia relapse, GVHD, infections, interstitial pneumonia/idiopathic pneumonia syndrome, graft rejection, etc.) in the SS-BM group. In contrast, only 25.6% (11/43) of the G-BM group and 26.0% (32/123) of the G-PBSC group died due to the same reasons.

Meanwhile, there was no significant difference between AML and CML on OS ([59.8 ± 5.0]% versus [67.7 ± 4.7]%, $P > 0.05$), LFS ([57.3 ± 5.1]% vs. [66.0 ± 4.8]%, $P > 0.05$), and TRM ([23.7 ± 4.4]% versus [24.1 ± 4.4]%, $P > 0.05$). However, AML is associated with more leukemia relapse compared to CML ([27.7 ± 5.1]% versus [16.4 ± 4.2]%, $P < 0.05$).

Discussion

Steady-state bone marrow, G-PBSC, and G-BM are the main stem-cell sources in allogeneic HSCT. A number of groups have reported on the clinical outcomes of patients who received G-BM, G-PBSC, or SS-BM during HLA-identical sibling HSCT.[7-16] These studies show that G-BM and G-PBSC resulted in significantly faster neutrophil and platelet recovery than SS-BM, which is consistent with the results presented here. However, previous studies indicated that G-BM appeared to have no advantage in survivals when compared to SS-BM.[7-9] In this study, compared with patients treated with SS-BM, those patients who were treated with G-BM and G-PBSC

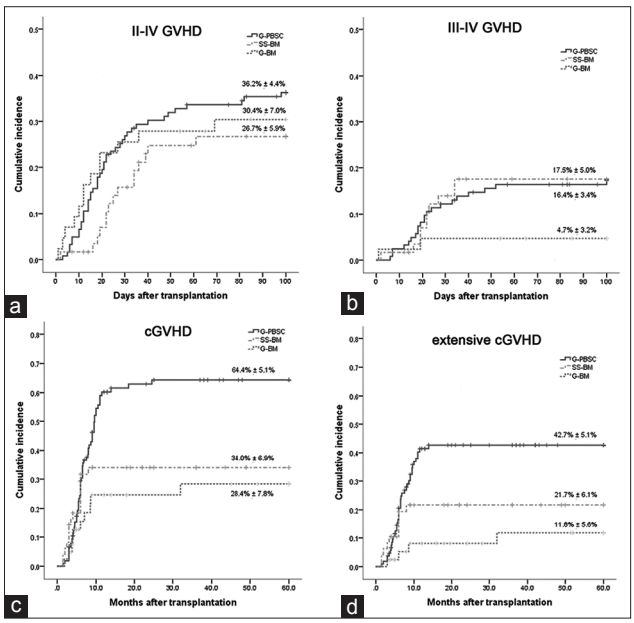

Figure 2: Cumulative incidence of graft-versus-host disease (GVHD). (a) Grades II–IV acute GVHD. (b) Grades III–IV acute GVHD. (c) Chronic GVHD. (d) Extensive chronic GVHD.

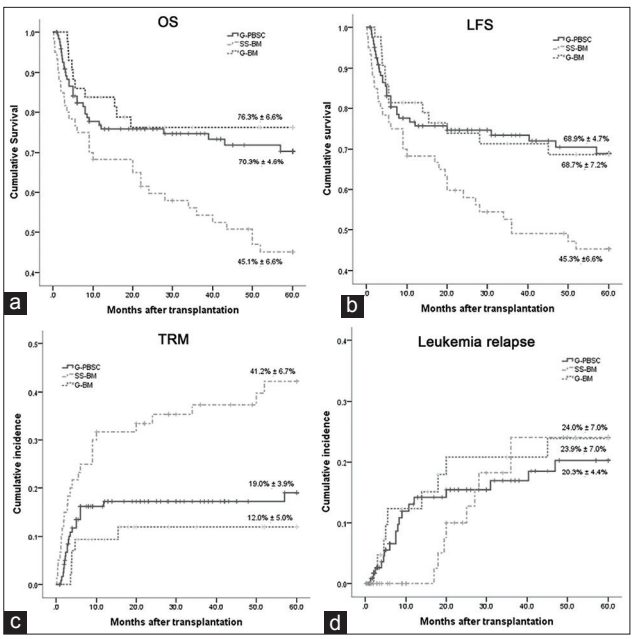

Figure 3: Survival of the entire cohort by therapy. (a) Overall survival. (b) Leukemia-free survival. (c) Transplant-related mortality. (d) Leukemia relapse.

Table 2: Causes of death

Items	G-BM (n = 43)	SS-BM (n = 60)	G-PBSC (n = 123)
Leukemia relapse	6	8	11
aGVHD (or with infections)	1	6	7
cGVHD	1	5	4
Infections	1	5	5
Interstitial pneumonia/ idiopathic pneumonia syndrome	0	2	3
Graft rejection	1	2	0
HVOD	0	1	0
Cerebral hemorrhage	0	1	0
Organ dysfunction	1	0	1
Gastric cancer	0	1	0
Hemocytolysis	0	1	0
Asthma	0	0	1
Hepatitis B	0	1	0
Total (n (%))	11 (25.6)	33 (55.0)	32 (26.0)

aGVHD: Acute graft-versus-host disease; cGVHD: Chronic graft-versus-host disease; HVOD: Hepatic veno-occlusive disease; G-PBSC: G-peripheral blood stem cell; G-BM: G-CSF-primed bone marrow.

had significantly higher OS [Figure 3a] and LFS [Figure 3b]. As to TRM and III–IV grade aGVHD, the incidences of patients treated with G-BM were significantly lower chance to develop aGVHD and greater chance of survival than those treated with SS-BM [Figure 2a and b]. Interestingly, G-BM could significantly decrease the incidences of cGVHD and extensive cGVHD, compared with G-PBSC [Figures 2c and d], which was consistent with a previous study.[13] However, G-BM did not increase the incidences of leukemia relapse [Figure 2d]. These results clearly indicated that G-BM shared the advantages of both G-PBSC and SS-BM, which was characterized by fast engraftment, low incidences of very severe aGVHD/cGVHD/TRM, and high incidences of LFS/OS. This report was the first study that included all three main stem-cell sources (G-BM, G-PBSC, SS-BM), and we concluded that G-BM was an excellent stem-cell source for HLA-identical sibling HSCT.

Many groups have compared the different clinical outcomes of G-BM with SS-BM or G-PBSC in HLA-identical sibling HSCT,[7-13,15,19] however, the results have been very controversial, especially regarding the OS. Our study indicated that G-BM was superior to SS-BM and G-PBSC, and that a significant improvement in OS was observed in the G-BM group. The variances might be caused by several factors. First was the number of the enrolled patient and the follow-up durations. Previous reports studied fewer patients (22, 48, and 50 patients) with shorter follow-up duration (the median time <12 months).[7-9] We have conducted the current study with more patients (226) and longer follow-up time (median time, G-BM: 60 months; G-PBSC: 30 months; SS-BM: 40 months), which could reach a sufficient statistical power. The second was the G-CSF priming schedules. Previous studies have shown that G-CSF stimulation caused a 1.4–1.7-fold increase in CD34 + cell count, a 3-fold increase in colony-forming cells, and 50–90-fold increase in short-term repopulating cells in G-BM, when compared to SS-BM.[20] However, different priming schedules (doses and duration of G-CSF administration) might cause controversial results regarding the engraftment capability of G-BM,[21,22] which would in turn cause different treatment outcomes. The priming schedules in previous studies were very diverse.[10-13,15,19] The dose of G-CSF for BM priming ranged from 5 $\mu g \cdot kg^{-1} \cdot d^{-1}$ to 12.1 $\mu g \cdot kg^{-1} \cdot d^{-1}$ and the length of G-CSF treatment ranged from 2 to 5 days. In the present study, all donors received a uniformed G-CSF priming schedule, which was 5.0 $\mu g \cdot kg^{-1} \cdot d^{-1}$ for 3 consecutive days. In addition, the disease status before the transplantation would have an impact on the outcome. To rule out the interference of disease status, we only included patients with *de novo* AML (CR1) and CML (CP1). We found that AML patients had higher leukemia relapse rates than CML, which suggested that different underlying disease before transplantation might play a role in the treatment effect of HSCT. Finally, the preparative regimens, the GVHD prophylaxis, and the supportive care might play a role in the outcome. We used the classic Cy routine combined with fractionated TBI as preparative regimens and standard CSA plus short-term MTX as prophylactic measures to prevent GVHD in all patients. The uniform management could reduce the interferences of these factors and give more credible results. Further investigation is needed to address how these factors influenced the treatment effects in HSCT.

Despite the availability of many new immune suppressive drugs and antibodies, GVHD still remained the most serious complications in HSCT. To obtain the optimal results, we need to decrease the GVHD while enhance the graft-versus-leukemia (GVL) effect. To effect, a lot of approaches have been developed to minimize the GVHD, such as the depletion of T-cells *in vitro* and *in vivo*, and the introduction of suicide gene into T-cells.[23,24] These approaches could decrease the incidence of GVHD, but the lower GVHD rates might be due to using of anti-thymocyte globulin, depletion of T-cells, or other factors. In this study, we found that the GVL effect in G-BM was superior to G-PBSC and SS-BM. As presented in this study, G-BM could remarkably lower the risk of GVHD (III–IV grade GVHD, cGVHD, extensive cGVHD), and accordingly improve the survival. However, the incidence of leukemia relapse did not increase, suggesting that G-BM might be an alternative way to enhance GVL effect and lower the risk of GVHD. Meanwhile, the use of G-BM in HSCT might be a simple and "low prices" approach to separate GVHD and GVL effects which did not require additional immunosuppression drugs or special measurements.

This was the first retrospective report on HLA-identical sibling HSCT that was conducted in a single center with all three main grafts (G-BM, G-PBSC, SS-BM). Compared with previous studies, the overall clinical outcomes of G-BM, G-PBSC, and SS-BM in this study might be more credible because the number of patients was higher and the treatments (preparative

regimens, GVHD prophylaxis, and supportive care) were uniform. Recently, a phase 3, randomized trial comparing G-BM and SS-BM is ongoing,[15] and another randomized multicenter study comparing G-PBSC and G-BM in patients receiving HLA-identical sibling HSCT is also being conducted in Canada.[25] Although the corresponding results are not released yet, we believe that these studies will further illuminate the advantages of G-BM in HSCT.

This study has several limitations including the retrospective nature, the heterogeneous patient cohorts, and lacking of molecular typing. However, the results are remarkable because of a comparatively large number of patients with a long follow-up as well as uniform data collection.

In summary, our study has provided sufficient data to conclude that G-BM is an excellent stem-cell source in HLA-identical sibling HSCT. G-BM transplant is characterized by fast engraftment, low incidence of severe aGVHD/cGVHD, and improved survival. We recommend G-BM rather than G-PBSC or SS-BM for patients receiving HLA-identical sibling HSCT. Meanwhile, G-BM is potentially a good stem-cell source in unrelated and haploidentical HSCT, which need to be further investigated in the future.

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