ALLOGENEIC PERIPHERAL BLOOD AND BONE MARROW STEM CELL TRANSPLANTATION FOR CHRONIC MYELOGENOUS LEUKEMIA: A SINGLE CENTER STUDY

A. Ghavamzadeh, M. Iravani*, M. Jahani, B. Bahar, A. Mousavi, S. Gholibeikian, M. Jafari and F. Safavifar

Department of Hematology-Oncology, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract- In this center, from 1991 to 2002, 89 chronic myelogenous leukemic (CML) patients, age ranging between 8-48 years with a median age of 29, underwent hematopoietic stem cell transplantation. Eighty-eight patients were in the first chronic phase of disease. Twenty-three patients received bone marrow transplantation (BMT) and 66 patients received peripheral blood stem cell transplantations (PBSCT). Transplantation was performed at a median interval of 19 months post-diagnosis. All with five exceptions received busulfan + cyclophosphamide (Bu Cy) conditioning regimens. To maintain graft vs. host disease (GVHD) prophylaxis, all with three exceptions received cyclosporine + metothrexate. Administration of granulocyte colony stimulating factor (G-CSF), per protocol, was included in post-transplantation regimens from the year 1999 on 48 patients. All patients received marrow transplantations from sibling donors. Fifty seven of transplanted patients are alive. Disease free survivals (DFS) from 6.2 to 9.5 and from 2.2 to 6.2 years for BMT group were 38.2% and 47.8%, respectively. DFS for PBSCT group was calculated as 54.3% in a period of 1.9 to 4.6 years.

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INTRODUCTION

Allogeneic marrow transplantation is the preferred treatment for 'young' patients with chronic myelogenous leukemia (CML) who have human leukocyte antigen (HLA)-identical sibling donors. However, because most individuals with CML are older than 40 or 50 years threshold, below which early transplantation is generally recommended (1-3), or lack histocompatible sibling donors, only a small proportion undergo allogeneic marrow transplantation shortly after diagnosis. Many patients undergo transplantation beyond the first year after diagnosis (4-6) and/or after they have progressed to an accelerated or blastic phase (5-7) circumstances which compromise success rates (4-10). Delay in transplantation often results from hesitancy by patients and physicians because of the early mortality associated with allogeneic marrow transplantation and controversy regarding its optimal timing (11).

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*** Corresponding Author:**
M. Iravani, Department of Hematology-Oncology, Shariati Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 8004140
Fax: +98 21 8004140
E-mail: horcbmt@sina.tums.ac.ir

Improved success rates would directly benefit patients undergoing this procedure and would likely extend its timely application to individuals who otherwise might delay or avoid transplantation. The median follow-up period in most BMT-studies for CML is less than 5 years. The majority of patients relapse within 3 years following BMT. Occasionally however, patients who had leukemia relapse more than 10 years after transplant have been reported (12,13). This would emphasize the importance of long-term follow-up for these patients. Also, long-term follow-up is necessary to evaluate the probability of secondary malignancies and to study the quality of life of BMT survivors. In this study, we report our experience in 66 PBSC and 23 BM allogeneic transplantations for CML.

MATERIALS AND METHODS

Definitions of Disease Stage and Relapse

Diagnosis required demonstration of the Philadelphia chromosome or (Ph) hematologic situation. Accelerated and blastic stages were defined according to published definitions (13). CML phases

were defined according to published criteria.(14) Relapse was defined as the detection of Ph positive metaphases on two or more separate occasions after day of 60 or hematological evidence of recurrent CML. Transplant-related mortality was defined as death due to causes other than disease recurrence.

Tissue Typing

HLA matching was based on serologic typing or molecular methods for HLA A, B, C and DR antigens. A single mismatching at HLA A, B, or DR was permitted for related donors.

Patients and Donors Characteristics

Eighty-nine consecutive CML patients, 51 men and 38 women, were evaluated between 1991 and 2002 in our center. They had a median age at transplantation time of 29 years (range 8-48) and received hematopoietic stem cell transplantation from HLA-identical sibling donors (7 patients had one antigen-mismatching). Ten patients (11.23%) were 40 years or older. All patients were Ph positive except four who were Ph negative (those were diagnosed by molecular rearrangements BCR/ABL or hematologic evidence of CML). Eighty-six patients were in chronic phase, two in accelerated phase and one in blastic crisis. Transplantation was performed at a median interval of 21 months from diagnosis of CML. The donor ages were between 11 and 69. The patients and donors demographic data are shown in Table 1.

Preparative Regimen and Supportive Care

All patients with five exceptions received cyclophosphamide (Cy) 60 mg/kg/day for 2 days (IV) and Busulfan 4 mg/kg/day for 4 days (PO) as conditioning regimens. Patients received unmanipulated marrow infusion the day after the last dose of conditioning. The median marrow cell dose infused was 6.25×10^8cells (range 2 to 20.39×10^8). PBSC donors were treated with G-CSF at a dose of 10 µgr/kg/day, administered by subcutaneous injection. PBSC were collected by leukapheresis on the 5^{th} day of treatment, approximately 4 to 8 hours after the last G-CSF injection. The median marrow cell dose infused in BMT patients was 3.22×10^8 cells (range 2 to 4.92×10^8) and in PBST patients median marrow cell dose infused was 7.33×10^8 cells (range 4.02 to 20.39×10^8). All patients were maintained in strict isolation in single rooms and were given prophylactic broad-spectrum antibiotics, acyclovir, amphotericin B or fluconazole and trimethoprim sulfamethoxazole. All blood products administered were irradiated at 25-30 Gy. Cyclosporine and methotrexate were given for graft-versus-host disease (GVHD) prophylaxis (12). We used cyclosporine 3 mg/kg (IV) from day -3 to +5 and then12.5 mg/kg (PO) from day +6 , Methotrexate 10mg/m^2 in day +1 and then 6 mg/m^2 on days +3, +6 and +11 as GVHD prophylaxis regimen. Growth factors were not routinely administered after transplantation until year 1999. From the year 1999, routine administration of growth factors has been practiced.

Table 1. Patients and donors characteristrics

	PBSC Group (n=66)	BM Group (n=23)
Male	38(57.6%)	13 (56.5%)
Female	28(42.4%)	10 (43.5%)
Median age		
Patients	28.5(8-48)	29(11-41)
Donors	29(11-69)	26(1.5-42)
Donor --- Recipient Gender		
M ---M	26	9
F--- F	12	4
M---F	12	4
F---M	16	6
HLA (Identical/Mismatch)	61/5	21/2
Median diagnosis	469	656
(Range of BMT interval in days)	(194-4192)	(199-1056)
Chronic/Advanced phase	64/2	22/1
Median nucleated cell (x10^8 /kg)	7.33	3.22
	(4-20.4)	(2-4.9)

Statistical Analysis

Univariate analyses of survival and event-free survival used the Kaplan Meier product limit method (15) with log rank tests (16) of survival curves. Cox proportional hazards regression (17) was used in multivariate analyses to identify possible prognostic factors.

RESULTS

Hematopoietic Recovery

Engraftment was judged to have occurred on the first of 3 consecutive days that the neutrophil count exceeded 0.5×10^9/L. Platelet recovery was defined as a platelet count exceeding 50×10^9/L without platelet transfusion. Seven patients who died before 21 days were not evaluated for engraftment analysis. Eight of the evaluated patients had rejection or graft failure. The median times of absolute neutrophil count (ANC) $>0.5 \times 10^9$/L was 18.4 days in PBSCT (61 out of 66) and 27 days in BMT (20 out of 23) groups (P=0.03). The ANC $>0.5 \times 10^9$/L was 16.8 days and 25.4 days in G-CSF included (one BMT, 45 PBSCT) and G-CSF non-included (19 BMT, 16 PBSCT) groups, respectively (P=0.017). The difference remained significant even after omitting the type of transplant as a co-finder (P=0.04). The median times of platelet count (plt) $>50 \times 10^9$/L was 32 and 38 days in PBSCT (48 out of 69) and BMT groups (21 out of 23), respectively (P=0.65). The median time of plt $>50 \times 10^9$/L was 19.8 and 52.3 days in G-CSF included [38] and G-CSF non-included [31], respectively (P=0.012). The difference, however, remained significant after omitting the type of transplant as a co-finder (P=0.042).

Transplant-Related Complications

GVHD

Total incidence rate of acute GVHD was 88.6% (78/88) with 87% (20/23) and 89.2% (58/65) for BMT and PBSCT patients, respectivly. One patient died 4 days after transplantation. Forty-five percent (9/20) of BMT patients developed grade I or II acute GVHD; 55% (11/20) developed grade III or IV acute GVHD. Fifty-three point four percent (31/58) of PBSCT patients developed grade I or II acute GVHD; 46.5% (27/58) developed grade III or IV acute GVHD. No significant difference by Fisher's test was observed. The incidence of acute GVHD was 91.7% (44/48) in G-CSF including patients and 85% (34/40) in non-including patients with no significant differences by Fisher's test. Forty-eight point six percent (34/70) of patients that were alive more than 100 days, developed chronic GVHD. The incidence of chronic GVHD was 29.4% (5/17) in BMT and 56.6 %(30/53) in PBSCT patients, indicating more chronic GVHD occurrence in PBSCT cases.

Infections

Majority of the patients experienced one or more episodes of Gram (-) and/or Gram (+) infections. The incidence of fungal infections (Candida species) was 3.3% (3). Fifteen (22.7%) patients developed cytomegalovirus infection. One patient developed tuberculosis. Patients who received BMT or PBSCT had similar incidences of infectious diseases. There was significant difference in the incidence of interstitial pneumonia in patients given PBST or BM (4 vs. 0, respectively).

Hospitalization

No significant difference was detected between the duration of hospitalization in PBST or BM (53.6 days vs. 51.6 days respectively).

Long-Term Complications

Obstructive bronchiolitis was diagnosed in 3 of 89 patients who died following the transplantation. Hypothyroidism developed in one patient (1.1%). None of the men could have children and no women became pregnant following transplantation. Thirty out of 54 patients (55.5%) are alive and disease-free more than 10 years after transplant. All but six patients are currently on no medication and have resumed all activities without any limitation.

Relapse, Causes of Death and Leukemia-Free Survival

Five patients relapsed one year following transplantation. Three patients who had a hematologic and cytogenetic relapse are currently on hydroxyurea treatment and/or donor lymphocytes infusion for more than one year. The major complications are described in Table 2.Collectively, 57 patients (64%) are reported alive by the time 30 August 2002 (11BMT patients and 46 PBSCT patients) at a range of 4 to 134 months after transplantation. Causes of death are described in Table 3. Six to nine and 2-6 years disease free survivals (DFS) for BMT group were 38.2% and 47.8%, respectively. DFS for PBSCT group was calculated as 54.3% in a period of 1.9 to 4.6 years, P= 0.34 (Fig. 1).

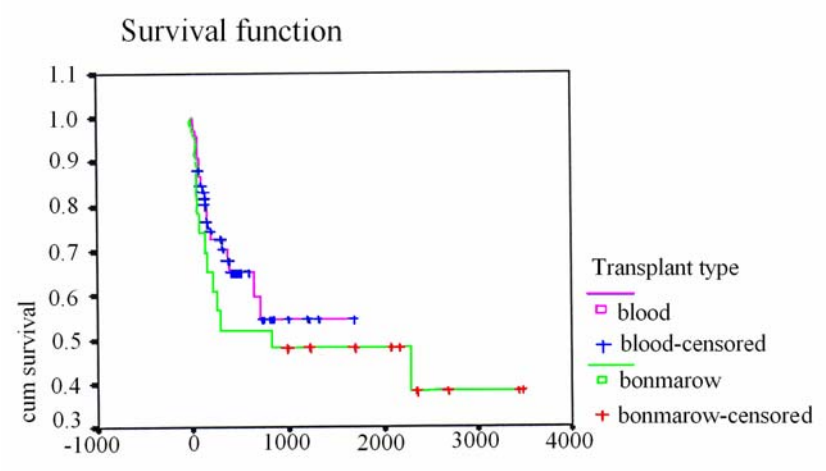

Fig. 1. Time of dfs in BMT and PBSCT patients

Table 2. Complications

	PBSC Group (n= 66)	BM Group (n= 23)
Infection /CMV	/15	/0
Acute GVHD	89.2%(58/65)	87%(20/23)
Grade I-II	31	9
Grade III-IV	27	11
Relapse	2	3(2;dead)
Chronic GVHD	56.6% (30/53)	29.4% (5/17)
Limited	9	3
Extensive	21	2
Mild	6	2
Moderate	10	1
Sever	14	2
Interstitial pneumonia and ARDS	7	4
Bronchiolitis obliterating	3	0
cardiac	4	0
Renal failure	3	2
Hemorrhagic Cystitis	10	1
VOD	2	2

Table 3. Causes of death

	PBSC Group (n=66)	BM Group (n=23)
Infection	3	0
Acute GVHD	3	4
Relapse	0	2
Chronic GVHD (extensive)	6	1
Interstitial pneumonia/ARDS	2.2	0.2
Multisystem failure	2	2
Other (TTP ,new malignancy, rejection)	2	1

DISCUSSION

Pervious studies showed that the project actuarial 3-year to 5-year survival rates in CML patients who had received allogeneic bone marrow transplantation ranged from 38% to80% (18). Relapse rate within 3-5 years are less than 20% in most studies (19). Normally, best results would be in young adults who had been subjected to bone marrow transplantation within one year after diagnosis (8-10). In our center, 64% of such patients are still alive. Two to six years and 6-9 years DFS for these patients has been recorded as 47.8% and 38.2%, respectively for BMT patients. Two to five years DFS of PBSCT patients has been recorded as 54.3%. Short-term DFS demonstrated similar patterns in both BMT and PBSCT groups (P= 0.34). In the first 3-4 year post transplantation; no survival advantage was seen with drug therapy, whether hydroxyurea or interferon – alpha, as compared to transplantation procedures. This could partly stem from mortal BMT side effects, e.g. GVHD, VOD or infections. Comparable survival advantage with BMT would be achieved 4 years post transplantation. Normally, after four years, those who have received chemotherapy would normally encounter blastic phase which is accompanied by increased mortality (18). This means that, in long-term, transplantation procedures show more efficacy than chemotherapy. In the present study, 88% of patients developed acute GVHD. No significant difference was seen between PBSCT and BMT groups. Mortal GVHD (grades 3 or 4) was recorded as 46.5% and 50% in PBSCT and BMT groups, respectively. It is also noteworthy that development of grades one or two GVHD might be associated with less mortality in relapsing patients. Less chronic GVHD cases have now been documented, thanks to the application of improved medical managements and advanced molecular diagnosis methods. There is increasing evidence that CML GVHD occurs in a significantly higher proportion of unmanipulated PBSC compared with marrow recipients (20). Vigorito et al (21) reported that 71% of patients allografted with PBSC developed extensive chronic GVH reaction, which was significantly more than the 27% incidence in the marrow recipients. This observation was confirmed in the much larger EBMT trial (22), as well as in the French study (23). In our center, chronic GVHD was estimated as 56.6 % and 29.4% in PBSCT and BMT groups, respectively. One reason for the higher chronic GVHD prevalence in PBSCT group might be the presence of higher lymphocytes in peripheral stem cell derived preparations applied in this group. Extensive chronic GVHD is reported as56.6 % and 29.4% in PBSCT and BMT groups, respectively. This phenomenon could cause less QOL (quality of life) in patients. In our study, there was no significant difference in the frequency of recurrent-disease between BMT and PBSCT groups. However, engraftment period was lower in PBSCT group (18.4 days) as compared to BMT group (27 days) (P= 0.03). Injectable G-CSF has been reported to expedite leukocyte and platelet engraftment which might be associated with less possibility of mortal infections and/or lesser thrombocytopenia-derived bleedings. Significant higher leukocyte engraftment (P= 0.017) and platelet engraftment (P= 0.012) was observed in those who had received G-CSF.

Major transplantation-attributable side effects could be classified as follows:

- infections 100%
- acute GVHD 88%
- chronic GVHD 50%
- pneumonia 12.3%
- cystic hemorrhagic 12.3%
- cardiac failure 4.4%

In terms of mortality, however, the above list could be rearranged as follows:

- acute GVHD 21.8%
- chronic GVHD 21.8%
- infections 9.3%
- pneumonia 18.75%
- multi organ failure 12.5%

In our study, no mortality was recorded 3-years post transplantation. This indicates that as time passes, lesser side effects and attributed mortalities would be developed in transplanted patients. In IBMTR studies, nearly 30% of patients encountered disabling problems which hindered them from leading a normal life. We did not study the QOL but our results showed that obliterating bronchiolitis was seen in 4.2%, endocrine complication in 10% and extensive GVHD in 32.8% of patients.

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