ORIGINAL ARTICLE

Post-transplant Outcome in Chronic Myeloid Leukaemia

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ABSTRACT

Objective: To determine post-transplant survival in chronic myeloid leukaemia patients undergoing allogeneic stem cell transplant.

Study Design: Longitudinal, descriptive study.

Place and Duration of Study: Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan, between April 2002 and August 2007.

Methodology: All patients of chronic myeloid leukaemia in chronic phase having HLA identical donor and age under 55 years, normal hepatic, renal and cardiac functions with good performance status were selected. Patients in accelerated phase or blast crisis, poor performance status, impaired hepatic, renal, cardiac functions or pregnancy were excluded. Survival was calculated from the date of transplant to death or last follow-up according to Kaplan-Meier and Cox (proportional hazard) regression analysis methods.

Results: Thirty seven patients with chronic myeloid leukaemia underwent allogeneic stem cell transplant from HLA identical sibling donors. Thirty two patients were male and five were females. Median age of patients was 28 years. All patients and donors were CMV positive. Post-transplant complications encountered were acute GvHD (Grade II-IV) (n=13, 35.1%), chronic GvHD in 18.9% (n=7), Veno Occlusive Disease (VOD) in 5.4% (n=2), acute renal failure in 2.7% (n=1), haemorrhagic cystitis in 2.7% (n=1), bacterial infections in 40.5% (n=15), fungal infections in 16.2% (n=6), CMV infection in 5.4% (n=2), tuberculosis in 5.4% (n=2), Herpes Zoster infection 2.7% (n=1) and relapse in 2.7% (n=1). Mortality was observed in 27% (n=10). Major causes of mortality were GvHD, VOD, septicemia, CMV infection and disseminated Aspergillosis. Overall Disease Free Survival (DFS) was 73% with a median duration of follow-up of 47.4 $\pm$ 12 months. DFS was 81% in standard risk and 54.5% in high-risk group.

Conclusion: Results of allogeneic stem cell transplant in standard risk group CML patients were good and comparable with other international centres, however, results in high-risk CML patients need further improvement, although, number of patients in this group is small.

Key words: *Chronic myeloid leukaemia. Allogeneic stem cell transplant. Complications.*

INTRODUCTION

Chronic Myeloid Leukaemia (CML) is a clonal haemopoietic disorder, characterized by proliferation of haemopoietic cells that for a variable period of time, retain the capacity to differentiate, leading to marrow hyperplasia and increased number of myeloid cells and platelets in the peripheral blood.[1] The annual incidence of CML is 1.6 cases per 100,000 per year in USA and accounts for 40% of all new leukaemias.[2]

Haematopoietic Stem Cell Transplantation (HSCT) has greatly expanded effective treatment options and improved the survival of patient with malignant and non-malignant haematological disorders. During the past three decades, bone marrow transplantation and transplantation of peripheral blood stem cells have become a well-established treatment.[3,4] As per European Bone Marrow Transplant Group (EBMT) activity survey 2003 report, 21,028 HSCT were performed in 597 centers in 42 European countries for various disorders. Main indications in order of frequencies included leukaemia, lymphoma, solid tumours and non-malignant haematological disorders.[5]

Introduction of Imatinib mesylate in late 1990's in the armamentarium against CML has revolutionized the treatment and is considered first choice as compared to HSCT in the developed countries. However, it is different in developing countries where resources are limited and Imatinib is not freely available. Cost of one year treatment with imatinib in CML patients is more than the cost of transplant procedure including 06 months post-transplant follow-up. As a result, HSCT remains treatment of choice in newly diagnosed CML patients having HLA-matched donor.[6,7]

The aim of this study was to determine post-transplant survival in chronic myeloid leukaemia patients undergoing allogeneic stem cell transplant.

METHODOLOGY

Patients with chronic myeloid leukaemia in chronic phase having HLA-matched sibling donors with ALT more than two times the normal values, serum

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creatinine < 120 mic mol/l, ejection fraction > 50% and Eastern Cooperation Oncology Group (ECOG) 0-2 were selected for transplant. The age limit was 55 years. Patients in accelerated phase or blast crisis, ALT more than two times the normal values, serum creatinine > 120 mic mol/l, ejection fraction < 50%, ECOG 3-4, active tuberculosis and pregnancy were excluded. Patients were classified into standard and high-risk on the basis of duration of disease, phase of disease, response to therapy, age and patient / donor combination according to EBMT risk stratification criteria.

As per institutional transplant protocol, after HLA typing, all patients and sibling donors underwent pre-transplant infection surveillance. Prospective surveillance was carried out to detect the spectrum of microbial pathogens in those patients and to treat them with appropriate antibiotics. Surveillance cultures were taken from nose, throat, stool and urine to detect the pattern of pathogen organisms. Screening for tuberculosis was done by Mantoux test and chest X-ray, while sputum for AFB examination and PCR for *Mycobacterium tuberculosis* were done in suspected cases. Virological screening for hepatitis B and C, HIV, CMV, VZV and EBV were carried out by Enzyme-Linked Immunosorbent Assay (ELISA) and molecular analysis (PCR) where indicated. Cytomegalovirus antigenemia was monitored weekly for first hundred days after transplant and thereafter on monthly basis for one year. After admission in the hospital, patients were kept in protective isolation rooms, equipped with HEPA filter and positive pressure laminar airflow ventilation system. All patients were provided bacteria reduced diet. Leukodepleted and irradiated blood products were used during post-transplant period.

Early post-transplant haematological recovery was assessed by absolute neutrophil count. Patients were discharged from hospital after haematological recovery and were followed-up as outdoor patients every week for next 3 months, fortnightly for 3 months and then monthly for 6 months. Thereafter patients were regularly followed-up every 3-6 months for next 5 years. Survival was calculated from date of transplant to death or last follow-up. Bone marrow aspiration was done every 3 months during first year post-transplant and every 6 months during second year post-transplant for Philadelphia Chromosome and BCR-ABL for disease relapse.

Neutropenia was defined as an Absolute Neutrophil Count (ANC) < 0.5 x 10^9/l and was considered to have ended on an ANC > 1.0 x 10^9/l. Febrile spike of > 99°F on two occasions, 30 minutes apart or > 100°F on one occasion in neutropenic patients was considered as febrile neutropenia. Antimicrobial prophylaxis consisted of Ciprofloxacin 500 mg twice daily in two divided doses from the start of conditioning. Empiric broad spectrum anti-pseudomonal penicillin/tazobactum 90 mg/kg, 6 hourly in combination with Amikacin 15 mg/kg/day were started once neutropenic patients developed febrile spikes as defined. Antibiotics were modified in the light of clinical condition and culture reports. Oral Fluconazole 50-100 mg daily and Acyclovir 200 mg three times daily were used as antifungal and antiviral prophylaxis respectively started from day-2 and continued till day +180. Pentamidine sulfate (300 mg) nebulization monthly was used as prophylaxis for *Pneumocystis jiroveci* infection at the time of conditioning. Sulphamethoxazole/ Trimethoprin combination was used as prophylaxis against *Pneumocystis jiroveci* after haematological recovery and continued for 6 months post-transplant.

Patients with CML received Busulphan 4 mg/kg daily for 4 days (total dose: 16 mg/kg) followed by Cyclophosphamide either 50 mg/kg daily for 4 days (total dose: 200 mg/kg) or 60 mg/kg daily for 2 days in high-risk CML patients (total dose: 120 mg/kg).

Peripheral Blood Stem Cells (PBSC) were the main stem cell source. All donors received G-CSF (Filgrastim) 10 ug/kg/day for 5 days prior to PBSC harvest. Peripheral blood stem cells were harvested on day-2 and day-1 to achieve standard dose of mononuclear cells > 4.0 x 10^8/kg body weight of patient by using COBE spectra cell separator. PBSC harvests were transfused to the patient on the day of transplant under cover of steroids and antihistamines.

As prophylaxis against Graft versus Host Disease (GvHD), intravenous (I.V.) cyclosporin (CsA) (5 mg/kg/day in two divided doses) and Prednisolone (0.5 mg/kg/day) were started from day-2 onwards. The I.V. dose of CsA was switched over to oral CsA at the time of discharge from hospital. The oral dose of the CsA at the time of switch over from I.V. dose was doubled and continued for 6 months. Thereafter, CsA was gradually tapered off in the next 3 months (total duration being 9 months). Cyclosporine dose was adjusted according to blood levels as well as according to renal status of the patient. Trough levels of CsA were maintained between 200 and 300 ng/ml. Prednisolone was gradually tapered off till day + 90 Post SCT. Intravenous Methotrexate (10 mg/m^2) was given on day +1, +3, +6 and +11 along with folinic acid rescue therapy. GvHD was diagnosed and graded both clinically and histologically.[8]

Survival was calculated from the date of transplant to death or last follow-up according to Kaplan-Meier and Cox (proportional hazard) regression analysis methods. The analysis was performed with Stats Direct software and MS excel software.

RESULTS

From April 2002 to August 2007, a total of 37 patients with CML received allogeneic stem cell transplants from HLA-matched sibling donors at the study centre. Thirty-

two patients were male and 5 females. Median age of the patients was 28 years (ranging from 7-54 years). Nine patients were transplanted across the gender. Eleven patients had ABO mismatch transplant with major ABO mismatch in 8 patients and minor ABO mismatch in 3 patients. All patients and donors were CMV positive.

CML patients were categorized into standard risk (n=26) and high-risk group (n=11). All CML patients were Ph+ve and had BCR-ABL mutation. Patients in standard risk group were in the first chronic phase of disease, and received only hydroxyurea before transplant. Those patients were transplanted between 1-12 months of diagnosis (median duration: 9 months). The patients in high-risk group had long duration of disease ranging between 2-7 years. Those patients had received hydroxyurea Interferon-α and Imatinib mesylate for a variable period of time before transplant.

Stem cell source was mainly PBSC in the studied patients. Details of patients and donor characteristics along with transplant procedure adopted are summarized in Table I. All patients achieved successful engraftment. Median time of neutrophil recovery (ANC > 0.5 x 10^9/l) was 14 days (ranging from 11-21 days) and platelet recovery (> 20 x 10^9/l) was 18 days (ranging from 14-35 days).

Post-transplant complications were acute GvHD (grade II-IV) in 35.1% (n=13), chronic GvHD in 18.9% (n=7), VOD in 5.4% (n=2), haemorrhagic cystitis in 2.7% (n=1), acute renal failure in 2.7% (n=1), gram-positive and gram-negative bacterial sepsis in 40.5% (n=15), tuberculosis in 5.4% (n=2), fungal infections in 16.2% (n=6), CMV disease in 5.4% (n=2) and Herpes Zoster infection in 2.7% (n=1). GvHD was the major cause of morbidity in the high-risk group. Disease relapse was seen in one patient (2.7%). However, that patient achieved donor chimerism after Donor Lymphocytes infusion (DLI). Major post-transplant complications both in standard and high-risk groups are tabulated in Table II.

Table I: Patient/donor characteristics and transplant procedures.

Characterstic	Patient	Donor
Male	32	29
Female	05	08
M/F ratio	6.4:1	3.6:1
Age		
Median age	28 years	27 years
Range	(7-54 years)	(7-54 years)
CMV status		
Positive	37	37
Negative	-	-
Risk group		
Standard risk	26	
High risk	11	
ABO incompatibility		
Major	08	
Minor	03	
Conditioning regimen	Bu16/Cy 200 and Bu16/Cy 120	
source of stem cell		
BM	01	
PBSC	34	
PBSC+BMT	02	
Transplant		
First	37	
Second	-	
Transplant across the gender		
M/M	24	
M/F	03	
F/M	10	
F/F	0	

Table II: Post-transplant complications (n=37).

		Standard risk (n=26)	High risk (n=11)
Non-infective			
Acute GvHD	35.1% (n=13)	19.2% (n=5)	72.7% (n=8)
Chronic GvHD	18.9% (n=7)	3.8% (n=1)	54.5% (n=6)
VOD liver	5.4% (n=2)	3.8% (n=1)	9.0% (n=1)
Haemorrhagic cystitis	2.7% (n=1)	3.8% (n=1)	-
Acute renal failure	2.7% (n=1)	3.8% (n=1)	-
Infective			
Bacterial infections	40.5% (n=15)	34.6% (n=9)	54.5% (n=6)
*Gram-positive	16.2% (n=6)	11.5% (n=3)	27.2% (n=3)
**Gram-negative	24.3%(n=9)	23% (n=6)	27.2% (n=3)
Tuberculosis	5.4% (n=2)	-	18.1% (n=2)
***Fungal-infections	16.2% (n=6)	7.7% (n=2)	36.3% (n=4)
CMV-infection	5.4%(n=2)	3.8% (n=1)	3.8% (n=1)
Herpes Zoster infection	2.7% (n=1)	3.8% (n=1)	-

** Staph. aureus, (Coagulase negative), 4; Staphylococcus aureus (Methicillin resistant), 2*

*** Pseudomonas* spp, *7; Klebsiella pneumoniae, 1; Acinetobacter* spp, *1*

**** Candida* spp, *2; Aspergillus* spp, *4*

Mortality was observed in 10 patients (27%). The mortality related to non-infective causes was 10.8% (4/37) and to infection was 16.2% (6/37). Main causes of mortality were GvHD (n=2), VOD liver (n=2), septicemia (n=2), CMV infection (n=2) and disseminated aspergillosis (n=2). Survival and mortality in different risk groups is shown in Figure 1.

At the end of 5 years, Overall Survival (OS) and Disease Free Survival (DFS) was 73% (26/37), with a mean

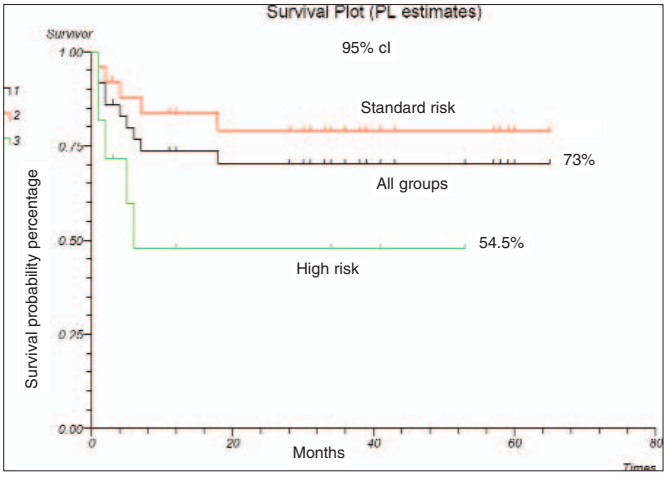

Figure 1: CML Post-transplant, Survival- all risk groups.

survival time 47.4±12 months. DFS was 81% (21/27) in standard risk group CML patients and DFS was 54.5% (6/11) in high-risk group.

DISCUSSION

HSCT remains the only established cure for CML. International Bone Marrow Transplant Registry (IBMTR) data between 1994 and 1999 showed the probability of survival to be 69 ± 2% for 21,876 patients transplanted within the first year of diagnosis and 57 ± 3% for 1391 patients transplanted more than one year from the diagnosis.[9] Results of allogeneic SCT in chronic myeloid leukaemia in a study between 1982 and 1998 showed 61% event-free survival at 05 years. Survival was higher in patients who were transplanted in first chronic phase as compared to those who were transplanted in advanced phases (73% vs. 32%).[10] The recently reported data from Seattle group showed 86%, 3 years post-transplant survival with 87% of surviving patients molecularly negative for BCR-ABL mRNA by PCR analysis.[11] GvHD, multiorgan failure, sepsis, disseminated fungal infections, CMV pneumonitis and relapse are common causes of transplant failure.[12,13] Leukaemia recurs in 20-70% of patients after allogeneic SCT depending on the type of leukaemia and disease status at transplantation.[14] Between 1989-1997, a large study revealed 14.2% (447/3142) relapse rate in CML. Prognosis of patients who relapse is poor and optimal salvage therapy has yet to be established.[15] In a multi-centre study from Spain, out of 836 CML patients who underwent allogeneic SCT between 1984-2002 from HLA identical sibling donors, 143 patients relapsed. Those patients were put on salvage therapy. The probability of survival with different treatment regimens was 52.7% with α-interferon, 80.4% DLI, 25% with second cell transplant, 50% with Imatinib and 0% with both hydroxyurea and palliative care. The probability of survival and probability of progression free survival were 53.6% and 52.2% at 5 years respectively in that study.[16]

In this study, OS and DFS in CML was 73% with a mean survival time of 47.4 ± 12 months. In good risk group CML patients DFS was 81%, whereas in high-risk group DFS was 54.5%. In the present set of 33 CML patients who received SCT, one patient had haematological relapse. He was given escalating dose of DLI. On follow-up, his blood counts gradually dropped down to normal and bone marrow also became normocellular. Serial cytogenetics and BCR-ABL molecular analysis initially revealed mixed chimerism and later on complete donor haemopoiesis established. Other complications during post-transplant period having a major impact on ultimate outcome were acute and chronic GvHD (35.1% and 18.9%), bacterial infections (40.5%), fungal infections (16.2%) and CMV disease (5.4%).

Since the availability of Imatinib mesylate, doctors as well patients of CML are often confused about which treatment to opt for. On the face of it, allo-BMT is associated with significant peri-transplant morbidity and mortality, has limited availability, dependant on availability of HLA-matched sibling donor and significant amount of funding but provides realistic chance of cure after a few months treatment. Imatinib mesylate, on the other hand, is not associated with significant immediate risk, has excellent short-term results but cost, late treatment failure, indefinite treatment and significantly lower results of transplant in imatinib failure patients remain major drawbacks.

Transplant is offered to all newly diagnosed CML patient who fall in standard risk and has HLA matched donor. The studied group of patients had excellent outcome after transplant. Rest of the patients were open to other available treatment options.

CONCLUSION

The OS and DFS in CML in the studied patients was comparable with survival reported by other international centres. Results in high-risk group, however, need further improvement. With more experience, modification of protocols according to local needs and careful patient selection, the results are likely to improve even further.

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