Allogeneic stem cell transplantation in chronic myeloid leukemia two and a half year experience

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Turk J Haematol 2005;22(2): 79-86

Received: *10.11.2004* ***Accepted:*** *26.02.2005*

ABSTRACT

This study is performed to evaluate outcome of allogeneic stem cell transplantation (SCT) in chronic myeloid leukemia at Armed Forces Bone Marrow Transplant Centre, Rawalpindi from Apr 2002 to Oct 2004. Twenty-two patients with CML underwent allogeneic SCT from HLA matched siblings. Patients were divided into standard (n= 14) and high-risk (n= 8) groups. Patients were subjected to conditioning regimens consisting of busulphan and cyclophosphamide. Cyclosporin, prednisolone and methotrexate were given for GVHD prophylaxis. All donors were subjected to PBSC harvest after G-CSF therapy for five days. All patients received G-CSF from day + 5 until ANC > 0.5 x 10^9/L. The median age of the patients was 29 years (range 7-53 years) with a male to female ratio of 6.3:1. Engraftment was achieved in all patients. Median time to achieve neutrophil (ANC 0.5 x 10^9/L) and platelet (20 x 10^9/L) recovery was 13 days and 12 days respectively. Median stay in hospital was 18 days. Acute GVHD (Grade II-IV) was observed in eleven patients (50%) while chronic GVHD was seen in four patients (18%). One patient relapsed 8 months post-transplant. Two patients (9%) developed VOD liver. One patient had haemorrhagic cystitis. Four patients (18%) developed post-transplant infectious complications, which included *Pseudomonas* septicemia, aspergillosis, tuberculous pleural effusion and herpes zoster. Overall mortality was 22.7% (n= 5). The major causes of mortality were VOD liver, GVHD grade IV, *Pseudomonas* septicemia and aspergillosis. Overall survival was 77.2% (n= 17) and disease free survival was (n= 16) 72.7%. Follow up ranges from 23 to 828 days (median 212 days). The preliminary results of SCT in this small series of patients with CML are very encouraging. To improve the long-term survival it is imperative that patients are transplanted early after diagnosis and conditioning regimens are selected carefully.

Key Words: Chronic myeloid leukaemia, Allogeneic stem cell transplantation, Graft Versus Host Disease.

ÖZET

Kronik myeloid lösemide allojeneik kök hücre nakli 2.5 yılık deneyim

Bu çalışma Rawalpindi Silahlı Kuvvetler Kemik İliği Nakli merkezinde kronik myelositer lösemi hastalarına 2002 Nisan-2004 Ekim arası uygulanan allojeneik nakillerin sonuçlarını değerlendirmektedir. KML tanılı 22 has-

taya HLA uyumlu kardeşinden allojeneik nakil yapılmıştır. Hastalar standart riskli (n= 14) ve düşük riskli (n= 8) olmak üzere iki gruba ayrılmıştır. Hazırlama rejimi olarak busulfan artı siklofosfamid kullanılmıştır. GVHH profilaksisi için siklosporin, prednizolon, metotreksat verilmiştir. Tüm olgularda kök hücre toplanması beş günlük G-CSF ardından yapılmıştır. Ayrıca nakilden beş gün sonra başlayıp, MNS> 0.5 x 10^9/L olana kadar devam edilmiştir. Hastaların median yaşı 29 yıldır (7-53 yıl) olup erkek/kadın oranı 6.3/1'dir. Tüm hastalarda engraftman gerçekleşmiş olup, nötrofil toparlanması (MNS > 0.5 x 10^9/L) median 13 gün ve trombosit toparlanması (PLT > 20 x 10^9/L) median 12 günde gerçekleşmiştir. Hastanede median kalma süresi 18 gündür. Onbir hastada (%50) akut GVHH (Evre II-IV) gelişmiş ve 4 hastada kronik GVHH (%18) görülmüştür. Bir hasta nakilden 8 ay sonra relaps olmuş, iki hastada (%9) VOD gelişmiş, bir hastada ise hemorajik sistit görülmüştür. Dört hastada (%18) nakil sonrası infeksiyöz komplikasyonlar görülmüştür. Bunlar arasında psödomonas sepsisi, aspergilloz, tuberküloz plevral efüzyon ve Herpes Zoster yer almaktadır. Genel mortalite %22.7'dir (5 hasta). Temel ölüm nedenleri VOD, Evre IV GVHH, psödomonas sepsisi ve aspergillozdur. Genel sağkalım %77.2 (n= 17), hastalıksız sağkalım ise %72.7 (n= 16)'dir. İzlem süresi median 212 (23-828) gündür. Bu küçük serideki ilk sonuçlar KML açısından yüz güldürücüdür.

Anahtar Kelimeler: Kronik mwyeloid lösemi, Allojeneik kök hücre nakli, Graft Versus Host Hastalığı.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant haematopoietic disorder characterized by clonal expansion of primitive haematopoietic 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. The natural history of untreated CML is a relatively benign chronic phase (CP) lasting on average three years followed by accelerated phase (AP) lasting several months and then eventually terminating in a rapidly fatal blast crisis (BC)[1].

The cytogenetic hallmark in 90% patients of CML is a reciprocal chromosomal translocation t(9;22) (q^{34};q^{11}) that creates a derivative 9q+ and a small $22q^-$, known as Philadelphia (Ph) chromosome. The later harbours the BCR-ABL fusion gene encoding a chimeric BCR-ABL protein with a deregulated tyrosine kinase activity, the expression of which is necessary and sufficient for the transformed phenotype of CML Cells[2].

The annual incidence of CML is 1.6 cases per 100.000 per year in USA. CML represent 40% of all new leukaemias in USA. There is a slight male predominance and very little geographic variation[3].

The management of the newly diagnosed CML patients has changed very greatly in the last 10-15 years. Busulphan (BU) was introduced as therapy for CML in 1953 and was the most commonly used agent until surpassed by hydroxyurea (HU) in the 1980s. Like busulphan, hydroxyurea provides an excellent method to control white cell count, platelets and splenomegaly in most patients but does not generally affect the percentage of Ph positive cells in the marrow[4]. Interferon alpha (IFN-α) was first reported to have activity in chronic phase CML in 1986. Unlike busulphan or hydroxyurea, partial or complete cytogenetic responses are seen in 20-30% of patients treated with IFN-α[5].

Recently several new therapies have been developed that may change the natural history of CML and patient prognosis. In particular imatinib mesylate (ST1571), an oral Bcr-Abl kinase inhibitor, has demonstrated activity in all phases of CML, and may replace IFN as the initial therapy for this disease. The first clinical trials with imatinib mesylate were initiated in 1998. Presently over 60.000 patients have been treated worldwide with

imatinib. Responses are short lived and in advanced phase of disease the patients invariably undergo disease progression following the brief period of respite. This results from the emergence of leukaemic clones resistant to drug following its regular administration[6].

Other agents and therapies with potential value, either alone or in combination, include polyethylene glycol (PEG) IFN, homoharringtonine, decitabine, oral cytarabine and growth factor modulation[7].

Allogeneic bone marrow transplantation is the therapy of choice for younger patients of CML who have age < 40 years and HLA matched donor. First allogeneic BMT in CML was done in Seattle in 1979[8]. In 1986 Seattle group published the results of first large study and updated results till Nov 2002 show that 40% of patients transplanted more than 17 years ago are surviving[9].

IBMTR data between 1994 and 1999 shows a probability of survival of 69 ± 2% for 21.876 transplanted within the first year of diagnosis and 57 ± 3% for 1391 patients transplanted more than one year from the diagnosis[10].

The recently reported data from Seattle group showed 86% 3-years post-transplant survival and 87% of surviving patients were molecularly negative for BCR-ABL mRNA by PCR analysis[11].

In this paper we describe our initial experience of allogeneic stem cell transplantation in the cure of chronic myeloid leukaemia.

MATERIALS and METHODS

From April 2002 to Oct 2004 twenty-two patients were transplanted for the treatment of CML. Recipient and sibling donors were genotypically HLA identical. Thirteen recipient/donor pairs were ABO identical whereas nine were mismatch for blood groups. Seven patients were transplanted across the gender. Out of these seven, four patients were male and three were female. The age of sibling donors ranged from 5 to 54 years (median 27 years). Three female donors were married and multiparous. All patients and donors were CMV positive. The patients were grouped into standard risk and high risk on the basis of duration of the disease, age of the patient at the time of diagnosis, type of treatment received before transplant and phase of the disease (Table 1).

After complete pre-transplant evaluation these patients were subjected to conditioning regimens either with Bu_{16}/Cy_{200} or Bu_{16}/Cy_{120}. Twelve patients received Bu_{16}/Cy_{120}. Out of these, two patients also received etoposide ($Bu_{16}/Cy_{120} + E_{50}$). All the patients received G-CSF mobilized peripheral blood stem cells (PBSC) harvest from sibling donors, however two patients also received bone marrow harvest. All donors received G-CSF 5 μg/kg body weight 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 > 4.0×10^8/kg body wt of patient by using cobe spectra cell separator. Median apheresis time was 245 minutes (range 220-270), depending upon the volume and rate of blood flow through the apheresis system.

Bone marrow harvest/PBSC harvest was infused on day 0 of the conditioning under cover of steroids and antihistamines. Cyclosporin (5 mg/kg/day) and prednisolone (0.5 mg/kg/day) were given from day-2 onwards as GVHD prophylaxis. The IV dose of cyclosporin was reduced to 3 mg/kg/day from day + 6 and then switched over to oral cyclosporin therapy as the patient's condition permitted. The oral dose of the cyclosporin was adjusted according to trough therapeutic levels and renal status of the patient. Trough levels of cyclosporin were maintained in between 200 and 300 ng/mL and continued for 6 months, then gradually tapered off in next six months (total duration one year). Prednisolone was gradually tapered off in 90 days post-transplant. Short course of I/V methotrexate (10 mg/m^2) was given on day + 1, 3 and 6 in high-risk patients.

Table 1. Risk stratification criteria and patient characteristics

	Standard risk	High risk
a. Risk stratification		
Age	< 40 yrs	> 40 yrs
Duration of disease	< 1 yr	> 1 yr
Stage of disease	Early chronic phase	Long duration chronic phase, accelerated/blast transformation phase
Type of therapy	HU	BU, HU, IFN-α, STI 571
Response to therapy	Good	Poor
b. Patient characteristics		
Age (median)	25 years (7-36 years)	42 years (23-53 years)
Duration of disease (median)	9 months	3 years (2-7 years)
Stage of disease		
Chronic phase	n= 14	n= 6
Accelerated phase		n= 1
Blast transformation		n= 1
Types of therapy		
HU	n= 14	n= 08
BU, IFN-α, STI 571		n= 3
Response to therapy	Good	Poor

BU: Busulphan, HU: Hydroxyurea, IFN-α: Interferon-alpha, STI571: Imatinib.

All patients received G-CSF 5 μg/kg/day SC from day + 5 till neutrophil recovery (ANC > 0.5 x 10^9/L). Prophylactic antimicrobial therapy consisting of broad-spectrum antibiotics, antifungal and antiviral was started from day-2 and switched over to therapeutic doses according to clinical status of the patient as per laid down guidelines[12]. Besides this all patients also received prophylaxis against malaria, tuberculosis and *Pneumocystis carinii*.

All patients were nursed in special rooms equipped with positive pressure filtered (HEPA filters) air conditioning system. During early post-transplant aplastic phase, the patients were given leukodepleted, irradiated blood products. Early haematological recovery was defined as absolute neutrophil count of > 0.5 x 10^9/L and platelet count of > 20 x 10^9/L. GVHD was diagnosed and graded both clinically and histologically[13].

RESULTS

Out of 22 patients who were transplanted, 19 were males and 3 females (M:F ration 6.3:1). Age ranged from 7-53 years (median 29 years). All the patients were Philadelphia chromosome positive. Eight patients were placed in high-risk group, whereas 14 were placed in standard risk group.

All the patients in standard risk group were in the first chronic phase of disease, and received hydroxyurea only, in pre-transplant period. They were transplanted between 1-12 months (median duration 9 months) of diagnosis. Whereas patient in high-risk group were having long duration of disease, ranging between 2-7 years (median 3 yrs). Age range was 22-53 years (median: 36.5 years). All the patients received hydroxyurea for a variable period of time ranging between 2-7 years (median duration 3 years). Two patients received IFN therapy for 6 months and one year respectively. Other two patients also received imatinib mesylate therapy for one year. One of them was having CML for the last 7 years, which did not respond to other non-transplant modalities and disease progressed into accelerated phase.

Other patient who went into blast transformation 2 years after the diagnosis was refractory to maximum dose of imatinib mesylate (Table 2).

Until now all the surviving patients (77.2%) are being followed up duration on ranging form 2-30 months (median follow-up 7 months). Engraftment was achieved in all patients and was monitored with cytogenetic/molecular analysis and change of blood group. Early haematological recovery was monitored with absolute neutrophil count of 0.5 x 10^9/L, which ranged from 10-17 days (median: 13 days). The platelet recovery > 20 x 10^9/L was between 8-18 days (median 12 days).

Major post-transplant non-infective complication encountered was acute GVHD 50% (n= 11). Acute GVHD skin Grade II occurred in 13.6% (n= 3), GVHD skin Grade III 18.1% (n= 4), GVHD intestine 9% (n= 2), GVHD liver Grade II 9% (n= 2) and chronic GVHD skin 18.1% (n= 4). Other non-infective complications were VOD liver 9% (n= 2), haemorrhagic cystitis 4.5% (n= 1), post-transplant aplasia 9% (n= 2) and disease relapse 4.5% (n= 1). Post-transplant aplasia was observed in two patients at 2 months and 6 months post-transplant. Aggressive, immunosuppressive therapy with cyclosporin and steroids resulted in allogeneic haematological recovery. However both the patients developed cyclosporin induced nephrotoxicity. The dose of cyclosporin was reduced and mycophenolate mofetil (Cellcept) was added as an immunosuppressant. One patient developed haematological relapse of disease at 6 months post-transplant.

Post-transplant infective complications were *Pseudomonas* septicemia 4.5% (n= 1), systemic aspergillosis 4.5% (n= 1), pulmonary tuberculosis 4.5% (n= 1) and Herpes zoster 4.5% (n= 1). Five patients (22.7%) died of various infective and non-infective complications. Main causes of mortality were VOD liver 9% (n= 2), GVHD intestine 4.5% (n= 1), *Pseudomonas* septicemia 4.5% (n= 1) and disseminated aspergillosis 4.5% (n= 1) (Table 3).

Out of 22 patients who were transplanted, 16 have fully recovered with 72.7% disease free survival. Median follow up in surviving patients is 212 days (23-828 days).

Table 2. Transplant related complications

		High risk (n= 8)	Standard risk (n= 14)
Acute GVHD (50%)			
Skin		Grade III (n= 4)	Grade II (n= 3)
Liver		Grade II (n= 1)	Grade II (n= 1)
Intestine			Grade IV (n= 2)
Chronic GVHD skin (18.1%)		n= 3	n= 1
VOD liver (9%)		n= 2	
Transient post transplant aplasia (9%)		n= 2	
Disease relapse	(4.5%)	n= 1	
Haemorrhagic cystitis	(4.5%)		n= 1
Pseudomonas septicemia	(4.5%)	n= 1	
Pulmonary tuberculosis	(4.5%)		n= 1
Systemic aspergillosis	(4.5%)	n= 1	
Herpes zoster infection	(4.5%)		n= 1

GVHD: Graft versus host disease, VOD: Veno occlusive disease.

Table 3. Outcome

	Standard risk (n= 14)	High risk (n= 8)	Overall relapse	Overall mortality	Overall survival	Disease free survival
Survival	92.8% (n= 13)	50% (n= 4)	-	-	77.0% (n= 17)	72.7% (n= 16)
Mortality	7.1% (n= 1)	50% (n= 4)	-	22.7% (n= 5)	-	-
Relapse	-	12.5% (n= 1)	4.5% (n= 1)	-	-	-

DISCUSSION

Haematopoietic stem cell transplantation remains the only established cure for CML. Efforts should be made to prevent GVHD and minimize early mortality. The advent of STI 571 (imatinib mesylate) has brought the issue of managing newly diagnosed patients of CML, especially those with available donors, to the cross roads. The curative potential of this agent remains unknown and patients invariably develop early resistance due to the emergence of resistant leukaemic clones to this drug[14].

G-CSF primed donor PBSC accelerate early haematopoietic engraftments, and shortens duration of stay in the hospital. Moreover it is a safe procedure and the required yield of stem cell dose can be harvested with out subjecting donors to invasive procedure like bone marrow harvest[15].

GVHD, multi-organ failure, sepsis, disseminated fungal infection, cytomegalovirus (CMV) pneumonitis and relapses are the common causes of transplant failure. Many studies have shown that G-CSF mobilized PBSCT manifest quicker allogeneic haematopoietic recovery than conventional bone marrow transplant. This potential advantage of PBSCT still needs to be balanced against the risk of acute and chronic GVHD associated with the infusion of 10-15 fold higher donor lymphocyte number in unmanipulated allogeneic PBSCT than the marrow graft[16]. In most studies, the incidence of acute GVHD is 40-70% while the risk of chronic GVHD range between 20-50%[13]. In our series acute GVHD was observed in 50% of patients, while chronic GVHD was seen in 18.1% cases.

Veno-occlusive disease (VOD) of the liver is another common and fatal complication, which occurs usually within 30 days in 20% of allogeneic bone marrow transplants about 10% of autologous bone marrow transplantations[17]. It is associated with transplant related chemo-radiotherapy, particularly myeloablative therapy in combination with BMT. An incidence of 25% with mortality in excess of 30% has been reported in large prospective studies[18]. The incidence of fatal VOD liver was 9.1% (n= 2) in our series.

Haemorrhagic cystitis (HC) is potentially a life threatening complication of chemotherapy. It most often occurs following treatment with high dose cyclophosphamide. The reported frequency ranges from 6.5 to 52% despite the use of hydration protocols in bone marrow transplant procedures. The mortality from HC has been reported to be 4% and morbidity from severe HC is extremely high[19]. In our series the incidence of haemorrhagic cystitis was 4.5%.

A small but significant number of patients develop severe and potentially fatal infections in post-transplant period. The post-transplant infections are the major causes of mortality and morbidity, tend to occur during first 3-4 months of transplantation but may also occur later if immunosuppressive therapy is continued for chronic GVHD. The incidence of fatal infections has been reported to be 9%[20]. Most frequent organisms are *Staphylococcus aureus, Streptococcus viridans, Candida, Aspergillus,* CMV, Varicella

zoster and *P. carinii*[21]. In our series, incidence of fatal infections was 9% (*Pseudomonas* septicaemia 4.5%, disseminated aspergillosis 4.5%).

In our series all patients received prophylaxis against malaria, tuberculosis and *P. carinii*. Despite this one patient developed pulmonary tuberculosis, however she recovered after anti-tuberculosis therapy.

The combination of type of donor, stage of disease and age of recipient at transplantation are important prognostic factors for relapse after SCT. There are other important factors like gender, donor and recipient sex combination and waiting time from the diagnosis to transplantation are also important factors responsible for relapse.

In a large study between 1989-1997 the incidence of relapse rate was 14.2% (447/3142). The type of donor, stage of disease and age of recipient were important prognostic factors[22]. In our series a 36 years male patient with three years disease status relapsed six months post-transplant who received allogeneic PBSCT from his 40 years multi-parous sister.

Disease status at transplantation remains the unique factor influencing survival in patients undergoing transplantation from matched sibling donor with a better outcome for those who are transplanted in first chronic phase. Result of allogeneic SCT in CML in children and teenagers in a Japanese study between 1982 and 1998 show 61% event free survival at five years. The five years event free survival was higher in patients who were transplanted in first chronic phase as compare to those who were transplanted in advanced phases (73% vs 32%)[23].

Recent reports show continued improvement with more than 80% survival after allogeneic transplant from matched siblings at 3-5 years[24].

Peripheral blood stem cell transplantation for patients with haematological malignancies has recently started in Pakistan. The first five years data between September 1999-June 2004 published by "Shamsi et al" shows 82%, 47% and 40% post-transplant survival at 100 days, one year and five years respectively[25].

The overall survival in our series was 77.2% with disease free survival of 72.7% at 30 months post-transplant. Our results are in parallel with other studies mentioned above. The survival rate in standard risk was higher (92.8%) as compared to high risk group (50%). The better survival in standard risk patients was due to young age, short duration of disease and better tolerability to the conditioning chemotherapy.

In conclusion, allogeneic bone marrow transplantation is currently the only curative therapeutic approach for several fatal malignant and non-malignant haematological disorders. This is a procedure feasible for patients with CML in early and late chronic phase who have a human leukocyte antigen (HLA) identical donor and are under 40 years of age. The strategies directed to decrease the incidence of acute GVHD, would improve the outcome of these patients.

Allogeneic stem cell transplantation is in initial phases in our country, the early results are quite encouraging[25]. Post-transplant complications are to be managed effectively and we recommend the prophylaxis against tuberculosis and malaria because both of these diseases are quite prevalent in our part of world, which could prove fatal if not recognized and treated early.

Acknowledgement

We thank Dr. Masood Anwar Commandant Armed Forces Institute of Pathology, Rawalpindi, Pakistan for helpful contributions, technical assistance and discussions. We also thank Dr. Farhat Abbass Bhatti, Commandant Armed Forces Institute of Transfusion, Rawalpindi, Pakistan for generously providing us blood products.

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