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Allografting

Allogeneic bone marrow transplantation in the developing world: experience from a center in India

M Chandy, A Srivastava, D Dennison, V Mathews and B George

Department of Hematology, Christian Medical College Hospital, Vellore, India

Summary:

We describe our experience of setting up an allogeneic BMT program at the Christian Medical College Hospital, Vellore over a period of 13 years, from October 1986 to December 1999. Two hundred and twenty-one transplants were performed during this period in 214 patients, with seven patients undergoing second transplants. Indication for BMT were thalassemia major – 106 (48%), CML – 30, AML – 35, ALL – 10, SAA – 22, MDS – six and six for other miscellaneous disorders. The mean age of this patient cohort was 15.6 years (range 2–52). Graft-versus-host disease of grades III and IV was seen in 36 patients (17%) and this was the primary cause of death in 20 patients (9.2%). All patients and donors were CMV IgG positive. Sepsis was the primary cause of death in 16 patients (7.4%), 10 bacterial, four fungal and two viral. One hundred and ten of this series of patients are alive and disease free (50%) with a median follow-up of 24 months (range 2–116). These results are comparable to those achieved for patients with similar disease status in transplant units in the Western world and cost a mean of US$15 000. *Bone Marrow Transplantation* (2001) **27,** 785–790.
Keywords: bone marrow transplantation; developing countries

Bone marrow transplantation is today a life-saving treatment for many hitherto incurable diseases. In 1997, 17 000 allogeneic and 30 000 autologous bone marrow transplants had been performed worldwide as estimated by the International Bone Marrow Transplant statistical center.[1] However, because of the multidisciplinary high-level support required, there are only a few centers in the developing world which are performing bone marrow transplants. Here, we describe our efforts to develop an allogeneic bone marrow transplant program and the results achieved.

Correspondence: Dr M Chandy, Hematology Department, Christian Medical College Hospital, Vellore 632004, Tamilnadu, India
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Patients and methods

Patient selection

Currently, patients with diseases amenable to BMT who have the necessary resources and a 6 antigen HLA matched related donor are considered for BMT. Only about 5% of the population in India would be able to afford a transplant either from their own income, insurance, employer or government.

Methods

Some hospitals in the West perform transplants in standard single rooms. The much higher level of anti-microbial resistance[2] and poor quality of the environment in developing countries makes it prudent to have a dedicated unit where there is a high level of control of the environment. We have a three-bed positive pressure HEPA filtered transplant unit and air quality is monitored every month with blood agar and Saboraud's dextrose agar settle plates in each room. All water used for the patient and for the unit is boiled and cooled. We use dual lumen Hickman Broviac catheters, which are inserted surgically under anesthesia.

For thalassemia and other genetic disorders conditioning has been with busulphan 16 mg/kg or 600 mg/m^2 with cyclophosphamide 50 mg/kg/day for 4 days with or without anti-lymphocyte globulin. Conditioning for leukemia and myelodysplastic syndromes has been with the Tutschka protocol of busulphan 16 mg/kg and cyclophosphamide 120 mg/kg.[3] For aplastic anemia we have used various conditioning protocols including the standard Seattle protocol of cyclophosphamide and ALG.[4] Prevention of GVHD has generally been with cyclosporine and short-term methotrexate.[5] The target cyclosporine level is 200–300 ng/ml. Staging of GVHD has been with the Glucksberg scale.[6] GVHD has been treated with steroids and in severe cases with anti-T cell monoclonal antibody (OKT3 or IORT3) or ATG/ALG.

TPN is prepared in house in the transplant unit using amino acid solutions, dextrose, and electrolytes, trace elements and vitamins manufactured in India. Lipids are not given routinely and all TPN is administered using a Pall 0.22 micron posidyne filter. TPN is started on the day after the bone marrow has been transfused and stopped

when the patient is able to take fluids orally: usually patients receive TPN for 2 weeks. If there is intestinal GVHD then TPN is administered for prolonged periods.

Acyclovir is administered at a dose of 15 mg/kg/day i.v. starting day +1 and switched to oral after day 14. This is continued for 2–3 months as CMV prophylaxis. All patients and donors are tested for CMV antibodies and if there is GVHD requiring immunosuppression the patient's CMV PCR is checked. If positive, ganciclovir is administered at doses depending on the blood counts. We currently do not attempt to sterilize the gut after our initial experience with fracon and ofloxacin showed that this only resulted in colonization with resistant coliforms. Our first line antimicrobial therapy for febrile neutropenia consists of gentamicin, cefotaxime and fluconazole. If the fever persists or the patient is toxic this is rapidly escalated to ceftazidime/imipenem and amoxycillin/clavulinic acid or vancomycin. We have a high index of suspicion for fungal sepsis based on our autopsy data[7] and the fluconazole is changed to amphotericin if the fever persists or there is a pulmonary infiltrate. Stool and throat surveillance cultures are performed once a week and guide antibiotic policy, particularly if there are resistant bacteria.

In most cases the stem cell source was bone marrow and the harvest is taken from the iliac crests with a target nucleated cell dose of 3×10^8/kg recipient weight. Autologous blood transfusion is used except for very small donors. Sternal aspiration needles were used, as in our experience these produce much less local trauma and very little postoperative pain. We have not had any cases of needle breakage. For the occasional obese patient Jamshidi needles are used. Harvested marrow is collected into a 1-l bag, which has a 120-micron filter online (Tuta Laboratories, Lane Cove, Sydney, Australia). Anticoagulation of the harvested marrow is with ACD (one volume to 7 volumes of marrow) and preservative free heparin (5000 unit/500 ml of marrow). The donor is given 25 units/kg of heparin just before the harvest. All syringes and needles are rinsed with saline followed by ACD.

For ABO mismatched transplants, initially red cell depletion was undertaken using the Hemonetics V50 cell separator but recovery of nucleated cells was poor and hence we started sedimentation with hydroxyethyl starch at a ratio of 1:6 HES to marrow volume.[8] This procedure is much easier to perform and in most cases nucleated cell recovery has been over 90%. In those harvests where the cell recovery has been poor with gravity sedimentation, the marrow is reprocessed on the Hemonetics Cell Separator. For patients with high-titer anti-A or -B antibodies we reduce the titer by administering donor group plasma. Engraftment and chimerism are documented by checking the blood group in a major mismatched transplant. For sex mismatched transplants monitoring is carried out with an amylogenin PCR.[9] For others VNTR analysis of ApoB, ACTBP2 or the vonWillebrand gene is carried out. WHO recommended screening procedures are used in the blood bank but donors are not screened for CMV since 98% of the population is sero-positive. Prophylactic platelet transfusion is given if the patient's platelet count is below 2000/mm^3. All patients have dedicated donors available for platelet pheresis to provide single donor platelets when the blood bank supply is inadequate.

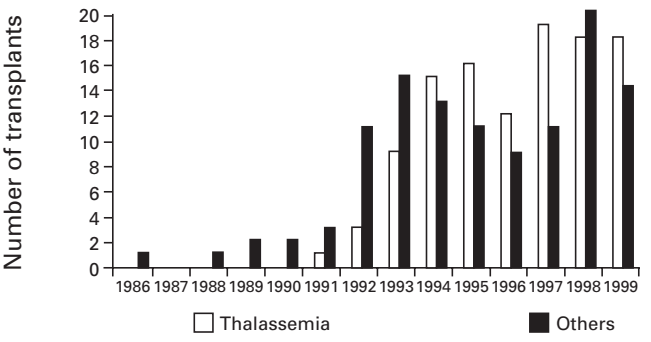


Figure 1 Annual number of transplants.

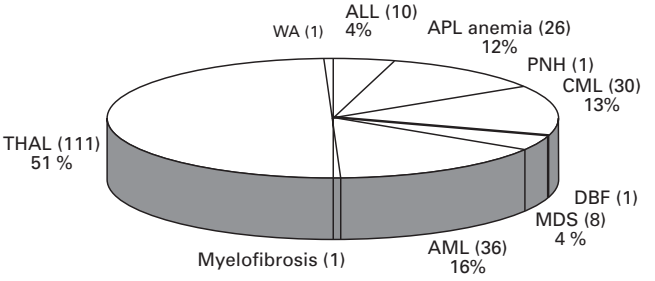


Figure 2 Indications for BMT at CMCH, Vellore.

Results

Figure 1 illustrates the year-wise distribution of transplants. After initial teething problems the program has now become steady with approximately 30 transplants carried out each year. After the first transplant for thalassaemia in 1991 there has been a steady increase and more than half the transplants are for thalassaemia.

Figure 2 illustrates the distribution of patients with regard to the indication for bone marrow transplantation.

Bone marrow harvests have been performed on 214 donors with ages ranging from 6 months to 50 years. Apart from mild local pain there have been no major complications and the donor has been discharged 24 to 48 h after the harvest.

Figure 3 shows the Kaplan–Meier survival curves for the

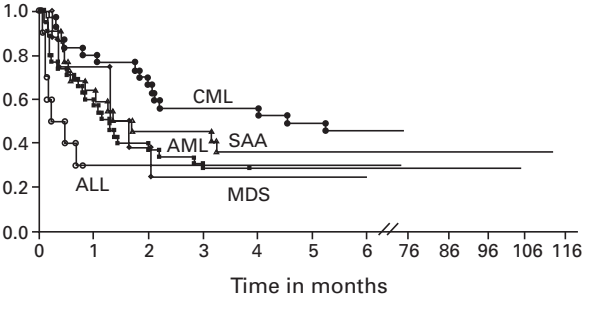


Figure 3 Kaplan–Meier probability of survival for the whole group excluding thalassemia.

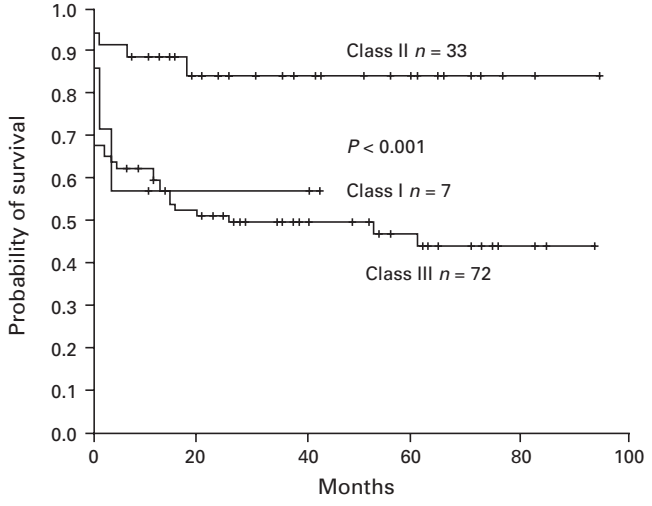


Figure 4 BMT for thalassemia – EFS with respect to class.

whole group and survival curves for patients with thalassemia are given in Figure 4. Table 1 shows the results of all patients except for the miscellaneous category.

Thalassemia

Of the 106 patients with thalassemia who were transplanted only six were class I, 30 class II and 70 class III, reflecting poor pre-transplant transfusion chelation therapy for patients with thalassemia in India. There were 71 males and 35 females. The event-free survival was 66% in class I (two of the six patients died, one due to grade IV gut GVHD and the other due to interstitial pneumonia), 90% in class II and 55% in class III patients with a median follow-up of 26 months (range 2–87 months). Only one of the four patients who received a second transplant is surviving free of disease.

Acute myeloid leukemia

Thirty-five patients with AML were transplanted with only 12 in first remission. Eight (24%) of these patients are alive and free of disease at a median follow-up of 72 months (16–106 months). Nineteen (54%) have succumbed to transplant-related complications, while eight (22%) have relapsed.

Chronic myeloid leukemia

Of the 30 patients with CML transplanted, 26 were in chronic phase, one in accelerated phase and two in blast transformation. There was one syngeneic BMT and this patient relapsed 24 months post transplant. Fourteen of the 30 patients with CML are in complete hematological remission (all patients tested so far are also bcr/abl negative on RT-PCR) with a median follow-up of 30 months (range 4–76). Of the two patients who relapsed, one is now in remission post-donor leukocyte infusion. GVHD was the

Table 1 Results of bone marrow transplantation

Disease	*No. patients/No. transplants*	*M*	*F*	*Disease status*	*CR (%)*	*Follow-up (months) mean range*	*Mortality (non-relapse)*	*Relapse*
Acute myeloid leukemia	35/36	22	13	CR1: 12, CR2: 9 CR3: 1, R1: 5, R2: 2, R3: 1, REF: 6	8 (24)	72 16–106	19 GVHD: 4, IP: 2 Sepsis: 7, DAH: 2 Rejection: 3, IC Bleed: 1	8
Chronic myeloid leukemia	30	20	10	CP: 26, AP: 1 BT: 2 Syngeneic: 1	14 (46)	30 4–76	15 GVHD: 7, IP: 2 Suicide: 1 Other: 5	2 one 2nd CR after DLI
Acute lymphatic leukemia	10	7	3	CR1: 3, CR2: 4 CR3: 1, CR4: 1 R2: 1	3 (30)	33 4–76	3 GVHD: 1 IP: 1 Sepsis: 1	4
Aplastic anemia	22/24	14	8		8 (36)	61 12–116	7 Fungal sepsis: 3 GVHD: 2 VOD: 1 IC bleed: 1	7 Rejection
Myelodysplastic syndrome	8	7	1	RAEB: 4 RAEBt: 4	2 (25)	4 3–5	6 VOD: 1, GVHD: 1 Bleed: 1, Sepsis: 1. Rejection: 2	
Thalassemia	106/110	71	35	Class I 6 Class II 30 Class III 70	4 (66) 27 (90) 39 (55)	26 2–87	21 GVHD, 1 IP 32 GVHD 1 IP 23 GVHD5, VOD6, IP5, Misc 7	0 1 8

CR = complete remission; R = relapse; REF = refractory disease; CP = chronic phase; AP = accelerated phase; BT = blast transformation; RAEB = refractory anemia with excessive blasts, (RAEBt = in transformation); VOD = veno-occlusive disease; GVHD = graft-versus-host disease; IP = interstitial pneumonia; IC = intra-cranial bleed; DAH = diffuse alveolar hemorrhage.

major cause of mortality (23%). Subset analysis shows that only three of the first 15 patients with CML transplanted at Vellore between 1988 and 1996 are alive and free of disease (20%) while the survival is 73% in the 15 patients transplanted between 1996 and 1999; this is illustrated in Figure 5.

Acute lymphatic leukemia

Ten patients have been transplanted with only three in first remission; three patients are surviving free of disease with a median follow-up of 33 months (4–76). Four patients have relapsed, and sepsis, GVHD and interstitial pneumonia resulted in death in the other three patients.

Aplastic anemia

Twenty-four transplants have been performed in 22 patients with one of the two patients who received a second transplant being a long-term survivor. Eight of (36%) this cohort of patients have normal hematopoiesis with a median follow-up of 61 months (12–116). Rejection has been the most important cause of failure (31%), the other causes being fungal sepsis (three), veno-occlusive disease (one), GVHD (two) and intra-cranial bleeding (one).

Myelodysplastic syndrome

Only two of the eight patients with MDS transplanted are surviving, but the follow-up in these two patients is short at 3 and 5 months.

Miscellaneous

There were two patients with Fanconi's anemia in this group, 12 and 17 years old, both of whom had received multiple transfusions before transplant. One was conditioned with total abdominal radiation and low-dose cyclophosphamide and the other with fludarabine, anti-T cell monoclonal antibody (IORT3) and cyclophosphamide. One patient failed to engraft while the other, a mother to son transplant rejected very shortly after initial engraftment. One patient with myelofibrosis failed to engraft and autopsy showed extensive tuberculosis and disseminated fungal infection. A child with Blackfan Diamond syndrome unresponsive to steroids and transfusion dependent received a graft from his HLA matched grandmother. This child developed grade IV hemorrhagic cystitis requiring urinary diversion but is now transfusion free with a stable graft and mild chronic GVHD 30 months post transplant. One patient with PNH is now 2 years post transplant with a stable graft, and a 6-month-old child with Wiskott–Aldrich syndrome is now 2 years post transplant with a normal platelet count and immunoglobulin levels.

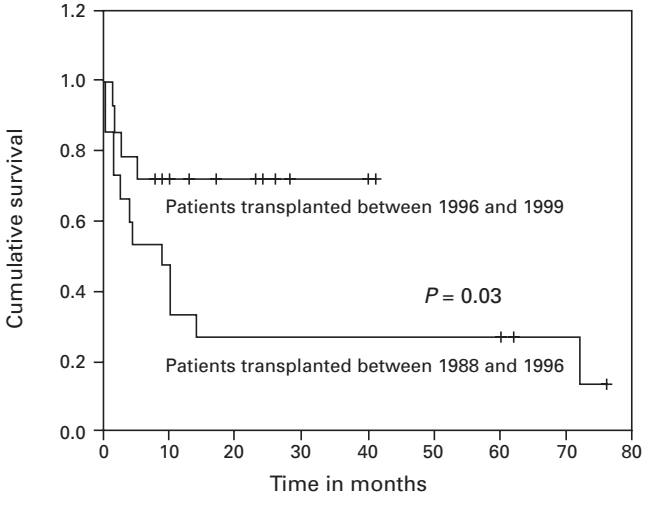


Figure 5 Kaplan–Meier survival curve in CML patients.

Discussion

The bone marrow transplant program at the Christian Medical College Hospital Vellore started in 1986 and the first patient had AML in third relapse. He failed to engraft, became colonized with Pseudomonas as a result of attempted gut sterilization and expired on day 30 with Pseudomonas septicemia and persistent leukemia. We have come a long way since then, with many protocols having been modified to suit local conditions and we now undertake approximately three transplants a month. We have a waiting list of 40 patients who have matched sibling donors, with diseases such as thalassaemia and CML and we are unable to accommodate all those patients who need urgent transplantation. We receive requests for BMT from all the neighboring countries which do not have programs: Pakistan, Sri Lanka, Bangladesh, Nepal, Bhutan and Sikkim. This suggests that there is a need to develop bone marrow transplant facilities in other centers in India and in neighboring countries.

Bone marrow transplantation today offers an alternative to life-long transfusion and chelation for patients with thalassemia major. In December 1981 the first allogeneic bone marrow transplant for thalassemia major was performed in Seattle. That patient is now alive and well 19 years post transplant.[10] The team at Pesaro in Italy under the leadership of Professor Guido Lucarelli has since shown with 805 patients that bone marrow transplantation is in fact a good alternative to transfusion chelation for thalassemia.[11] However, the procedure is associated with a significant risk of infection, regimen-related toxicity, GVHD and relapse, particularly in those patients who, because of inadequate transfusion and poor chelation, have developed hepatomegaly and hepatic fibrosis.[12] The team in Pesaro has developed risk stratification based on these three criteria: class I (well chelated, no hepatomegaly, no hepatic fibrosis); class II (one to two adverse risk factors); class III (all three adverse risk factors). In Table 2 data from Pesaro are compared to the results achieved at CMCH, Vellore. The 90% disease-free survival in the 30 patients in class II transplanted in our series is comparable to the best results achieved anywhere in the world and so is the data in class III. The number of patients in class I in our series is small and the loss of two patients illustrates the fact that bone marrow transplantation is unpredictable in terms of GVHD and RRT even in good risk patients. The cost of transfusion

Table 2 Results of bone marrow transplantation in Pesaro, Italy 1997 compared with data from CMCH, Vellore

Class	*Pesaro OS %*	*Pesaro DFS %*	*CMCH OS %*	*CMCH DFS %*
I	97	93	66	66
II	88	85	90	90
III				
pre 1989	54	49	55	44
post 1989	91	60		

and chelation with desferrioxamine for 1 year for a 30 kg child in India is US$5000. The US$15 000 required for a bone marrow transplant is equivalent to 3 years of transfusion and chelation, and therefore BMT is a cost effective alternative to life-long transfusion in India.

The results of transplantation in acute myeloid leukemia are disappointing but considering disease status at transplant with more than half the patients being in second or subsequent remission or with relapsed and refractory disease, they are comparable to International Bone Marrow Transplant data.[13] It is possible that peripheral blood stem cell transplants rather than bone marrow, with more rapid engraftment and possibly more GVL with reduced relapse rates will solve our problems of sepsis and relapse in this group but with more chronic GVHD.[14]

Chronic myeloid leukemia is the commonest leukemia among adults in India and allogeneic bone marrow transplantation offers curative treatment.[15] For the small subset of patients who achieve a complete cytogenetic remission with interferon and therefore are likely to have a prolonged survival, BMT may not be the first option, particularly if the patient is older, but the cost of interferon at US$7500 to US$12 000 a year is prohibitive.[16] In a report from the International Bone Marrow Transplant Registry (IMTR) the 3-year probability of leukemia-free survival was 57% for patients who underwent transplantation in chronic phase with marrow from HLA-identical siblings between 1987 and 1994.[17] Forty percent of all the patients transplanted with CML at our center are alive and free of disease. If the patients in accelerated phase (two) and the one patient with an identical twin donor are excluded the result of 52% is comparable to IBMTR results. Subset analysis shows that only three of the first 15 patients with CML transplanted at Vellore between 1988 and 1996 are alive and free of disease (20%) while the survival is 73% in the 15 patients transplanted between 1996 and 1999. This shows clearly that results improve as the transplant team gains experience and supportive care infrastructure and technology are improved. Since 1996 we have been administering 10 μg/kg G-CSF for 2 days prior to harvest to the donor and this may have also contributed.

We have only eight patients with acute lymphatic leukemia for whom bone marrow transplantation has been performed and many of these have been in second or subsequent remission or in relapse and therefore our result of 30% DFS is comparable to data from the West.[18]

In patients with aplastic anemia our survival of 36% is disappointing. Most patients come to transplant after having received multiple transfusions. It is well known that rejection rates are higher in this group.[19] Patients with aplastic anemia in India have many episodes of sepsis before they come to transplant and in two of our patients activation of fungal sepsis post transplant has been the cause of death. If the results of transplantation in aplastic anemia in India are to improve we need to get patients into transplant early but the logistics are formidable. Also, prompt treatment of sepsis and transfusion with only irradiated or leukodepleted blood products will reduce rejection.[20]

The successful transplant of a 6-month, 5-kg baby with Wiskott–Aldrich syndrome who is now 15 months post transplant with a normal platelet count and free of sepsis suggests that the unit has now acquired a reasonably high level of expertise in bone marrow transplantation.[21]

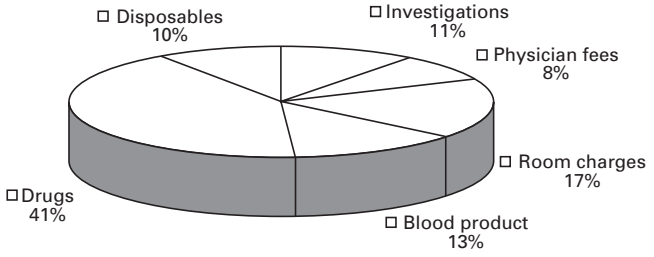
BMT in tropical countries poses a significant problem in terms of unusual infections. All patients transplanted at our center are positive for CMV IgG, unlike in the West where over 30% of patients and donors are CMV negative. Documented biopsy-proven CMV disease was seen in nine patients (seven intestine, three lung and one both) while 30 patients (13%) became CMV PCR positive in the peritransplant period. In those patients with positive blood cultures, gram-negative bacilli were isolated in 75%, with Pseudomonas species being the commonest (24%). Biopsy- or culture-proven fungal sepsis (some at autopsy) was seen in 36 patients (Aspergillus 21, Candida nine, Mucor one and Zygomycetes one). Three patients developed malaria: two *P. vivax* and one *P. falciparum*: all were successfully treated. Five patients developed tuberculosis (2.2%). We do not administer anti-tuberculosis or anti-malarial drugs prophylactically.

Acute GVHD was seen in 92 patients. The severe form (grades III and IV) was seen in 36 patients (17%) and this is similar to data from the West for the mixed cohort of patients in the group. Chronic GVHD was seen in 35 patients with most being limited. Aggressive histological documentation where possible, rapid initiation of treatment and very slow tapering of immunosuppression are some of the lessons that we have learnt in the management of GVHD.

For our initial transplants we used only hydration or Mesna and hemorrhagic cystitis was a significant problem. However, after using a combination of hydration at 3 l/m^2 and Mesna (seven doses at 20% of the dose of cyclophosphamide), this has ceased to be a major problem. Veno-occlusive disease related to conditioning with busulphan and cyclophosphamide is still a problem, particularly in class III patients with thalassaemia and this contributes to the morbidity.

Figure 6 shows that drug and disposables account for most of the transplant cost. Our first successful transplant in a 6-year-old girl with CML cost US$2000 in 1988. Today, the cost ranges from US$6500 for an uncomplicated transplant in a child to US$40 000 for a complicated transplant in an adult and the actual cost billed to four representative patients is indicated in the legend which accompanies the figure.

This study demonstrates that it is possible to develop an allogeneic bone marrow transplant program in the developing world with results that are comparable to those



Actual cost of BMT from admission to discharge in US$ for four patients

UPN	214	229	217	171	Mean
Disease	THAL*	THAL*	CML*	CML*	
BSA – M2	0.9	1.2	1.5	1.66	
Period – Days	62	90	43	60	
Investigations	1241	3131	928	1642	1735.50
Physician fees	631	1931	1174	1603	133475
Room charges	2571	4287	2168	2438	2866.00
Blood product	1606	5265	228	1349	2112.00
Drugs	3393	13034	3500	7549	6869.00
Disposables	1107	2398	511	2346	6362.00
Total	11,152	30,049	8,512	16,930	16666.75

*Uncomplicated
**Complicated
(GVHD, sepsis)

Figure 6 Cost breakdown of BMT in US dollars.

achieved in the West at a significantly lower cost. The infrastructure developed for a bone marrow transplant program will improve the quality of care in terms of transfusion support, infection control and management of neutropenia in tertiary referral institutions in the developing world.[22]

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