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Original Article

Bone Marrow Transplant for Low Risk Thalassemia Patients in Low Resource Setting

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Abstract

Objective: To evaluate performance of a newly developed low resource Bone Marrow Transplant unit for thalassemia major in Islamabad.

Materials and Methods: Medical Records of 26 bone marrow transplants performed were revisited. Their survivals, complications, management of complications and cost of treatment were evaluated.

Results: 23 had successful engraftment with transfusion free survival. Two patients had transplant related mortality. The manageable complications included hypertension and hemorrhagic cystitis. One patient developed VOD.

Conclusion: Bone Marrow transplant for transfusion dependent Thalassemia is possible in low resource setup with results that are comparable with the centers in developed countries and the complications are manageable.

Key words: Bone Marrow Transplant, Thalassemia major, Low resource setup.

Introduction

Bone marrow transplant from HLA-identical siblings is the only curative treatment for Thalassemia major.[1] Since 1981 more than 2000 bone marrow transplants have been performed in centers all over the world. This mode of treatment is expensive therefore it not accessible for the children who need it the most.

Bone Marrow Transplant unit was established in the Children Hospital, PIMS, Islamabad in collaboration with Cure2Children Foundation (C2C), Florence, Italy. The Cure2 Children Foundation has supported, both financially and professionally according to shared recommendations and within an intensive cooperation program based on online and on-site focused training followed by continuing collaboration.[4, 5]

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Thalassemia Major is the most common cause of transfusion dependent anemia in Pakistan. The gene frequency varies from 5-8 %.[1] Supportive treatment includes regular safe packed cell transfusions to keep pre transfusion hemoglobin above 9 g /dl and regular Chelation therapy to remove excess iron from the body.[2] Unfortunately most of Pakistani Thalassemia patients are under transfused and has iron overload because of inaccessible or unaffordable safe blood products and Chelation therapy. The cost of supportive treatment for an average 10 year old child is approximately 3000 USD/ year.

Thalassemia centre, Children Hospital, PIMS has more than 1000 registered patients who receive supportive treatment on day care basis. Low risk children were evaluated for transplant and were offered the treatment.

Annual cost of supportive treatment

Blood transfusions	800 USD
Chelation	2000 USD
Investigations	100 USD
Miscellaneous expenditures	100 USD
Total cost/year	**3000 US**

Most of the patients live below poverty line and cannot afford treatment. This is the reason why 80% of our patients die between 10 to 20 years of age.

Bone marrow transplantation (BMT) remains the only available definitive cure[8,9] and success rates can be very high in appropriately selected patients, i.e. low-risk younger children with a matched family donor. In these circumstances BMT may be justified medically, ethically as well as financially, in fact, the cost of low-risk BMT is equivalent to that of a few years of non-curative supportive treatment.

Pakistan Institute of Medical Sciences Islamabad is a tertiary care institute and drains patients from Rawalpindi-Islamabad capital territory and adjacent areas, Northern Areas, North Punjab and Azad Kashmir. It also entertains referred cases from remote areas and other parts of the country. To cater the needs of patients, a 2 bedded facility for Bone Marrow Transplant was initiated in PIMS in 2008 through an MOU signed with an Italian NGO Cure 2 Children Foundation (C2CF).

In addition to PIMS, there are only three centers in the country, viz. Armed Forces Bone Marrow Transplant Centre, Rawalpindi, National Institute of Blood Diseases, Karachi and Aga Khan University Hospital ,Karachi.[6,7] Further the charges for other modalities of treatment of the Blood Diseases in private sector organization are too high and the general public can barely afford the expenses of these hospitals. The result is that they prefer to use the facility at PIMS.

Materials and Methods

Selection Criteria: Between January 2009 and August 2013, twenty six patients were selected according to the following criteria

a. Transfusion dependent Thalassemia (at least 8 transfusions/year)
b. HLA matched sibling donor.
c. Age below 7 years.
d. Liver size less than 3 cm palpable below right costal margin.

Pre transplant Evaluation: All patients and donors were evaluated with a complete blood count (CBC), biochemical profile and serology for HIV, HBV, HCV and CMV.

Conditioning Regimen: Conditioning consisted of Thiotepa (10 mg/kg), oral Busulfan (14mg/kg) and Cyclophosphamide (200mg/kg) with triple drug (PDN/ MTX/CSA) as GVHD prophylaxis (Lucarelli's regimen 6.i).

Procedure: Bone marrow was collected from donor on transplant day under general anesthesia by multiple punctures from the posterior superior iliac spine and crest. The harvest kit which consisted of Gauge 16 spinal needled, a blood bag and heparin as anticoagulant, was improvised. Blood complete picture was done during harvest to evaluate the number of nucleated cells in collected marrow and access required amount of bone marrow to achieve for the required cell dose (2-5 $x10^8$ nucleated cells/kg of recipient's body weight).

Bone marrow harvested was infused to recipient on the same day under the cover of Anti histamine. Cyclosporine 5mg/kg was given as GVHD prophylaxis[10] from day 2 to day 5 then it was reduced to 3mg/kg iv from day 6 onwards. Oral cyclosporine was given 21 days onwards. The peak level of cyclosporine was maintained (800 - 1200 ng/dl). Cyclosporine was given in full dose for 9 months followed by gradual tapering off in next 3 months. Prednisolone 0.5 mg/kg was giv-

en orally from day 2 - 4 weeks of transplant followed by tapering off in next 2 weeks. Three doses of Methotrexate 10mg/m^2 were given on day 1, 3, 6 followed by folonic acid rescue IV on the next day.

Post Transplant care included, weekly monitoring of CMV by PCR after ANC became more than 1000 /cm^3, IV acyclovir, fluconazole upto 90 days post transplant. Prophylaxis for pneumocystis carani by Co trimexazole from day 21 till the discontinuation of cyclosporine. Patients were transfused according to transfusion policy i.e. Platelet transfusion if platelet counts < 10,000 or clinical bleeding and packed red cell transfusion if hemoglobin was 8 or less. All blood products were irradiated. Febrile neutropenia was treated according to the hospital policy. Parentral nutrition was given according to the degree of mucositis and caloric intake of the patient. GVHD was graded clinically according to EBMT guidelines. On day 28 bone marrow aspirate was sent to AFIP for the test of donor chimerism.

Results

Since Jan. 2009, out of 26 low risk patients 23 had successful engraftment with transfusion free survival. Median follow up of 460 days (range is 30 to 1550) days. Two patients had transplant related mortality. One patient died after 38 days of transplant due to activation of TBM the other patient developed septicemia leading to multiple organ failure on 30th post transplant day. One patient remained transfusion dependent after autologous reconstitution.

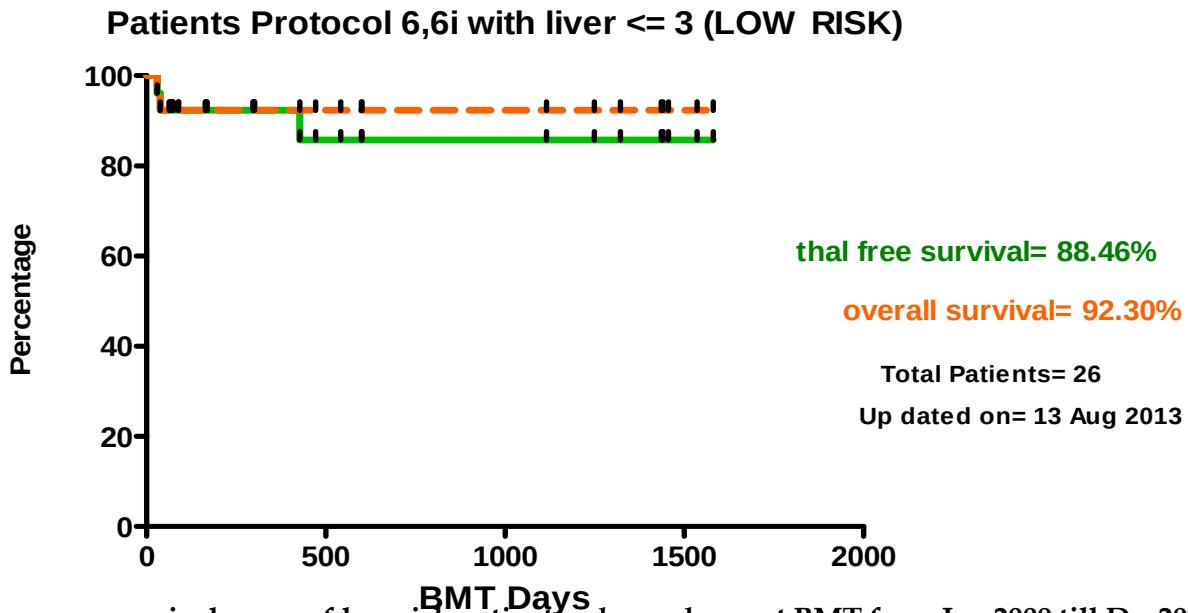
Complications included grade 3 acute GVHD in one patient. One patient had subclinical CMV activation diagnosed by real time CNV-PCR.

Other manageable complications included hypertension and hemorrhagic cystitis. One patient developed VOD.

Bone Marrow transplant for transfusion dependent Thalassemia is possible in low resource setup with results that are comparable with the centers in developed countries and the complications are manageable.

Discussion

It was a great challenge to establish a safe bone marrow transplant unit in a public hospital which is under- funded, under staffed and over worked. A pharmacy store house was renovated into a two bedded transplant unit with two sepa-



Kaplan mare survival curve of low risk patients who underwent BMT from Jan.2009 till Dec2013

rate easy to clean rooms and attached bathrooms, a kitchen and a doctor's duty room. Each room had a High efficiency Particulate Air (HEPA) filter. Subsequently the doctor's duty room was also used for transplant and 3 more beds were added to the service for the outpatient care. The cost of civil work was funded by the parents of 3 year old child Simone Montomoli who died of teratocarcinoma in Italy. His picture on a china plate, which adorns our unit, is a gift from his parents and our unit is named after him.

BMT *Unit Median (range)*	
Pre-Transplant evaluation	$ 532 (141-1,026)
Diagnostic	$ 1,704 (733-4,548)
Blood products	$ 132 (88-374)
Hospitalization charges	$ 535 (455-1,320)
Surgical devices (CVL)	$ 396 (311-437)
Drugs	$ 1,577 (1,212-5,518)
Professional Cost	$ 4,324 (3,817-10,660)
Follow up cost	$ 1,714 (375-2,350)
Total	**$ 11,513** (7,518-21,176)

A memorandum of understanding was signed by the Children Hospital, PIMS and the Cure2children foundation after approval from federal ministry of Health to ensure smooth working of public private relationship. All the local staff of BMT unit was jointly selected by PIMS and C2C. Training of local team by Italian Transplant Specialists and initial transplants was done under their supervision. All Patients and donors are selected through well defined policy managed as per standard guidelines. All the therapy administered according to patient specific treatment plan generated by international consultants, reviewed and implemented by local consultants. Regular entry of all patient specific medical data in web based centralized clinical data base so that all patients can be followed by both international and national consultants. Most of the diagnostic support has been provided by the PIMS but few transplant specific investigations and irradiation of blood products has been outsourced because of their non availability in PIMS.

Conclusion

In low resource settings safe and effective matched-related low-risk BMT for thalassemia can be performed with outcomes comparable to richer countries and with a fraction of the costs even from the very beginning of newly developed BMT units and by relatively untrained personnel provided a structured and intensive cooperation program with BMT experts is provided.

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