Transplantation in low resource countries

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Abstract

Thalassemia major (TM) is the most common deadly genetic disorder, a major cause of chronic non-infectious morbidity and financial burden in many low and middle-income regions. In these settings few children reach adulthood because proper long-term supportive care is seldom available. Bone marrow transplantation (BMT) is the only available curative modality and it can be very successful and cost-effective for young children with low-risk features and a compatible related donor. However, in countries where TM is most prevalent, there is a dire shortage of BMT centers. The Cure2Children Foundation has supported a feasibility study evaluating safety, efficacy and costs of developing a new BMT center in an underserved lower-middle-income country with relatively untrained professionals within a structured collaboration and knowledge-transfer program. A total of 24 consecutive patients who underwent BMT in Pakistan between September 2008 and August 2010 are included in this prospective analysis. 17 from an established bone marrow transplant center, the National Institute for Blood Diseases in Karachi, Pakistan and the initial 7 BMTs from a start up unit in a government civil hospital, the Pakistan Institute of Medical Sciences Children’s Hospital in Islamabad. Patients were matched for age, nutritional status, growth, disease, disease status and post-BMT follow-up time. All patients had a matched-related sibling donor, were younger than 10 years of age at the time of transplantation, received the same conditioning regimen. All needy families could rely on a support program throughout the 8-month post-transplant period. The Cure2Children Foundation provided professional and financial support as well as a structured web-based data management and cooperation platform. At a median follow up of 19.6 months (range 8.7 to 31.5) actuarial thalassemia-free survival is 85.6% and 85.7% and overall survival 94.1% and 85.7% in the established and start-up center respectively with no statistically significant differences. Other outcome indices like infectious complications, engraftment parameters, transplant-related complications, and post-BMT performance scores also did not differ. The median cost of matched-related transplants in the start-up center, including pre-BMT evaluation, was 11,513 USD (range 7,518 to 21,176). Within structured cooperation strategies bone marrow transplantation for thalassemia major can be performed safely, effectively, and affordably even in start-up centers in lower-middle-income countries, like Pakistan, were most thalassemia patients live. This observation may have important implications to increase access to cure for thalassemia worldwide.

Introduction

Aslam’s story

Aslam is a 2 year and 3 months old boy with thalassemia major. His father is a mill worker and his mother a housewife, they live in interior Sindh, Pakistan. The father can read and write Sindhi (the local language). They need a 5-hour bus ride to the nearest thalassemia care center in Karachi were Aslam gets a transfusion once a month, the parents are aware they should go more often but it is very hard for them, the whole family income is less than 1,000 USD/year and a substantial part of it goes for the care of Aslam. Nine children have died of thalassemia in their extended family.

Aslam’s doctor explained in Sindhi that an international NGO was supporting access to cure of thalassemia by bone marrow transplantation for needy families in Pakistan and presents this option to the parents because he has a 4-year-old healthy sister who could be the potential donor, even if she had thalassemia minor. The parents know that it will be very hard for them to provide Aslam with the long-term care he will need to be able to survive, they know and trust their doctors and decide to go for a cure even if they are aware that there is chance he may die from transplantation. The NGO will also provide accommodation and family support in Karachi.

Aslam’s sister turns out to be compatible by HLA testing and three months later he is transplanted her bone marrow, he stays in hospital with his mom for a little over a month and then another 6 months with his family in the Karachi apartment provided by the NGO which also regularly sends a nice lady (herself cured by transplantation), to make sure they have the basic necessities and are able to keep the apartment clean.

Almost 8 months later they go back to their village, Aslam has not needed transfusions for over 7 months, his parents are very happy and grateful for their new life even though the doctor explained that he might have problems having children when he grows up. Prenatal diagnosis, should the mother expect another baby, was also discussed.
Thalassemia disease burden

Thalassemia major is the most frequent deadly genetic defect worldwide and accounts for a substantial proportion of childhood mortality, morbidity and related healthcare expenses in many densely populated regions in North-Africa, Eastern Mediterranean, South-East Asia and Western Pacific where the carrier rate ranges from 3% to 40%.1,2

Thalassemia outcomes in lower-income countries

In spite of significant progress in supportive care, which may extend life expectancy well into adulthood,3 most patients in low to middle-income areas, where thalassemia is most prevalent, do not survive beyond 20 years of age and the risk of blood-borne infections, primarily hepatitis C, is still substantial.4

Bone marrow transplantation for thalassemia: accessibility and costs

Bone marrow transplantation (BMT) remains the only definitive cure for thalassemia major with reported thalassemia-free survival rates consistently over 80% in selected young low-risk patients with a related histocompatible donor.5,6 BMT is also associated with improved quality of life7,8 and is generally recommended in young low-risk patients with a matched related donor.10 In areas where thalassemia is endemic there is a severe shortage of centers for its cure.11,12 This is not only due to lack of financial resources, in fact BMT is less expensive compared to long-term supportive care,13 but other factors may contribute such as lack of specific professional expertise or the perception that setting up a BMT center is highly complex and expensive.

The Cure2Children experience supporting BMT for thalassemia in Pakistan

Cure2Children (C2C) is a non-profit and secular International Non-Governmental Organization founded by parents who lost their child to cancer. The mission of C2C is to promote and support the care of children with malignancies and severe blood disorders directly in developing countries.

The Pakistan project originated from the passion, commitment and capacity of a Pakistani family with a thalassemic child transplanted in Italy by a team connected to C2C. The primary aim of this initiative has been to increase access to care for children with thalassemia by capitalizing on available local expertise and facilities. The strategy relied on the prospective assessment of outcomes within a structured knowledge-transfer and support program applying common treatment protocols and standards for patient selection and management. We sought to assess if reported differences in outcome related to socio-economic conditions, are due primarily to patient selection, inconsistent or no access to appropriate drugs, lack of professional expertise, rather than to local conditions increasing the risk of infectious complications or causing poor family support and follow-up care. In addition we tested the hypothesis that within structured cooperation and assistance from third-party non-governmental organizations, like C2C, a relatively complex procedure like BMT could be set up safely and effectively with limited resources.

Patient characteristics

A total of 24 consecutive patients with transfusion-dependent thalassemia transplanted in Pakistan between September 2008 and August 2010 were included in the analysis. Selection criteria included age less than 10 years, no hepatomegaly (liver <2cm from the right costal mar-
both ganciclovir and foscarnet were available. Co-trimoxazole at 5 mg/kg/dose twice daily for three consecutive days a week was administered for *Pneumocystis* prophylaxis from the day neutrophil counts reach 500/mL to day +90.

**Family support program**

A patient coordinator as well as housing and monthly allowance was provided by C2C. This family support program was implemented throughout the eight months post BMT.

**Collaboration methodology**

Structured cooperation and communication strategies involving international and national transplant specialists were employed. Management standards for therapy administration, central venous access, severe pancytopenia, immunosuppression, and hospital infection control were addressed by local training, a specific web-based open-source data management software developed by C2C (CDATA, www.cure2children.org/ws/thdb) and Skype videoconferencing (www.skype.com). Patient-specific treatment plans were provided as Microsoft Excel-generated pre-calculated treatment sheets meant to reduce the physician’s workload and prescription errors and also to supply nurses with clearly written order sheets in keeping with good clinical practices.

**Statistical analysis**

Statistical analysis was performed using GraphPad Prism software version 5 March 2007 (www.graphpad.com/prism/Prism.htm). Kaplan-Meier survival curves were compared by Log-rank (Mantel-Cox) Test and patient characteristics by Mann-Whitney nonparametric test using two-tailed P Anthropometric z-score values were calculated with the World Health Organization shareware Anthro.15 For patients above 60 months of age WHO Child Growth Standards reference tables were used.16

At a median follow up of 20 months (range 10.9 to 31.5) and 17.7 (range 8.7 to 24.2) for patients managed in an established unit or in a start-up unit respectively, no significant difference in outcomes was observed with actuarial thalassemia-free survival of 85.6% and 85.7% (log rank P 0.8609) and overall survival 94.1% and 85.7% (log rank P 0.5322) respectively.

**Discussion**

To our knowledge this is the first study prospectively comparing homogeneous patient groups undergoing bone marrow transplantation in start-up versus established BMT centers in low-resource settings in the context of a structured knowledge-transfer strategy. The objective of this study, in keeping with the mission of the C2C, was to assess the potential to extend access to BMT for severe hematological disorders in underserved regions.

There is general perception that bone marrow transplant centers need complex engineering standards requiring undue investments, even more in poor countries were infectious risk may be higher. In fact there is no evidence that the latter is true.17,18 Even if available international guidelines call for placement of allogeneic BMT recipients in highly protected environments with positive pressure gradients, intensive air exchange and filtration,20 these recommendations are not based on well-designed clinical trials. In fact, safe care of allogeneic transplantation recipients has been reported even in the outpatient setting.21,22 Many widely held practices which may unnecessarily increase BMT-related expenses are being reconsidered worldwide and cost-containment considerations are even more important in settings with more limited resources.

### Table 1. Characteristics of patients treated at the established institution (NIBD) versus a start up service (PIMS).

|               | Established Unit | Start-up Unit | P     |
|---------------|------------------|---------------|-------|
| Age (years)   | 3.5 (1.8 to 9.4) | 3.0 (0.9 to 5.4) | 0.43  |
| Gender        | 8 M, 9 F        | 6 M, 1 F      |       |
| Height for age (z-score) | -0.82 (-3.47 to 1.92) | -1.17 (-2.48 to 0.72) | 0.94  |
| Weight for age (z-score) | -0.51 (-3.55 to 0.73) | -0.72 (-2.60 to 0.12) | 0.43  |
| Body mass index (z-score) | -0.11 (-2.78 to 1.68) | -0.71 (-2.49 to 0.77) | 0.53  |
| Pre-BMT Ferritin | 1200 (289 to 2960) | 2476 (616 to 8008) | 0.58  |
| Consanguinity  | 14/17 (82%)      | 5/7 (71%)     |       |
| Donor thalassemia minor | 10/17 (59%) | 6/7 (86%) |       |
| Nucleated cell dose/kg x10⁹ | 8.6 (1.4 to 23) | 5.8 (3.1 to 8.0) | 0.27  |
| Follow up from BMT (months) | 20 (10.9 to 31.5) | 17.7 (8.7 to 24.2) | 0.59  |

### Table 2. Engraftment data.

|                          | Established Unit | Start-up Unit | P     |
|--------------------------|------------------|---------------|-------|
| Median day ANC>500/μL    | 19.5 (12-35)     | 15 (10-23)    | 0.15  |
| Median day Plt >20,000/μL| 23.5 (10-49)     | 15.3 (12-20)  | 0.07  |
| Median n. Plt transfusions | 6.5 (1-26)  | 4 (1-18)      | 0.25  |
| Median n. RBC transfusions | 2 (1-6)    | 2 (0-7)       | 0.47  |
| Last RBC transfusion day | 12.5 (1-36)      | 16 (0-152)    | 0.59  |
| Median discharge day post-BMT | 26 (12-60) | 38.5 (22-109) | 0.02  |

### Table 3. Summary of adverse events.

| Infections                              | Established Unit | Start-up Unit | P     |
|-----------------------------------------|------------------|---------------|-------|
| CMV activation                          | 7 (41%)          | 3 (43%)       |       |
| Aspergillosis (probable or proven)      | 0                | 0             |       |
| Fever and neutropenia                   | 11 (63%)         | 4 (67%)       |       |
| Tuberculosis (probable)                 | 1 (6%)           | 1 (14%)       |       |
| Acute GVHD grade 1-2                    | 1 (6%)           | 2 (29%)       |       |
| Acute GVHD grade 3-4                    | 0                | 2 (29%)       |       |
| Limited chronic GVHD                    | 1 (6%)           | 1 (14%)       |       |
| Extensive chronic GVHD                  | 0                | 0             |       |
| Hemorrhagic cystitis                    | 2 (17%)          | 1 (14%)       |       |
| Mucositis (> ECOG grade 1)              | 5 (29%)          | 2 (28%)       |       |
| Death                                   | 1 (6%)           | 1 (14%)       |       |

### Table 4. Cost comparison. Pakistan costs obtained from the seven transplants performed in the start-up unit in a government hospital, all patients had at least 8 months follow up post-BMT.

|                          | Start-up 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)      |
In this study patients and their caretakers were admitted to single rooms with private bathrooms and split air conditioning. Strict hand washing of all personnel and visitors was enforced and BMT units were cleaned daily.

Infectious complications observed in Pakistani centers did not seem to be substantially different from those encountered in Europe or North America, with the exception of two possible cases of probable pulmonary tuberculosis. CMV reactivation was the main opportunistic infection observed. Of the two centers participating in this project one was a newly developed service heavily relying on initial local training followed by daily interaction via video-conferencing and web-based data management, the second an established BMT service which had been performing transplantation for 8 years.

This experience may set a useful precedent to extend access to bone marrow transplantation in lower-middle income regions and limit the emigration of thalassemia major patient to richer countries or even increase attraction of patients from abroad. In our experience BMT outcomes in low-risk cases with a compatible related donor were comparable to those obtained in high-income countries but with one-tenth of the costs.

Given the great case load, high success rates and much lower costs, thalassemia BMT programs in developing countries may achieve high standards of care, international competitiveness and self-sustainability. This may not only contribute to boost advances in the cure of thalassemia worldwide but also to increase access to BMT for other life-threatening diseases such as severe aplastic anemia and high-risk leukemia, and contribute to biomedical research. The prospect of cure may also increase the attraction of affected families and increase opportunities to cascade screening and prevention programs as well as improve compliance with supportive care.

The lower than expected incidence of severe acute and chronic GVHD in Pakistani patients might be attributable to consanguinity as improve compliance with supportive care.

This study, in addition to the establishment of a proof of principle with potential important effects on increasing the number of BMT centers and empowerment of tertiary medical care in developing countries, might also be relevant to health care cost containment, comparative-effectiveness assessments, and current practices of bone marrow and stem cell transplantation worldwide.

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