

Setting up low-risk bone marrow transplantation for children with thalassemia may facilitate pediatric cancer care

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Abstract

Background: In many South Asian countries there is shortage of centers providing care for pediatric malignancies. This report describes the experience of the Cure2Children Foundation (C2C) in supporting, both financially and professionally, the startup of two bone marrow transplant (BMT) centers, one in Pakistan and one in India, for the cure of transfusion-dependent thalassemia. Even though transplantation is generally considered as a more complex and advanced step relatively to basic pediatric cancer care, the authors argue that BMT for low-risk thalassemia patients with a matched sibling is a relatively simple procedure amenable to focused training. **Materials and Methods:** Since 2008 the C2C, an Italian Nongovernmental Organization (NGO), has supported a BMT network in Pakistan. The primary aim of this project was to assess feasibility, outcomes, and costs of matched-related BMT for thalassemia in young low-risk children employing a well established and quite tolerable strategy employed in Italy. This initiative relied primarily on focused training and task-shift strategies within a structured cooperation program. The initial success of that strategy led to its replication in India with 100 total BMTs performed over the past 4 years, 91 of which were for thalassemia major. **Results:** Low-risk matched-related BMT in children younger than 5 years could deliver a 92% thalassemia-free survival with 100% performance score and no extensive chronic graft versus host disease (GVHD), for an average cost of 10,000 USD per BMT. Within an existing hospital facility, 50,000 USD were sufficient to renovate and fully equip a 2-3 bedded start up BMT unit capable of performing safe low-risk compatible marrow transplantation. **Conclusions:** In low resource settings matched-related low-risk BMT for thalassemia can be performed with outcomes comparable to richer countries and with a fraction of the costs. Within structured and intensive cooperation, good outcomes can be obtained from the very beginning. This observation may have important implications to increase access to cure for both nonmalignant and malignant.

Introduction

Pediatric cancer is a challenging field of medicine largely because of its wide range of relatively rare disorders each one with its own diagnostic and therapeutic peculiarities combined with the emotional burden and urgency associated with life-threatening situations in children. The pediatric oncologist in low- and middle-income countries (LMICs), may be faced with frustrating diagnostic and therapeutic limitations, often related to financial and human resources shortcomings, which may compromise outcomes.^[1] Governmental and institutional support is frequently inadequate both because of the stigmata related to cancer, too often considered incurable, and because of cost issues, which make pediatric oncology services difficult to sustain. Both national governments and international health organizations have historically paid little attention to childhood malignancies, which account for less than 2% of all cancers and for which there is poor

awareness among the general population. Only recently has the World Health Organization recognized the increasing burden of Noncommunicable Diseases (NCD) in developing countries as a major disease burden, unfortunately largely for adults.^[2] Last but not least the issue of treatment abandonment related to cultural, educational, and financial barriers.

In contrast, thalassemia major (TM) is probably the most frequent life-threatening childhood NCD in the Middle East, South Asia, and Pacific Islands where it accounts for a significant proportion of childhood mortality, morbidity, and related health care expenses.^[3,4] In spite of major advances in supportive care in the past decade,^[5] many patients in LMICs still fare poorly because of treatment costs and lack of accessible multidisciplinary teams, not to consider the risk of blood-borne infections, primarily hepatitis C.^[6] In selected low-risk patients with a compatible sibling, TM is highly curable by bone marrow transplantation,^[7] which also improves quality of life,^[8,9] is highly cost-effective,^[10] and may not require unduly expenses for set up.^[11-12] Being a hereditary and chronic disease, families with affected children understand the severity of TM, are generally very cooperative and committed.

Bone marrow transplant (BMT) is a relatively complex medical procedure with positive ripple effects in terms of best practices and professional motivation on the whole institution taking over the challenge and is generally well received by administrators and decision-makers, as it is the basic form of stem cell transplantation and has great

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potential for research, development, and scientific visibility. This reports summarizes the experience of the Cure2Children Foundation (C2C) supporting a network of institutions, primarily in Pakistan and India, performing low-risk BMT and run by relatively inexperienced staff within an intensive cooperation program.

Materials and Methods

Since 2008 the C2C, an Italian Nongovernmental Organization developed by parents who lost their child to cancer together with pediatric hematology–oncology professionals, has supported a BMT network in Pakistan, primarily thanks to a locally influential couple whose daughter with thalassemia was transplanted in Italy. The primary aim of this project was to assess feasibility, outcomes, and costs of matched-related BMT for thalassemia in young low-risk children employing a well established and quite tolerable strategy.^[13] This initiative relied primarily on focused training and task-shifting within a structured cooperation strategy.^[12] The program was replicated in India and other developing countries with the following general collaboration methodology:

- After the initial contact and manifestation of interest from local centers or other stakeholders the medical coordinator of C2C performs a first site visit to assess feasibility, justification, dedication, basic requirements, and potential for sustainability. Relevant general and locally pertinent issues are discussed with health care professionals and decision-makers so that a process of mutual understanding according to shared principles and vision is initiated.
- Technical and professional aspects such as start up BMT unit location, size, design, infection control issues, and most importantly, roles and responsibilities as well as doctor and nurses team-building approaches are addressed. Local nursing personnel requirements include confidence with managing sick children or neonates and handling central venous lines. A list of essential drugs and supplies is provided together with reference material. The only BMT-specific procedures and tests that are considered mandatory are blood product irradiation (by any radiotherapy unit), cyclosporin blood levels, and cytomegalovirus (CMV) reactivation monitoring, all of which can be outsourced in the early phase provided turnaround times are acceptable. More complex and expensive tests like flow-cytometry or chimerism analysis are not an absolute requirement in transplantation for thalassemia, the former because standard blood count-based nucleated cell dose is used to estimate marrow dose, and the latter because, as long as transfusion independency is achieved, the degree of chimerism is not clinically relevant.
- Candidate patients, primarily children with severe thalassemia younger than 7 years with at least one healthy sibling, are evaluated and tested for human leukocyte antigen (HLA) compatibility.

- Online tools, namely a centralized database, as well as videoconferencing tools, primarily Skype, are used to discuss and monitor each patient throughout BMT: This online medical record system is designed specifically to follow BMT patients and filled in daily with diagnostic tests and progress notes by both physicians and nurses. The compliance with this prospective database has been quite good because it helps daily clinical management and continuing interaction with BMT consultants. At least one “shadow” physician and nurse are available to answer emergency questions by cell phone 24 hours a day for 7 days a week. A total of over 1700 potential BMT candidates, largely with thalassemia, from 20 different LIMCs are currently registered from C2C partner institutions or self-referred.
- On-site hands-on training starts when all basic requirements are in place: A team of volunteer professionals composed of nurse and doctors with BMT experience rotates during the first 2-3 BMTs covering from day -14 of the first BMT to day +30 of the last one for a total of approximately 2 months. The local team thus learns by hands-on training with constant expert supervision.
- Computer-generated (MS Excel) individualized treatment plans developed according to good clinical practices are generated for each patient.
- Quality management is facilitated by this remote procedure- and patient-specific collaboration in which results and outcomes are shared both within the network of collaborating institutions and on peer-reviewed scientific media.
- A comprehensive “standard BMT Manual” is continuously updated in collaboration with local medical and nursing staff.

Treatment regime employed for low- and intermediate-risk thalassemia matched sibling transplantation (Lucarelli’s protocol 6.1):^[13] Oral busulfan 3.5 mg/kg/day in four divided doses on days -10 to -7 (total dose 14 mg/kg), thiotepa 10 mg/kg in two divided doses on day -6 (total dose 10 mg/kg), and cyclophosphamide 50 mg/kg/day once daily on days -5 to -2 (total dose 200 mg/kg) followed by the infusion of freshly harvested HLA-compatible marrow on day 0. Graft versus host diseases (GVHD) prophylaxis consisted of intravenous cyclosporin A starting at 5 mg/kg from day -2 to +5 then 3 mg/kg from day +6 to +22 to be followed by 10 mg/kg/day in two daily oral doses for up to day +90 after which it was tapered by -5%/week and discontinued at 8-12 months post-BMT unless otherwise indicated. A short intravenous methotrexate course consisting of 10 mg/m² on days +1 (24 hours after marrow infusion), +3 and +6, with folinic acid rescue at 24 hours after each methotrexate with three doses of 10 mg/m² at 8 hour intervals, that is, at hours +24 +32 and +40. Intravenous

methylprednisolone at 0.5 mg/kg/day from day -1 to +30 and tapered by -30% every 5 days over 15 days and stopped on day +45 was also used.

For high-risk patients Lucarelli's protocol 26 was used based on fludarabine, busulfan, and reduced dose cyclophosphamide after 6 weeks of hydroxyurea and azathioprine therapy as previously published.^[14]

Patient-specific precalculated treatment plans were provided. For antihelminthic prophylaxis mebendazole 100 mg twice daily for three days was administered before conditioning. For Candida infection prevention fluconazole 3-6 mg/kg/day as a single dose was used and for herpes virus acyclovir 250-500 mg/m²/dose three times a day from day +1 to +90. CMV was monitored by real-time polymerase chain reaction (PCR). No routine antibacterial prophylaxis was used. For antifungal therapy voriconazole was the first-line drug, for CMV activation 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/ μ L to day +90.

All patients were admitted in single rooms with split air conditioning, private bathrooms, and daily cleaning. None of the centers in Pakistan and India had positive pressure gradients or centralized high-efficiency particulate air (HEPA) filtration systems. Hand washing was strictly enforced but routine use of gloves and gowns was not mandatory.

A patient coordinator as well as housing and monthly allowance was provided by C2C to patients in Pakistan and India as needed. This family support program was implemented throughout the first 8 months post-BMT.

Statistical analysis

Kaplan–Meier survival estimates in Table 1 were obtained using GraphPad Prism software version 5 March 2007.

Results

A total of 100 BMTs were performed over the past 4 years, 91 of which for TM [Table 1], 4 for severe aplastic anemia, 4 for Fanconi's anemia and 1 for relapsed acute lymphoblastic leukemia. Low-risk matched-related BMT in children younger than 5 years could deliver a 92% thalassemia-free survival (a result comparable to that obtained in high income countries)^[15] with 100% performance score and no extensive chronic GVHD. For higher risk patients cure rates are significantly lower.

Table 1: Summary of outcomes for all patients by disease and risk group

	No. of patients	Thalassemia-free survival (%)
Thalassemia low-risk (liver \leq 2cm, age $<$ 5 yrs)	50	92
Thalassemia intermediate risk (liver 2-5 cm or age $>$ 5 years)	32	72
Thalassemia high-risk (liver $>$ 5cm, all ages)	9	50

The average cost of 10,000 USD per BMT^[7] and within an existing hospital facility, 50,000 USD were sufficient to renovate and fully equip a 2-3 bedded start up BMT unit; this was possible through a cost-conscious approach whereby each significant expense was to be supported by evidence of efficacy so that, for example, complex and costly air-control with HEPA filtering and positive pressure gradients were not implemented.^[11]

Discussion

Most BMT centers build on a previous background in oncology and chemotherapy complications management. In our experience, provided there is a structured cooperation program with expert physicians and nurses and a highly manageable target patient population, BMT maybe successfully implemented even with relatively inexperienced personnel having no oncological background. This paradigm shift is understandable based on the assumption that pediatric oncology is composed of a wide range of disorders requiring different treatment plans and drugs while BMT for TM deals with essentially three drugs (thiotepa, busulfan, and cyclophosphamide) and a single repetitive treatment protocol, which is thus amenable to focused training. Most importantly, oncological patients often present with advanced diseases and unstable clinical status while TM patients allow enough time to optimize pre-BMT clinical conditions and, given the lack of prior exposure to chemotherapy, generally tolerate conditioning quite well. In fact, the regimen employed for low- and intermediate-risk thalassemia, in which the only drug given at maximal doses was cyclophosphamide, is well known to be quite manageable.^[13] The routine supply of computerized patient-specific treatment regimens designed according to good clinical practices may also have played a major role in minimizing transcription errors and providing clear and legible prescriptions in a context of relatively complex therapy with potentially toxic drugs.

In keeping with the missions of the C2C, the ultimate goal of this project was to increase worldwide access to cure for TM by exploring the ability to export and reproduce results obtained in affluent countries in low-risk patients with severe thalassemia having a compatible family donor. This objective might be important to increase access to sustainable and scalable tertiary health care by increasing capacity and self-reliance of local centers in underserved regions. Local personnel requirements include confidence with managing sick children or neonates and handling central venous lines. In fact the latter was probably the most challenging issue.

There is general perception that BMT centers need complex engineering standards requiring undue investments, even more in poor countries where there might be a greater risk for opportunistic infections. In fact, there is no evidence that the latter is true.^[11,16] Available international guidelines call for placement of allogeneic recipients in highly protected environments with positive pressure gradients, intensive air

exchange and filtration,^[17] these recommendations, however, are not based on clinical trials but rather on limited data largely derived from single-center retrospective studies or expert opinions. In fact, there is increasing evidence that allogeneic transplant patients may be safely cared for in regular hospital rooms^[11] or even as outpatients^[18,19] and many widely held practices in managing the transplant environment are being reconsidered.

The issue of cost-containment is of paramount importance in settings with very limited resources, where financial restraints directly influence access to cure and thus probability of survival. Any significant expense should be backed up by evidence of positive impact on outcomes. Based on this consideration we did not consider mandatory the need for inpatient rooms with pressure differentials and HEPA filtration as well as masks, gowns, or shoe covers. Patients and 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 did not seem to be substantially different from those encountered in Western countries.

This report may provide a proof of principle with potential important effects of increasing sustainable and scalable access to cure of both nonmalignant and malignant disorders in lower-income regions.

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News

Can-India Conclave (conference for cancer NGOs and support groups).

The first Can-India Conclave is being held at Tata Memorial Hospital, Mumbai, India from 19th to 21st December 2013. It is supported by NCI, USA by IKCC and more than 23 other NGOs/ organizations. It includes keynote speakers from around the world. It also has workshops, award sessions, debates and panel discussions.

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