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A GLOBAL RESPONSE TO A GLOBAL PROBLEM: THE RISING BURDEN OF HEMOGLOBINOPATHIES

Lawrence Faulkner, MD

Cure2Children Foundation, Florence, Italy

lawrence.faulkner@cure2children.org

Introduction

It has been estimated that if the survival rate of children with sickle cell disease (SCD) in Africa increases to only 50% the African norm, more than 6 million Africans will be living with SCD[1].

Severe hemoglobinopathies, namely SCD and thalassemia major, are the most frequent life-threatening non-communicable disease of children globally: A minimum estimate of 300.000 newborns yearly have some symptomatic globin disorder, these births occur largely in low- and middle-income countries (LMICs) where screening and prevention programs are often lacking or insufficient[1,2].

Hematopoietic stem cell transplantation, also known as blood or marrow transplantation (BMT), is the only established curative modality with success rates over 90% in low risk children with a compatible sibling[3–5], moreover, BMT can normalize long-term health-related quality of life (HRQoL)[6,7] and be highly cost effective[8,9].

There is a dire shortage of BMT centers in emerging regions[10] and often families have to migrate to affluent countries seeking cure for their beloved ones; this not only aggravates misery, psychological and economical burden but perpetuates the hemorrhage professional and financial resources to high-income countries (HICs).

Within structured collaboration programs low-risk matched-related BMT can be associated with very good results even in startup centers in LMICs[11] and thus may provides a unique opportunity for saving lives, improve HRQoL, decrease financial burden of disease and at the same time promote capacity-building and health care sustainabilty[12].

BMT indications and outcomes: HICs *vs.* LMICs

The spectrum of BMT indications and procedures differ between West and East[10]: in North America and Europe hematological malignancies are the most frequent indication and unrelated donors are often employed because of small average family size. In the Middle East and Asia non-malignant disorders, e.g. hemoglobinopathies and aplastic anemia, tend to be more common indications and matched related donors more frequently available[13–15]. Moreover, in addition to financial and logistic issues, the very limited use of unrelated volunteer donors in the East is also due to the fact that non-malignant disorders require stringent HLA matching and non-Caucasian ethnicities are generally underrepresented in donor registries[16].

There is no evidence that, at least for low-risk matched related BMTs, outcomes are substantially different in HICs compared to LMICs. Gliebel et al. assessed the impact of Human Development Index (HDI) on BMT results in adults with acute leukemia and found that transplantations performed in countries with an

upper HDI were associated with improved leukemia-free survival, this however was not due to higher transplant-related mortality (TRM) but rather to higher relapse rates, suggesting that the survival differences were probably related to patient selection and residual disease monitoring rather than the BMT procedure itself[17], and thus may not apply to non-malignant disorders.

In the experience of the Cure2Children Foundation in supporting the start up of centers in Pakistan and India performing primarily low-risk matched-related BMTs for severe thalassemia aided by a structured peer to peer collaborative platform[18], outcomes where comparable to those obtained in Western centers[19]. There is also no evidence that in LMICs the spectrum of transplant-related infections is substantially different compared to the West[20,21].

Cost issues

BMT is one of the most expensive tertiary care procedures with costs generally above 100.000 Euros in high-income countries[22]. Figure 1 compares the relative cost breakdown of BMT for adult leukemia in HICs to the one for childhood thalassemia in LMICs. This comparison is somewhat unfair, nevertheless it underlines several interesting points: a) the major difference is related to follow up costs, probably because chronic GVHD is far more common, and to some extend therapeutically desirable, in adult leukemia; b) the second major difference is in hospitalization charges, which are related mostly to differences in salaries but also to BMT units construction and maintenance, in fact, complex infection control environments may not be needed for low-risk in children with non-malignant diseases who arrive to transplant with no prior exposure to chemotherapy, no previous prolonged neutropenia episodes, no infections and in good general conditions[19]; c) diagnostics are also much less expensive in BMT for thalassemia since, for example, residual leukemia quantification or frequent chimerism analysis post BMT are not an absolute requirement as long as transfusion-independency is achieved; d) drugs and transfusion support is also different because of patient size and complication frequency, particularly fungal infections, the treatment of which may substantially impact on final costs. In the Cure2Children experience in Pakistan the incidence of possible, probable or proven fungal infections[23] in young thalassemic children undergoing matched-related BMT was in the 8% range[21].

Within an existing hospital facility, 50,000 USD where sufficient to renovate and fully equip a 2 bedded start up BMT unit[24]. Increasing evidence suggest that complex and costly infection control environments may not be required[25–27] and established international guidelines do not call for stringent air control systems, at least for low-risk BMTs[28].

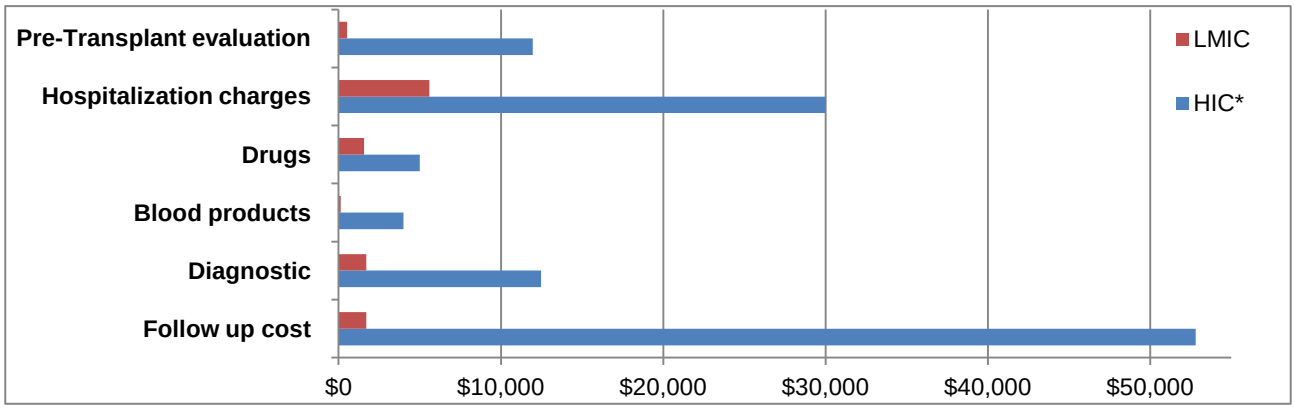

Figure 1. Cost breakdown comparison of matched-related BMT in HIC (adult leukemia[22]) and LMIC (children with thalassemia[24]); total cost $116,000* and $11,200 respectively (family support program not included).

The cure of severe hemoglobinopathies as a capacity-building opportunity

Optimal supportive care if often not available or not accessible in LMICs so that most children with severe hemoglobinopathies do not survive beyond 20 years of age and the risk of blood-borne infections, primarily hepatitis C, is still substantial[29].

As paradoxical as it may seem, BMT may actually be the best option for many patients with thalassemia in developing countries: It is a one-time procedure not depending on long-term access to appropriate medical care and at the same time greatly improves the quality of life for both patients and families by decreasing medical, psychological and financial burdens[6,7]. Even in situations where Hepatitis C positivity is prevalent, BMT should be considered and actually even more strongly recommended since not only it does not contraindicate BMT[30], but may mitigate the added effect of chronic iron overload and HCV for cirrhosis of the liver[29].

Technological requirements are largely related to availability of some tests and procedures requiring relatively short turnaround times like CMV monitoring (real-Time PCR), cyclosporine blood levels and blood product irradiation. The latter is required since leukodepletion filters may reduce but not abrogate transfusion-associated GVHD in immunosuppressed patients[31], but any radiotherapy unit can do the job. Buccal swab-based HLA-typing technology has greatly facilitated centralized compatibility testing so that there is no need to set up HLA laboratories locally, and patients can be easily typed worldwide and referred to BMT centers within South-South cooperation programs offering effective and cost-conscious BMT[32].

In the experience of the Cure2Children Foundation (C2C)-supported BMT network in Pakistan and India hinging on focused training and task-shift strategies within a structured cooperation program, 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 affluent

countries[3], with 100% performance score and no extensive chronic GVHD, for an average cost of 11.000 USD per BMT[4,24]. The realistic prospect of a definitive cure also improved compliance with supportive care and engaged families in cascade screening and prevention programs; most mothers of thalassemic children accepted the offer of free prenatal diagnosis for subsequent pregnancies.

Because of large patient loads, there is great potential for expertise on specific disease curable by BMT like thalassemia or SCD. For example, Pakistan has at least 100 times the incidence of thalassemia compared to the West, and many cases have a compatible sibling donor due to large family size. As a result, many more transplants for young thalassemic children with a compatible donor are currently carried out in LMICs compared to Europe or North America[33]. Increasing efforts will have to focus on quality assurance platforms[18] as a means of reassuring national and international patients, it seems reasonable to assume that if quality standards are assured, expertise is higher and costs are much lower, there might be the potential for patient attraction. Why should an insurances or national health systems refuse to cover a patient willing, for example, to go from the UK to India or Pakistan in centers that have much more experience on specific diseases, e.g. Thalassemia, where appropriate quality standards are assured and BMT costs much less? The strengthening of tertiary care in LMIC will also decrease the hemorrhage of financial resources to wealthy countries by local families seeking a cure for their child with a life-threatening disorder. High physician and nurse emigration rates are an increasing threat to healthcare strengthening in developing countries[34] fuelled not only by more attractive salaries but also by increased opportunities for professional development and motivation.

BMT for thalassemia offers several advantages for start up centers in LMICs: a) it is the least expensive and simplest form of allogeneic BMT with relatively basic technology requirements, e.g. freshly harvested bone marrow is used and autologous backup marrow cryopreservation is generally not required[35]; b) being a chronic disease there is enough time to adequately prepare patients in order to maximize initial success rates; c) high commitment and compliance of affected families; d) children generally enjoy high cure rates and excellent HRQoL due to aggressive cGVHD prophylaxis, this is also psychologically very important for BMT team-building; e) cost-effectiveness; f) potential for leading expertise and patient attraction.

Conclusions

BMT consists of a wide array of procedures which have very different complexities, outcomes and costs. The one used to cure young children with severe hemoglobinopathies having a compatible sibling sits on the simplest side of this spectrum, it's far less expensive than long-term supportive care and can restore a normal quality of life in most patients. It does not require complex hospital environments or sophisticated technologies and tests. It can save the life of many children while being a great opportunity for health care strengthening, professional development and higher medical

education. BMT may have positive ripple effects on institutions taking over the challenge as well as on screening and prevention programs in LMICs. The most important aspect however remains the passion and dedication of involved health care providers.

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