SANKALP-CURE2CHILDREN GUIDE TO STEM CELL TRANSPLANTATION FOR THE CURE OF SEVERE THALASSEMIA

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Sankalp India Foundation®

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SANKALP PROGRAM FOR THALASSEMIA CURE

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After working for almost 20 years in affluent counties as a pediatrician specialized in blood disorders such as thalassemia and sickle cell disease, Dr. Faulkner decided to dedicate himself, full- time, to international medicine by collaborating with professionals and institutions in developing countries committed to the cure of children with severe hematological diseases. He has enabled the setting up of 7 bone marrow transplantation centers in the developing countries – the centers which went on to achieve world class outcomes. Dr Faulkner is also an inspector for JACIE (Joint Accreditation Committee ISCT-EBMT).

THALASSEMIA - A DISEASE OF THE BONE MARROW

Thalassemia is a genetic blood disorder in which the bone marrow cannot form healthy red cell. Thalassemia is an inherited blood disorder. "Inherited" means they're passed on from both parents to children through genes. Because of the defect in the bone marrow, the child needs blood transfusions throughout life.

REGULAR TRANSFUSION, MEDICATION AND CHELATION A *MUST*

The management of thalassemia has improved significantly in the last few years.

If the following aspects are regularly and adequately, practiced, the child can have a near normal life:

- Timely blood transfusions are given (preferably maintaining the hemoglobin > 9 gm/dl).
- Iron chelation therapy is given in adequate dose (maintain serum ferritin below 1000 ng/ml).
- The child regularly undergoes medical tests to prevent any further complications.
- The child receives proper care and treatment.

Some issues, however, may still be unresolved by current best care such as drug or blood transfusion intolerance, infections transmitted with blood, pain due to bone thinning in older thalassemics and increased cardiovascular risk (pulmonary hypertension).

BONE MARROW TRANSPLANTATION (BMT) - COMPLETE CURE FROM THALASSEMIA

BMT is an option for complete cure from thalassemia. BMT is a procedure in which the diseased bone marrow in the child is replaced with bone marrow from a healthy donor. For this procedure, getting a donor whose bone marrow matches with the patient is necessary.

BMT at a young age is more successful because the child has fewer complications and the body is healthier. **It is necessary for each child with thalassemia to continue to seek proper medical care and management** so that whenever in future the option of BMT is available for them, the child is in a reasonably good shape for the procedure.

FINDING DONORS

HLA typing is a test that is used to find whether there is a matching donor for the patient or not. The patient can receive the bone marrow from one of the three sources:

- A family member, generally a sibling, who is a complete match.
- As a second choice, partially matched (haploidentical) family members, such as mother or father, can be used even though this is still in the development phase.
- Fully matched unrelated donors can also be used.

MATCHED SIBLING DONOR (MSD) TRANSPLANT

The chances of finding a donor within the siblings of the patient are the highest. Also, the BMT from siblings is the safest of all transplants with highest chances of the patient getting cured. If a patient has a healthy sibling, we will offer HLA typing test.

In general, if the transplant is done by an experienced team there is a 85% chance that the child will be completely cured. There is a 5% chance that the child may die of complications related to the transplant and another 5% chance that the transplant itself may fail. The remaining 5% chance is that your child develops a complication post transplant which may need months and sometimes even some years to get completely cured and may increase the risk of death. In-spite of a successful transplant there is a chance that your child may not be able to bear children.

HAPLOIDENTICAL TRANSPLANT

The mother and father are generally half matches to the child. A new method of transplantation from mother and/or father called haploidentical transplant is making

steady scientific progress. These transplants are still in the initial phase and development work is ongoing which will very likely make these transplants safer and comparable to the matched sibling donor transplants.

MATCHED UNRELATED TRANSPLANTS (MUD)

These type of transplants are done from matched donors who are unrelated to the patient. For these transplants, the match is found using registries that keep details of the HLA types of voluntary donors. However, these transplants are associated with higher risks of the patient's death, failure of transplant and post transplant complications. Therefore, we as an organization do not support MUD transplants for thalassemia patients.

HLA TYPING TEST

- HLA typing is required to find out if a BMT for your child is possible or not.
- HLA typing is a test that only needs to be done once in a lifetime. So, if you already have got HLA typing done, please bring the report and inform us.
- This test costs about Rs 12,000/- in market but is being offered free of cost to the patients by Sankalp India Foundation with support from Cure2Children, Italy and DKMS, Germany. We offer HLA typing to children up-to 14 years.

- We will need to enroll your child on the database and collect some personal information for the sake of unequivocal identification of each family member to be typed. We will also need information that helps us determine the eligibility of the child for free HLA typing. We will provide you a consent form for inclusion in our database. Please read the form and feel free to ask for clarifications from the staff. You must provide your consent for enrolment into our database by signing the form on behalf of your child and your family.

We will need your consent for HLA typing as well. We will provide you another consent form for HLA typing which you must read, understand and sign on behalf of yourself, your child and your family.

GETTING THE REPORTS

It may take anywhere between 90 days to 180 days for us to provide you with the results of HLA typing. The staff will call you once the reports are available. There will be a counseling session organized which will help you understand the options you have based upon the results of the HLA typing. In case there is a match, you will have the option of seeking Sankalp India Foundation's assistance for the transplant or you can directly seek help from one of the many BMT centres.

WHAT IF MY CHILD DOES NOT HAVE A MATCH

Rapid progress is being made in the field of haplo-identical bone marrow transplantation. We are confident that in near future we will be able to offer transplantations from parents with reasonable chance of success. Once haplo-identical transplantation are taken up on a regular basis, the limitation of a matching donor will go away for all children who have at-least one parent.

However, do keen in mind that we strongly recommend that regular management is undertaken as outlined above. Only those children who are well managed could expect to have good outcome from transplants whenever they are offered.

DOES GETTING A MATCH MEAN THAT MY CHILD CAN BE TRANSPLANTED IMMEDIATELY?

It is well established that patients with low iron overload and limited organ damage get better outcomes on being transplanted. Once there is a match, we do a detailed pre-transplantation evaluation to assess both the patient and the donor. Fortunately, today it is possible to control both high iron levels and reverse organ damage using appropriate medication. Based upon your child's condition the physicians will initiate the process of preparing the child for the transplantation – a process known as down-staging using aggressive iron chelation and hydroxyurea therapy.

Children who are well managed may only need minor course correction and preparation that could happen in a few weeks. For the others, depending upon the extent of existing damage to the body, the child may take anywhere between 3 months to a year to be able to reverse as much damage as is possible. A child is eventually offered the transplantation when the medical team is convinced that enough has been done to prepare the child for superior outcome.

It may be possible that some children do not respond to the down-staging process adequately. For such families, the physicians will reevaluate the risk-benefits of transplantation and share the same with the families, enabling them to make informed decision.

HOW MUCH WILL IT COST ME?

The cost of bone marrow transplantation ranges from Rs 8.5 lakhs to Rs 20 lakhs in India depending upon which institution is chosen for the transplantation and the preparatory protocols they employ. Transplantations generally are less expensive than the cost of management of thalassemia for several years. Many institutions indicate BMT charges often limited to the initial hospital period of 45 days and may not cover the whole recovery, generally lasting 1 to 2 years. Also, most institutions do not cover the complications that may arise during the transplantation.

The financial support for transplantation is increasing in India and the Central and State governments may provide in part support for the transplantation. It should be kept in mind that this support is limited to the initial estimated cost of transplantation and generally do not cover the cost of managing complications.

At Sankalp-Cure2Children centers the transplantations are done at a fixed cost, which includes the cost of managing any complications directly, associated with the transplantation. The cost of follow-up medication, consultation and labs is also included up-to a year. Part of the overall cost is fundraised by Sankalp India Foundation, wherever applicable, part of it can come from the Government. The families cover rest of the cost by either personal contribution or by fundraising.

WHY IS BMT COST SO VARIABLE?

Many institutions use expensive drugs, like thiotepa, treosulfan or intravenous busulfan, based on some small studies suggesting decreased short-term toxicity in high-risk patients compared to the far less expensive standard oral busulfan which has been used successfully for decades. The use of expensive drugs for high-risk cases is hardly justified when patients can be down-staged into a lower-risk category with aggressive chelation and hydroxyurea therapy. In general, what really makes the difference is how the patient is prepared for BMT rather than the drugs used.

The problem is that too often families are self-referred to transplant centers which do not have the set up for long periods of preparation. This should really be done by thalassemia centers. Lastly, the use of new and more expensive drug combinations like thiotepa and treosulfan, are associated with unknown risks of permanent infertility which may not be the case for the standard combination of oral busulfan with cyclophosphamide.

Many centres do the transplantation for thalassemia within the same setup that has been created keeping in mind the needs of more complicated and higher risk transplantations like those for malignant disorders (cancers). The additional cost of complex air purification systems etc. that are unnecessary for thalassemia transplants get's added to the transplantation cost inevitably.

Some institutions of course will have substantial overheads and public relations costs, which inevitably are borne by patients and their families.

HOW DO I CHOOSE THE BEST CENTRE?

Outcomes can vary widely depending on the experience and dedication of the BMT team involved. The family must take some time to visit different centers, speak with transplant doctors and nurses as well as other families who have undergone BMT in those centers. It is essential and recommended to have transparent and verifiable information on specific thalassemia BMT experience and long-term results. An important thing to look at, possibly with the help of a third-party medical professionals you know well and trust, is the number and quality of scientific publications from the medical team and professional profiles of the transplant physicains available at Google scholar. Another important question to ask is whether a given transplant center participates in the outcome reporting programs of established international registries like the American CIBMTR or European EBMT. Participation of the transplant service to internationally established quality assurance programs like FACT-JACIE might also be relevant for decision making.

WHAT FACTORS INFLUENCE THE CHANCE OF SUCCESS?

The chance of success depends primarily on the availability of a compatible sibling or other family member (it is important to have accurate and reliable compatibility testing possibly by an internationally accredited laboratory), and on the medical condition of your child. Liver enlargement, spleen enlargement or very high ferritin levels (greater than 5000 ng/mL) might affect outcome. Age is also an important factor, the younger the better. BMT should ideally be performed before age 7 years and probably avoided after 15 years of age.

WILL MY CHILD GO BACK TO A NORMAL LIFE?

Yes, it is very likely that your child will go back to a normal health-related quality of life after BMT, at least with the standard combination of oral busulfan and cyclophosphamide followed by donor bone marrow administration for which there is

very long-term follow up data. For newer combinations like thiotepa and treosulfan with peripheral blood stem cells this is not established.

MY CHILD SEEMS TO BE DOING WELL WITH SUPPORTIVE CARE AND WE ARE HAPPY WITH OUR DOCTORS, SHOULD WE CONSIDER BMT?

The decision whether to undergo BMT might be a difficult one for many families and patients. As a general rule most children born with thalassemia who have regular access to appropriate supportive care may have a long and productive life. However, even if chelation therapy has taken major steps forward and can potentially lead to negative iron balance (that is to remove more iron than that supplied by transfusions), some important complications of thalassemia which are not necessarily related to iron overload, might still be a problem. In a country like India appropriate care may not always be affordable and/or accessible on a long-term basis, and most individuals with thalassemia still do not reach adulthood. Lastly, health-related quality of life (HRQoL) is often an issue as well as being able to marry and bear children. Unfortunately, we don't really know the true frequency of deaths related to thalassemia or the real impact of this disorder on the quality of life of individuals with severe thalassemia living in India. The issue is further compounded by major inequalities in access to health care so that thalassemia has very different severity depending on family socio-economic background or geographical location.

AT OUR THALASSEMIA CENTER WE WERE ADVISED AGAINST BMT, HOW DO I KNOW WHO TO BELIEVE?

Many thalassemia centers have had bad experiences referring patients form BMT and their position may be understandable. As mentioned above (How do I choose the best center?) outcomes can vary widely depending on the experience and dedication of BMT centers.

I WOULD LIKE TO HAVE MORE CHILDREN BUT AM AFRAID TO HAVE ANOTHER ONE WITH THALASSEMIA, HOW CAN I AVOID IT?

In general we discourage families to plan for another kid purely with the intention of finding a donor for the child suffering from thalassemia. Do keep in mind that the chance of a match with a sibling is only 25%.

If you want to have a another child irrespective of whether the next child is a match, you must get screening done in the first 12 weeks of pregnancy. Prenatal diagnosis of thalassemia is relatively straight forward by Chrionic Villus Sampling or CVS.

Biomedical technology also allows to select and implant an embryo which is thalassemia-free and HLA-compatible, and is called as Preimplantation Genetic Diagnosis or PGD.This is not legalized in India, and is also expensive and only partially successful.

SHOULD I STORE THE PLACENTAL CORD BLOOD IF I BECOME PREGNANT AGAIN?

The short answer is no.

Why than many families with a child with thalassemia collect and store cord blood? Unfortunately, this is a consequence of business-oriented and unscientific practices ignoring evidence-based medical recommendations. We are referring to private banks storing your newborn child cord blood for a fee. You could consider donating cord blood to public cord blood banks that store the cord *free of charge* as a useful source of transplantable stem cell for unrelated individuals.

There is no clear medical indication to the use of your child's own cord blood and very few transplants have been done for thalassemia using compatible newborn sibling cord blood because it is generally considered safer to wait until the compatible newborn reaches 8-10 kg at around one year of age, and can donate fresh bone marrow. Cord blood is associated with increased rejection and more infectious risk related to delayed recovery of white blood cells which will also substantially increase costs and hospital stay.

In our view cord blood use for thalassemia transplantation is medically not indicated, largely profit-driven and ethically questionable.

DONATING BONE MARROW - PROCESS AND INVOLVED RISK FOR THE DONOR.

If your child finds a matched sibling, both of them will be tested thoroughly to check if they are fit for the transplant. Collection of bone marrow is a minor procedure that involves using syringes to extract bone marrow from the hip bone of the donor. The donor child is given anesthesia so that they experience no pain during the process. The donor needs to be admitted in the hospital for about one day. They may experience little pain for a few days after donation but any short- or long-term problems are extremely rare.

Many institutions use peripheral blood stem cell collections (leukapheresis) to take cells from the donor and might provide better short-term engraftment at the cost of substantially increased risk of chronic graft versus host disease (GVHD). This complication has the potential to make quality of life worse than the thalassemia itself.

Please feel free to ask the staff for any clarifications on this topic.

WHAT ABOUT GENE THERAPY?

The ideal cure for thalassemia would be to selectively correct the faulty gene in the relevant cell type in a safe, effective and affordable way. However, it is quite difficult to incorporate a new functional gene in any cell type, and adequate hemoglobin production requires a particularly active gene. The advantage of gene therapy (GT) is that the same hematopietic stem cell (HSC) of the patient is used and thus immunosuppression is not required, in fact, the patient's own bone marrow is collected and incubated with viral vectors capable of "infecting" the stem cell with the missing normal hemoglobin gene. This corrected autologous bone marrow is than infused back into the patient after the administration of drugs capable of reducing the amount of defective thalassemic marrow, so called myeloablative drugs, similarly to what is also used for BMT. In BMT however myeloablative drugs are combined with immunosuppressive drugs while in GT only myeloablative drugs are generally administered. The lack of immunosuppression and of graft versus host reactions are the primary reasons why GT is potentially more tolerable compared to

BMT and can be potentially applied to any patient at any age. However, BMT strategies are improving in parallel with GT so that is is increasingly possible to transplant between partially compatible individuals and older thalassemics. Last but not least the issue of cost and accessibility: BMT cost can vary between 8 to 40 lakhs INR depending on available donor type, while at present GT technology and regulatory issues make it quite expensive so that the preparation of gene-corrected marrow is currently costing in the range of 7 crores INR.

It should also be borne in mind that BMT has been done in over 4.000 thalassemic individuals while GT has only been tested in a handful of patients with still little follow up. Many uncertainties remain in terms of long-term safety and efficacy. Also GT seems to still struggle to induce full transfusion-independence in the most common type (β0/β0) of severe thalassemia. Lastly, GT protocols are incorporating increasingly aggressive drugs to get rid of the diseased marrow that may compromise fertility.

At present most young children with a compatible donor are expected to do very well with BMT and waiting for GT might not be justified, while for older patients or those lacking a compatible donor it is more difficult to provide sound recommendations.

OUR PARTNERS

Our mission to enable cure for each child suffering from thalassemia has been made possible only with the support and participation of our partner organisations.

Cure2Children Foundation, Italy	People Tree Hospitals, Bangalore – India
Care Institute of Medical Science, Ahmedabad – India	DKMS, Germany
Rashtrotthana Parishat, Bangalore – India	Jeevan Blood Bank and Research Centre, Chennai
Jagriti Innovations, Bangalore – India	

Sankalp India Foundation®

SANKALP-PROGRAM FOR THALASSEMIA CURE

OUR VISION: Thalassemia free India.

OUR MISSION: To provide high quality patient focused curative option to children suffering from Thalassemia irrespective of financial background with focus on transparency achieved through technology.

ABOUT US

Sankalp Program for Thalassemia Cure offers Bone Marrow Transplant - the permanent curative option to the children suffering from Thalassemia.

We have forged partnerships that enable reliable BMT on a non-profit basis bringing down the cost of the transplants substantially. The organisation seeks to identify the most suitable candidates and offer them the option of BMT. At the cost equivalent to 4-5 years of thalassemia management, the organisation offers complete cure from the disease.

Our team has vast expertise with BMT for thalassemia. The selection of patients for transplants is being done scientifically and judiciously to ensure that the patients who are most likely to benefit from the transplant are offered the same, keeping aside their financial limitations. We have established a program which will ensure systematic preparation of the chosen kids for transplant and their long-term follow-up – further enhancing the outcome and reducing the cost.

DONORS SUPPORTING US IN OUR MISSION

We are able to reach-out to every child who needs cure thanks to the support of all our donors.

CIPLA Foundation, Mumbai – India	Tata Trusts, Mumbai – India
Jaishiv Shakti Health & Educational Foundation, Bangalore – India	Didwania (Ratanlal) Charitable Trust, Mumbai – India
Cure2Children Foundation, Italy	Amit Iyer Memorial Foundation, Mumbai– India

Main donors

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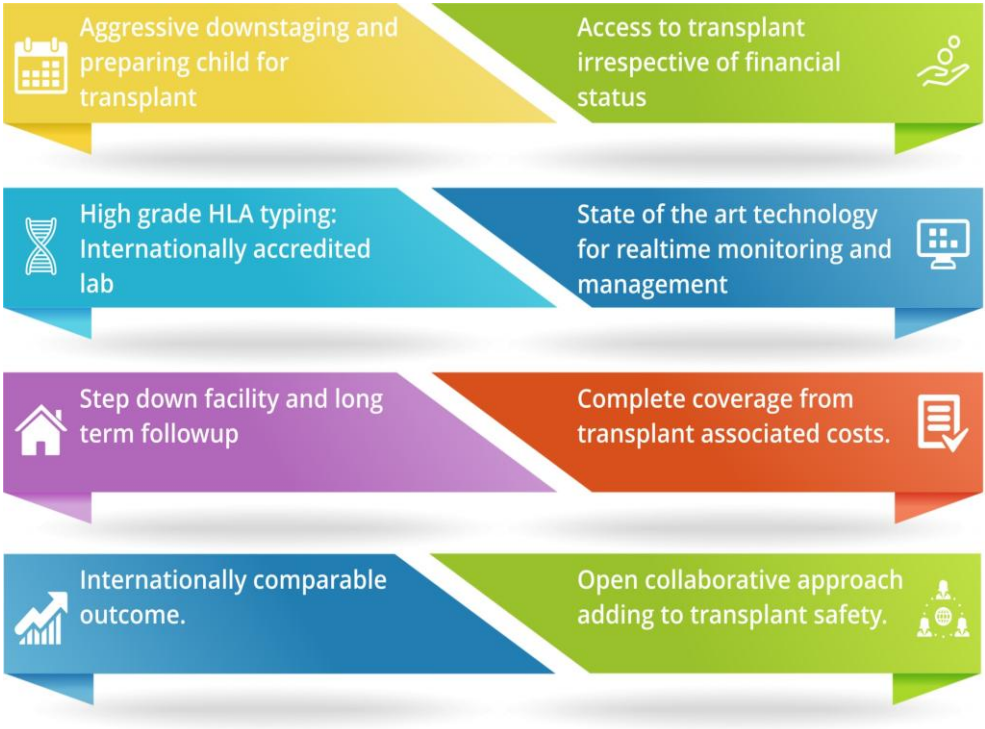

Let's give life a better chance!

Web version available at: www.sankalpindia.net/cureguide