Scottish Paediatric and Adult Haemoglobinopathy Network

Indications for a Haematopoietic Stem Cell Transplant and referral pathway for paediatric patients with Haemoglobinopathies at the Royal Hospital for Children SCT Unit, Glasgow

Introduction

With considerable improvement in supportive care over the past 50 years, the life expectancy for patients with Transfusion Dependent Beta Thalassaemia (TDBT) and Sickle Cell Disease (SCD) has changed dramatically (Quinn 2010; Telfer 2007).

In countries where adequate health resources are widely available to the population, the vast majority of SCD patients now survive childhood, where penicillin prophylaxis, appropriate immunizations, hydroxycarbamide, transcranial Doppler monitoring and safe red cell transfusions can be offered. Similarly, patients with β-Thalassaemia major will certainly benefit from starting from early age a regular and safe transfusion program to suppress endogenous haematopoiesis, and from adequate iron chelation to prevent complications from iron overload. Link

However, although many patients with SCD can now survive past their 60's (Serjeant 2009), life expectancy and quality of life (McClish 2005) can still be reduced, despite optimal supportive care (Hamideh 2013; Lanzkron 2013), due to cumulative chronic organ damage, pain (Taylor 2010) and disability (Swanson 2011).

Similarly, even with optimal chelation, patients with TDT are not free from complications, particularly cardiovascular (i.e.: arrhythmias) and the ones related to potential multi-organ toxicity of iron chelators, and are confined to a lifelong routine of frequent hospital visits. Although great advances have been made in the past years towards developing gene therapy as a safe and effective treatment for patients with haemoglobinopathies, in particular Beta Thalassaemia (Thompson 2018), the technique is not yet available for widespread use.

Over the past decades Haematopoietic Stem Cell Transplantation from allogeneic donors has established itself as a successful potential curative treatment for patients with severe phenotypes of Sickle Cell Disease and in Transfusion Dependent Thalassaemia. Overall transplant results in expert centres have been found to be exceedingly good, particularly when the donor is an HLA-matched sibling, the stem cell dose is adequate and with newer less toxic and yet myelosuppressive conditioning regimens, which greatly facilitate engraftment.

These guidelines describe pathways for referring patients with Haemoglobinopathies for consideration of a HSCT and indications for transplant at the Royal Hospital for Children SCT Unit in Glasgow.

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Sickle Cell Disease

Indications for a HSCT in Sickle Cell Disease
(based on Walters 1996; the 'UK Paediatric BMT Group - HSCT Indications Table' – 2015 update; and Angelucci 2014)

Patients must fulfill ALL 4 criteria below:

1. Be between 2 and 16 years of age (ideally pre-school age).

2. Have a diagnosis of SCD (homozygosity for Hb β^s or double heterozygosity for $S\beta^0$ or Hb SC) confirmed by β-chain gene analysis.

3. Have a severe phenotype, characterised by at least one of the below:

    a. Previous stroke on regular transfusion program for at least 6 months; any other documented cerebral vasculopathy with cognitive deficiency and poor school performance on formal assessment, enrolled on a regular transfusion program for at least 6 months.

    b. Recurrent acute chest syndrome episodes despite being on optimised dose of hydroxycarbamide with good compliance for at least 6 months (ie.: occurrence of a 3rd episode when hydroxycarbamide was started following the 2ndor occurrence of a 2nd episode when hydroxycarbamide was started following the 1st).

    c. Recurrent vaso-occlusive episodes (>3 episodes/year requiring hospitalisation or impacting schooling) despite being on optimised dose of hydroxycarbamide with good compliance for at least 6 months.

    d. Alloimmunisation (Flickinger 2006; Mijovic 2013) – multiple alloantibodies, when the theoretical availability of finding a compatible unit in a timely manner is deemed to be <1% according to SNBTS; alloantibodies to high frequency antigen (ie Anti-hrs, Anti-U); history of life-threatening hyperhaemolysis where an alloantibody (or auto) could not be identified and further transfusions are likely to be necessary, based on known phenotype.

    e. The following clinical scenarios can also be considered as criteria of disease severity in special circumstances, although indications for a HSCT in these cases should be discussed in depth in local and national MDTs:
        i. Any other organ dysfunction thought to be related to sickle when a trial of hydroxycarbamide is not thought to be of efficacy (or no objective improvement on optimised dose of hydroxycarbamide with good compliance for at least 6 months): ie stage I/II sickle lung disease, sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30 to 50% of the predicted normal value), bilateral proliferative retinopathy with significant visual impairment in at least one eye, osteonecrosis of multiple joints.
        ii. When supportive treatment is suboptimal

4. Have a suitable allogeneic HSC donor.

    a. The preferred donor is a 10/10 (A,B,C,DR,DQ) matched sibling, who is either homozygous for a normal β-chain gene (non-affected) or heterozygous for a variant (trait). Bone marrow is preferred to PBSC given the lower rates of GVHD. If cord blood stem cells from a non-affected or trait matched sibling were collected at birth and the nucleated cell dose is at least $\geq 4 \times 10^7$/Kg (ideally $\geq 4 \times 10^5$ CD34+/Kg), these can be used alone; if lower than that, a combined infusion with harvested BM cells should be done.

    b. 9-10/10 matched related donors found on extended family search are also suitable.

    c. The BSBMT (British Society of Blood and Marrow Transplantation) also considers allogeneic unrelated (9-10/10 adult donor of BM or PBSC, and 4-6/6 cord HSC) and haploidentical related (<9/10 donor of BM or PBSC) donors as potential 'Clinical Option' if no ideal donor is available. Transplants using these alternative sources of stem cells are now feasible (although with some, current results appear to be inferior to those when matched siblings are used) and cases should be discussed in an individual basis, preferably following discussion in national HSCT MDT forums.

Given the significantly improved transplant outcomes over the decades for patients with severe sickle cell disease who receive grafts from a well matched related donor, it may now be reasonable to discuss the theoretical possibility of transplanting children with Sickle Cell Disease and less severe phenotypes who do have a suitable matched related donor. Prospective studies to address the feasibility and efficacy of this approach seem to be ethically sound and are awaited (Nickel 2014).

Beta Thalassaemia

Indications for a HSCT in Transfusion Dependent β Thalassaemia (TDβT)
(based on the 'UK Paediatric BMT Group - HSCT Indications Table' – 2015 update; and Angelucci 2014)

Patients must fulfill ALL 3 criteria below:

1. Be between 2 and 16 years of age (ideally pre-school age).

2. Have a diagnosis of Transfusion Dependent β Thalassaemia, confirmed with a relevant β-chain gene analysis abnormality normally associated with a Thalassaemia major phenotype. Transfusion dependency in Thalassaemia is defined as requirement of >150ml/Kg of red cells/year.

3. Have a suitable allogeneic HSC donor.
    a. The preferred donor is a 10/10 (A,B,C,DR,DQ) matched sibling, who is either homozygous for a normal β-chain gene (non-affected) or heterozygous for a β-thalassaemia one (trait). Bone marrow is preferred to PBSC given the lower rates of GVHD. If cord blood stem cells from a non-affected or trait matched sibling were collected at birth and the nucleated cell dose is at least ≥ 4 x

10^7/Kg (ideally $\geq 4 \times 10^5$ CD34+/Kg), these can be used alone; if lower than that, a combined infusion with harvested BM cells should be done.

b. 9-10/10 matched related donors found on extended family search are also suitable.

c. Well matched adult unrelated donors have now been successfully used by many groups around the world (in conjunction with newer lower-toxicity conditioning regimens) to transplant patients with transfusion dependent β-thalassaemia and are classified as 'Clinical Option' by the BSBMT (Bernardo, Blood 2012; BSBMT 'HSCT Indications Table'). In the absence of a matched sibling, the suitability of such a donor should be discussed within the team and in national MDTs.

Note:

Thalassaemia genotypes other than the β^0/β^0 presenting with established transfusion-dependency (i.e.: 'Transfusion-Dependent Thalassaemia Intermedia' with red cell transfusion requirements of >150ml/Kg/year) may also be suitable for HSCT and should be discussed in an individual basis. These include:

a. α-Thalassaemia Intermedia and established transfusion-dependency:

a.1. Deletional haemoglobin H disease: --/-α

a.2. Non-deletional haemoglobin H disease: --/$\alpha^T\alpha$

a.3. Potential survivors of Hb Barts (alpha thalassaemia major): --/--

b. β-Thalassaemia Intermedia and established transfusion-dependency:

b.1. β°/mild β^+, β^+/mild β^+, mild β^+/mild β^+

b.2. β°/silent β, β^+/silent β, mild β^+/silent β, silent β/ silent β

b.3. β°/β°, β^+/β^+, β°/β^+ and deletion or non-deletion α-thal

b.4. β°/β°, β^+/β^+, β°/β^+ and increased capacity for γ-chain synthesis

b.5. Deletion forms of δβ-Thalassaemias and Hereditary Persistence of Foetal Haemoglobin (HPFH)

b.6. β°/β or β^+/β and ααα or αααα duplications

b.7. Dominant β-Thalassaemia (inclusion body)

c. HbE/β-Thalassaemia with a severe phenotype (Mahidol score of 7.5-10) and established transfusion-dependency

Referral pathway
Patients with:

a) Sickle Cell Disease known to have a severe phenotype as above or
b) Transfusion Dependent β Thalassaemia

should be referred to the Stem Cell Transplant Unit at the Royal Hospital for Children in Glasgow for an initial clinic appointment, if families are willing to discuss HSCT as possible therapeutic option in future. This initial assessment will include:

a) Previous medical history (including criteria for classification of severity of their diseases, transfusion requirements, review of CT/MRI scans, CXRs, previous admissions, atypical antibodies present) and family history, physical examination and current clinical status including current use of hydroxycarbamide (efficacy, tolerance, toxicity) and iron chelation treatment if applicable;

b) Review of results of FBCs, blood film, renal/liver functions, haemoglobin electrophoresis, HPLCs, α and β-gene analysis and iron overload assessment previously done by the referring services; if necessary, repeat/update of relevant tests;

c) Overview discussion of theoretical risks and benefits of HSCT, timing, donor choice, usual transplant course (pre-assessment, conditioning, post SC infusion period) and possible common complications (short and long-term);

d) HLA typing of patient and any direct and extended family member present in consultation; planning for HLA typing of any direct and extended family member not present in consultation;

e) Referral to the Genetic Counselling service at the Royal Hospital for Children in Glasgow if not yet done by the referring service;

f) Follow up appointment and written update to the referring centre.

Preliminary referrals for initial assessment can be done by letter, addressed to:

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Consultant in Paediatric Haematology and HSCT
Haematology/Oncology Department
Royal Hospital for Children
1345 Govan Road
G51 4TF - Glasgow
Fernando.Pinto@ggc.scot.nhs.uk

A formal referral for HSCT according to local SCT Unit SOPs will be needed at a later stage, if appropriate.

References

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NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.