4. Hematopoietic Stem Cell Transplantation (HSCT)

Principles

- To ensure patients and families receive adequate information on hematopoietic stem cell transplantation (HSCT) for informed decision-making.
- To ensure close follow-up of patients who have undergone HSCT.

Recommendation

- The option of HSCT, including its indications and complications, should be discussed with families while the patient is at a young age, ideally before entering puberty to maximize the likelihood of preserving fertility.
- The discussions should be initiated by the specialist centre and, if the patient is serious about pursuing HSCT and it is appropriate, referral should be made to a HSCT centre with experience in transplanting thalassemia patients where more detailed discussions should take place.
- The options of HLA-matched related donor (cord blood or bone marrow) and matched unrelated donor (bone marrow) should be discussed. The option of HLA mismatched related donor (haplo-identical donor) should be also considered.
- The intensity of the conditioning regimen – described as full intensity vs reduced intensity – as well as the advantages and disadvantages associated with each kind of them, should be also included in the discussion.
- Post-HSCT, patients should be closely monitored and managed for iron overload and other complications at least for the first 2 years after HSCT.

Background

HSCT is the only curative option available to thalassemia major patients. HSCT is a complex treatment which requires several weeks of hospitalization and several months of close follow-up. HSCT with a HLA matched (ie compatible) donor, either related or unrelated, and with a full intensity conditioning regimen, is considered as a standard of care for children with thalassemia major[172]. HSCT for adult patients with thalassemia remains unavailable in most centers and needs to be studied carefully given the increased morbidity.

Until recently, HSCT was limited by two main barriers. The first one was availability of a HLA matched donor, which probability is only 25% among siblings and ranges from 10 to 30% among donors from international registries. The second one was complications from thalassemia before HSCT, such as inadequacy of chelation treatment leading to hepatomegaly and portal fibrosis, which increase the risks of complications after HSCT[173] Depending on the importance of these complications before HSCT, patients are ranked in 3 different risk groups called Pesaro class 1 or class 2 (less severe), and Persaro class 3 (more severe).

Patients undergoing HSCT with a HLA-matched sibling donor have an overall survival (OS) ranging from 98% to 91% and disease-free survival (DFS) ranging from 95% to 83%, irrespective of the Pesaro classification.[174,175] Similar outcomes are obtained with matched unrelated donors from registries[176]. Age at HSCT is the main factor for outcome, but the cut-off for age varies among studies from 3 years, to 7 years, to 14-16 years. In the largest reported cohort, children less than 14 years of age have an OS of 96% and EFS of 86%, whereas adolescents and young adults more than 14 years of age have an OS of 82% and DFS of 74%[174]. In adults (age > 16 years), early trials in the 1980 and 90 reported poor outcomes (OS of 66% and DFS of 62%) related to advanced liver disease[177].

Currently, class 1 and 2 are considered similar regarding outcomes after HSCT, with a risk of death related to HSCT about 5% among children. The prognosis of class 3 children, historically with OS of 79% and EFS of 58%[178], has dramatically improved with the development of new conditioning regimens and the use of preconditioning protocols, in order to prevent graft rejection. With modern protocols, class 3 children have now outcomes similar to class 1 and 2, with EFS of 92%[179].

For patients who lack a HLA matched donor, haplo-identical donor (ie the father, the mother or a mismatched sibling) and unrelated cord blood from cord blood bank are the current options. Unrelated cord blood are associated with higher risk of engraftment failure and death. Ongoing protocols based on ex vivo expansion of cord blood before infusion may address this problem. Recently, major breakthroughs have been reported with haplo-identical donors and new protocols of conditioning. Children up to 19 year of age and class 3 have OS of 96% and EFS of 96%[180]. These very promising results open the door to an era of universal cure for every children suffering from thalassemia major.

The main complications related to HSCT are acute graft versus host disease (GvHD) and chronic GvHD, engraftment failure and secondary bone marrow rejection, hypofertility and sterility. The incidence of grade 2-4 acute GVHD is 9% and the incidence of extensive chronic GVHD is 6% in the european experience[174]. The incidence of graft failure is variable, from 5 to 30% depending on several factors of the patient, the donor and the protocol of HSCT. The main causes of deaths are infectious complications after HSCT rejection, Severe GVHD may also cause the death of the patient.

The incidence of sterility and gonadal deficiency is estimated about 60% after HSCT with full conditioning regimen[181], Higher risk are documented in girls transplanted in post-menarchial[182], and lower risk in children transplanted before puberty (62% of spontaneous puberty after HSCT)[182]. Better control of iron overload before HSCT, younger age at transplantation and new protocol of HSCT based on lower doses of alkylators chemotherapy should improve gonadal function.

Interventions

- HSCT should be performed in centres with experience in transplanting patients with thalassemia.
- Discussions about the role of HSCT in thalassemia should include benefits, risks, short and long-term complications, quality of life after HSCT and the psychosocial impact.
- The patient's risk factors and organ function should be assessed prior to HSCT.
- Possible long-term complications of HSCT include iron overload, chronic GVHD, delayed pubertal development, growth and endocrine deficiencies and infertility. There is also a theoretical but yet not proven, higher risk of malignancy after HSCT.
- Preservation of fertility should be part of the preparation to HSCT. For prepubertal children, enrolment in investigational trial of tissue preservation (either ovarian or testicular tissue) should be considered.
- After HSCT, reduction of pre-existing iron overload should continue by routine phlebotomy with or without chelation.[73,74] Phlebotomy is safe and effective for iron removal after HSCT and has been shown to reduce iron load and liver fibrosis. Patients should be phlebotomized to achieve a ferritin < 300 ug/l.
- If the patient's mother becomes pregnant, the option of chorionic villous sampling (CVS) or amniocentesis for pre-natal diagnosis should be discussed. If the fetus does not have beta thalassemia, the cord blood should be harvested and stored for potential future transplant. If antenatal testing has not been done, all cord blood should be collected and subsequently tissue typed and stored, if matched.
- Transplanted individuals should be counselled that they would still pass on a mutant thalassemia gene to each of their children.