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NOPHO Guidelines for Hematopoietic Stem Cell Transplantation in Pediatric Patients with Sickle Cell Disease

VÅRDRIKTLINJE

FRAMTAGEN I SAMRÅD MED VÅRDPLANERINGSGRUPPEN FÖR PEDIATRISK HEMATOLOGI

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Samarbete

Denna riktlinje har utvecklats i samarbete mellan de nordiska och baltiska länderna som deltar i NOPHOs SCT-grupp — Danmark, Finland, Norge, Sverige, Estland, Lettland och Litauen. Representanter från de deltagande pediatriska HCT-centren har aktivt bidragit till framtagande och utformning. Av detta skäl föreligger texten på engelska. För svenska förhållanden gäller det att skrivning är beslutad i konsensus med VPH (Verksamhetsplaneringsgruppen för Pediatrisk Hematologi), varför VPH står för att sätta sin logotyp på den svenska webpubliceringen.

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Abbreviations

BM	Bone Marrow
CNS	Central Nervous System
CVC	Central Venous Catheter
GVHD	Graft-Versus-Host Disease
HCT	Hematopoietic Cell Transplantation
HLA	Human Leukocyte Antigen
MRI	Magnetic Resonance Imaging
MSD	Matched Sibling Donor

MUD	Matched Unrelated Donor
NOPHO	Nordic Society of Pediatric Hematology and Oncology
PBSC	Peripheral Blood Stem Cells
PTCy	Post-transplant Cyclophosphamide
SCD	Sickle Cell Disease

Background

Sickle cell disease (SCD) is an autosomal recessive, progressively debilitating, multi-organ disorder caused by a point mutation in the HBB gene. This mutation leads to the production of abnormal hemoglobin S (HbS), which promotes hemoglobin polymerization and red blood cell sickling. These processes can result in severe vaso-occlusive crises and progressive organ damage due to systemic vasculopathy. Despite advances in care, overall survival remains more than 20 years shorter compared with age-matched peers [1].

Allogeneic hematopoietic stem cell transplantation (HCT) is a well-established curative treatment for SCD. The goal of HCT is to replace the patient's bone marrow (BM) with donor stem cells before the onset of major organ dysfunction and irreversible damage. Transplantation from an HLA-matched sibling donor (MSD) has demonstrated excellent outcomes, with disease-free survival exceeding 90% and overall survival greater than 92% [2-4]. HCT using a matched unrelated donor (MUD) shows results inferior to those achieved with MSD transplantation but has still been associated with favorable outcomes, with overall survival of approximately 90% and event-free survival around 76% [5]. However, fewer than 20% of patients have an MSD available, and the likelihood of identifying an MUD is often below 20–25% [6, 7]. Because of these limitations, alternative donor approaches such as haploidentical transplantation are increasingly being explored in SCD. Growing evidence supports the feasibility, safety, and efficacy of haploidentical HCT using either T-cell–depleted grafts or post-transplant cyclophosphamide (PTCy), offering a potential curative option for a broader group of patients [8, 9].

This document outlines the current guidelines for HCT in pediatric patients with SCD within the NOPHO countries. Emerging curative approaches, including gene therapy and gene-editing strategies, are not addressed in this recommendation.

Diagnosis of Sickle Cell Disease

SCD is primarily diagnosed through the detection of abnormal hemoglobin variants such as HbS. Molecular genetic testing of the HBB gene can confirm the diagnosis and further characterize specific mutations. While the most common and severe form is homozygous HbSS (sickle cell anemia), significant disease may also result from compound heterozygosity with other β-globin mutations, including HbS/β⁰-thalassemia, HbSC disease, HbSD disease, and others. The inheritance of both HbA and HbS is called sickle cell trait, not sickle cell disease.

Diagnostic evaluation is typically performed in pediatric hospitals, either in general pediatric clinics or pediatric oncology units, by specialists in pediatrics or pediatric oncology.

Hematopoietic Cell Transplantation

Several factors—including disease severity, genetic profile, availability of a related donor, and the family's attitude toward HCT—must be carefully considered when making decisions regarding transplantation.

Information about HCT

The initial information regarding HCT can be provided within the diagnostic unit by a specialist in pediatrics or pediatric oncology with advanced knowledge of benign pediatric hematology (pediatric hematologist), if possible, not an HCT physician. It is advisable to provide this information early after diagnosis— within the first six months—and then on an annual basis if HCT has not yet been performed.

If the patient is considered a candidate for HCT and the family is interested in the treatment, a referral should be sent to a Pediatric Cancer Center with an HCT unit.

If the patient is considered a candidate for HCT but the family does not currently wish to proceed with the treatment, no referral to an HCT unit is necessary; instead, a medical record entry can be made for documentation purposes.

HLA Typing

HLA typing may be offered to families who express an interest in HCT. In some cases, it may also be appropriate to offer HLA typing to families who do not currently wish to proceed with transplantation but have a positive attitude toward the treatment and wish to complete the typing. This approach can be justified after individual assessment, as knowing whether a compatible sibling donor is available may play an important role in the decision-making process regarding HCT.

Indications for HCT with an HLA-matched sibling donor

For patients with a severe genetic variant of SCD and an available MSD, HCT is considered indicated, regardless of clinical phenotype. The determination of which genetic variants are considered severe should be made in consultation with a pediatric hematologist.

Indications for HCT with MUD or haploidentical donor

Patients without an available MSD, might be considered for HCT with a MUD or with a haploidentical donor, if they have experienced at least one of the following severe or moderate SCD-related complications:

- Clinically significant neurological event (stroke)* or deficit.
- Silent cerebral infarct**.

- Pathological angio-MRI with TOF (time-of-flight) sequence.
- Transcranial doppler velocity >200 cm/s on two occasions, more than one month apart.
- Recurrent vaso-occlusive crises despite hydroxyurea treatment.
- Recurrent SCD-related hospitalizations despite hydroxyurea treatment.
- ≥ 2 episodes of severe acute chest syndrome, or one episode in the last 24 months.
- Chronic transfusion dependency or need for exchange transfusion.
- Transfusion-refractory allo-immunization.
- Early-stage pulmonary hypertension.
- Symptomatic osteonecrosis at ≥2 sites.
- Early-stage SCD nephropathy.
- Recurrent priapism.
- Repeated/severe splenic sequestration.
- Progressive organ dysfunction beyond early stage — e.g. worsening pulmonary, renal, hepatic, or cardiomyopathy.

According to the American Society of Hematology guidelines, the following definitions are used [10]:

*Stroke – acute neurologic injury of the brain, retina, or spinal cord that occurs as a result of ischemia or hemorrhage that last longer than 24 hours [11].

** Silent cerebral infarct – a lesion visible by magnetic resonance imaging (MRI) with no associated findings on neurologic exam [12], can be correlated with neurocognitive and behavioral deficits.

The decision to proceed with HCT should always be made by the transplantation center, in communication with the treating pediatric hematologist and in discussion with the family. It is not possible to apply rigid indication criteria based solely on symptoms; instead, each case must be assessed individually, considering the patient's overall disease burden, comorbidities, and the potential risks and benefits of transplantation.

Whenever possible, HCT with a haploidentical donor should be conducted within the framework of prospective studies.

In certain cases, such as (1) when there is a strong preference from the family to proceed with HCT, or (2) when patients have other complications not included in this list but that are debilitating, transplantation with a well-matched unrelated donor or with a haploidentical donor may be considered as a potential treatment option.

Contraindications to HCT

A comprehensive psychosocial assessment of the family is an obligatory step before initiating the HCT process. The evaluation ensures that caregivers have the capacity to manage complex home-based medical tasks, that communication with healthcare

providers can be conducted safely, and that the family has stable housing, adequate social support, and sufficient economic resources throughout the prolonged transplant and recovery period. If significant psychosocial risks are identified, appropriate interventions—such as support from social services—must be implemented and secured before HCT can proceed. Until these requirements are fulfilled, HCT should be considered temporarily contraindicated.

Advanced organ dysfunction, making HCT too high-risk or unlikely to prolong life, constitutes a medical contraindication. These decisions can be complex, and discussion at a national conference may provide support.

Time of HCT

If HCT is indicated, it should preferably be performed between 2 and 6 years of age, before irreversible organ damage occurs. HCT may also be performed later during adolescence or adulthood; however, with increasing age, the risk of complications and permanent organ damage rises, particularly in patients undergoing HCT beyond the age of 12-13 years [13].

Consequently, children over 10 years of age and those who have been waiting more than a year for HCT should be given higher priority for transplantation.

Stem Cell Source

- For MSD and MUD transplants, BM is the preferred source of stem cells, due to a lower risk of GvHD [14].
- PBSC may, in some cases, be accepted for both MSD and MUD transplants. For example, if the MUD cannot provide BM and no other HLA-matched donor is available.
- For haplo-identical HCT, PBSC with alpha/beta depletion is the preferred stem cell source, dependent on local experience and availability.
- Alternatively, a PTCy approach can be conducted.

MSD

- BM donation is indicated for siblings older than two years.
- Donation of PBSC may, in exceptional cases, be considered for HLA-matched siblings in adolescence, following an individual assessment of maturity.
- Carrier status for SCD is not regarded as a contraindication for stem cell donation.

MUD

- An HLA match of 10/10 (HLA-A, -B, -C, -DRB1, and -DQB1) is considered acceptable. When several suitable donors are available, a donor with a match—or a permissive mismatch—in the DPB1 locus may be prioritized to support optimal donor selection.

Preparation for HCT

This section addresses only SCD-related aspects.

- Approximately 4-6 and 1-2 weeks before conditioning, exchange transfusion should be performed to lower HbS to < 30%. In some cases, several exchange transfusions may be required before HCT.
- Fertility preservation should be offered before HCT. Treatment with hydroxyurea does not constitute a contraindication to fertility preservation.
- All surgical procedures, including fertility preservation and central venous catheter (CVC) placement, should be performed after exchange transfusion (within approximately 2 weeks after transfusion) and preferably no later than 4 weeks before HCT.

Conditioning regimen

Myeloablative conditioning is generally used in pediatric patients. Compared to Busulfan, Treosulfan is generally better tolerated, does not cross the blood-brain barrier, and might cause fewer side effects [15]. Established conditioning regimens for MSD and MUD transplants include:

- Thiotepa (5 mg/kg x 2)/Fludarabine (40 mg/m^2 x 4)/Treosulfan (14 g/m^2 x 3). A reduced Treosulfan dose of 12 g/m^2 × 3 may be considered in selected cases, such as very young children and patients with relevant comorbidities.
- Busulfan (AUC 75mg*h/L)/Cyclophosphamide (60 mg/kg x 2).

Serotherapy

- Thymoglobulin or Grafalon according to local protocols.
- Administered to all patients with MSD, MUD, or haploidentical donors.

GVHD Prophylaxis

- Tacrolimus (with target serum level 5-10 ng/ml) or cyclosporine-based (target serum level 150-220 ng/ml) GVHD prophylaxis combined with Methotrexate or Mycophenolate Mofetil according to local protocols.
- Immunosuppression tapering is initiated no earlier than 6 months after HCT, provided that the patient has sufficient donor chimerism. In cases of mixed chimerism, an individual assessment is made, and immunosuppression tapering may be initiated at a later time.

Supportive Care

This section addresses only SCD-related aspects.

- Hydroxyurea is administered until the start of conditioning (discontinued one day before).

- Seizure prophylaxis with levetiracetam is recommended for children with prior CNS complications, starting at the initiation of conditioning and continuing until day +180. For neurologically healthy children without previous CNS disease, seizure prophylaxis with levetiracetam may be used based on local practice and, if used, continued until day +30.
- Transfusion targets pre-engraftment to reduce the risk of CNS complications (e.g. bleedings/stroke):
    - A transfusion should be considered when hemoglobin levels fall below 70 g/L or as clinically indicated.
    - Transfusion thresholds for platelets is typically >20 × 10^9/L, based on individual assessment. In patients with a history of stroke, a higher platelet count (>50 × 10^9/L) might be considered.

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