

Sickle Cell Disease and Hematopoietic Cell Transplantation

AN EVOLVING THERAPEUTIC CHOICE

HCT as a therapy for sickle cell disease

In the last decade, an increasing number of patients with debilitating sickle cell disease (SCD) have undergone hematopoietic cell transplantation (HCT). Despite research showing the efficacy of HCT for SCD, experts estimate that less than 1% of the SCD population in the U.S. has received a transplant. [1]

- HCT is the only curative therapy for SCD [1]
- HCT for SCD can lead to improved quality of life post transplant [2,3]
- Related donor HCT for SCD can yield overall survival (OS) of >90% in both adults and children [1-2, 4-6]
- Clinical trials are a treatment option to consider and involve shared decision-making with patients and family

Risk/benefit analysis for decision-making

Discussing the implications of therapeutic options with patients and families is an important part of the shared decision-making process clinicians engage in throughout the disease course. When considering the efficacy of HCT, referral to a transplant physician for evaluation and treatment recommendation is key. [7]

Transplant Consultation Guidelines jointly developed by the National Marrow Donor Program® (NMDP)/Be The Match® and the American Society for Blood and Marrow Transplantation (ASBMT) recommend that patients with SCD should consult with a transplant physician if their disease has an aggressive course (stroke, end-organ complications, frequent pain crises). [8]

A transplant physician can provide a risk/benefit analysis of donor sources with predicted outcomes for each, including:

- Overall survival
- Graft-versus-host disease (GVHD)
- Relapse
- Quality of life (QOL) considerations

Improved quality of life

Research is emerging that addresses QOL issues for children and adults undergoing HCT to treat SCD.

In pre- and post-assessments of 29 children (mean age 14 years), significant “change in health” improvements were reported at 1 year post transplant compared to pre-transplant scores. HCT recipients reported better overall functioning related to their health after HCT,

despite a higher incidence of chronic GVHD compared to historical rates in similar patient populations. [3]

A study of 13 adults assessed QOL pre-HCT and at 30-365 days post-HCT. Results demonstrated an improvement in health-related QOL as early as day +30 after HCT, along with significantly greater improvements in general health, bodily pain, and vitality at 1 year after HCT. [2]

HCT outcomes

HCT using HLA-matched sibling donors can yield OS at 3 years of >90% in both adults and children with SCD. [1-2, 4-6] However, only 18% of patients with SCD have a healthy, matched sibling donor. [9]

The multi-center Sickle Cell Unrelated Donor Transplant (SCURT) study of 29 pediatric unrelated donor graft recipients showed 1- and 2-year OS rates of 86% and 79%, respectively. [3] An OS rate of 72% at 5 years was reported for 97 pediatric recipients of matched unrelated donors and umbilical cord blood units facilitated by NMDP/Be The Match [Figure 1]. [10] Priorities for future SCD trials have emerged including prevention of GVHD and mitigation of transplant-related mortality.

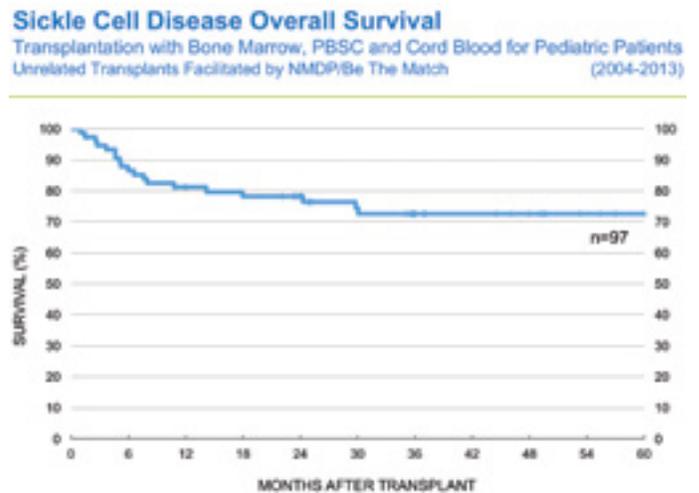


Figure 1. Overall survival in pediatric patients with SCD who had an unrelated donor transplant. Transplants facilitated by NMDP/Be The Match. [10]

Access to transplant for patients with SCD

The number of potential donors has increased significantly in the last 5 years, which is just one reason why the likelihood of finding a matching unrelated donor or CBU continues to improve [11]. Other factors contributing to this trend include:

- Ongoing efforts to add more African Americans and mixed ethnicity donors to worldwide registries.
- Use of cord blood as a cell source. The likelihood of having at least one matched CBU or 6-8/8 matched unrelated donor is 81% for African-American adults ≥age 20 and 95% for patients under age 20. [11]
- Growing use of haploidentical HCT, which improves access to HCT.

In 2015, 40% of new members to the Be The Match Registry® were people of color. [12] In addition, the growing use of haploidentical donors presents additional donor options for populations who may have faced challenges locating a donor in the past.

As a result of the increased donor and CBU choices, transplant center physicians can choose the most appropriate donor graft source for the transplant candidate to achieve optimal outcomes.

Clinical trials for treating SCD with HCT

In 2016, the Centers for Medicare and Medicaid Services (CMS) issued a decision memo that allogeneic HCT for SCD will be covered by Medicare for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical trial. Medicare beneficiaries can receive insurance coverage from Medicare for transplantation with participation in the BMT CTN 1503/STRIDE2 trial, which is an approved

Coverage with Evidence Development clinical trial. For more information, visit bmtctn.net.

Numerous other clinical trials are open for patients with SCD, and in multiple center locations. Table 1 provides an overview of a portion of the HCT-related trials for children and adults. Defined eligibility criteria with detailed information for each trial is available at ClinicalTrials.gov.

Trial Name and ClinicalTrials.gov Identifier	Age and Disease Criteria Complete eligibility criteria available on ClinicalTrials.gov	Eligible Donors
HCT vs. Standard of Care in Patients with Severe SCD NCT02766465 or BMT CTN 1503 (STRIDE2) – bmtctn.net	<ul style="list-style-type: none"> • 15-40 years old • Severe SCD (Hb SS, Hb SC or Hb Sβ) 	<ul style="list-style-type: none"> • HLA-matched related or unrelated donor
SCD-Haplo: Phase II Study of HLA-Haploidentical SCT for Aggressive SCD NCT02013375	<ul style="list-style-type: none"> • 16-60 years old • SCD with end organ complications 	<ul style="list-style-type: none"> • HLA-haploidentical relative – parents, offspring, siblings, cousins, aunts/uncles, grandparents
Treosulfan and Fludarabine Phosphate Before Donor Stem Cell Transplant in Treating Patients With Nonmalignant Inherited Disorders NCT00919503	<ul style="list-style-type: none"> • Up to 54 years old • Nonmalignant inherited diseases such as primary immunodeficiency disorders, bone marrow failure syndromes, hemoglobinopathies, and inborn errors of metabolism (metabolic disorders) treatable by allogeneic HCT and with disease-related complications 	<ul style="list-style-type: none"> • ≥9/10 related or unrelated donor, bone marrow preferred • ≥4/6 matched CBU
Improving the Results of HCT for Patients With Severe Congenital Anemias NCT00061568	<ul style="list-style-type: none"> • 2-80 years old • SCD: At high risk for morbidity and mortality defined by having irreversible end organ damage or potentially reversible complication(s) not ameliorated by hydroxyurea 	<ul style="list-style-type: none"> • 6/6 HLA matched family donor
Nonmyeloablative Peripheral Blood Mobilized HCT for SCD and Beta-thalassemia in People With Higher Risk of Transplant Failure NCT02105766	<ul style="list-style-type: none"> • 16-80 years old • SCD: At high risk for disease-related morbidity or mortality, defined by having severe end-organ damage or potentially modifiable complication(s) not ameliorated by hydroxyurea 	<ul style="list-style-type: none"> • 6/6 HLA matched family donor
Nonmyeloablative Conditioning for Mismatched HCT for Severe SCD NCT02678143	<ul style="list-style-type: none"> • ≥19 years old • SCD: At high risk for disease-related morbidity or mortality, defined by having severe end-organ damage or potentially modifiable complication(s) not ameliorated by hydroxyurea 	<ul style="list-style-type: none"> • One antigen mismatched unrelated donor • Haploidentical-related donor

Table 1. Ongoing clinical trials for SCD; detailed trial information can be found at ClinicalTrials.gov. BMT CTN=Blood and Marrow Transplant Clinical Trials Network, CBU=cord blood unit, HCT=hematopoietic cell transplantation, HLA=human leukocyte antigen, SCD=sickle cell disease

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Current treatment recommendations are based on small retrospective studies. As researchers and clinicians continue to add to the body of knowledge, treatment strategies will solidify.

Clinical Action Points

1

Discuss the risks, benefits and outcomes of SCD treatment options, including HCT, and make decisions with patients and family.

2

Recommend a transplant consultation for patients with an aggressive disease course.

3

Offer clinical trial enrollment options to patients and family/caregivers if appropriate.



TREATMENT GUIDELINES: REFERRAL TIMING AND POST-TRANSPLANT CARE

Our Recommended Timing for Transplant Consultation guidelines provide you with the HCT referral timing information you need most.

Updated annually, the guidelines provide up-to-date referral timing based on the latest research.

Available free in print, mobile app and online: BeTheMatchClinical.org/guidelines

References:

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We are the global leader in providing a cure to patients with life-threatening blood and marrow cancers like leukemia and lymphoma, as well as other diseases. We manage the world's largest registry of potential marrow donors and cord blood units, connect patients to their donor match for a life-saving marrow or umbilical cord blood transplant and educate health care professionals and patients. We conduct research through our research program, CIBMTR (Center for International Blood and Marrow Transplant Research), in collaboration with Medical College of Wisconsin. Learn more at BeTheMatchClinical.org