Clinical Policy: Hematopoietic Cell Transplantation in Sickle Cell Disease

Reference Number: IL.CP.MP.554
Last Review Date: 06/2021

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Sickle cell disease

Sickle cell disease (SCD) refers to a group of genetic disorders caused by an abnormal form of hemoglobin (Hb), called hemoglobin S (HbS). Under certain conditions, the HbS molecules link together in long polymers causing the red blood cell to adopt a sickle shape. Sickled red blood cells are inflexible and stick to the walls of the blood vessels, which causes blockage and hypoxia of the nearby tissues. Over time, the lack of oxygen can cause organ damage. SCD is a lifelong illness that causes significant morbidity and mortality.

Stem cell transplantation

Process in which stem cells are harvested from either a patient's (autologous) or donor's allogeneic bone marrow or peripheral blood for intravenous infusion.

Allogeneic stem cell transplant

May also be used to restore function in recipients having an inherited or acquired deficiency or defect. The key to achieving a successful allogeneic HSCT is to obtain an appropriate match between donor and recipient in the human leukocyte antigen (HLA) major histocompatibility complex.

Policy/Criteria

Hematopoietic cell transplantation is a potentially curative treatment for hemoglobinopathies. Sickle cell disease is associated with morbidity and leads to a poor quality of life as well as shortened life expectancy. The success rate for specific pediatric groups has been shown to be 85-90%. Survival has improved with increased surveillance, vaccinations and the use of hydroxyurea. However, hematopoietic stem cell transplantation is the only curative approach.

It is challenging to determine the optimal age for hematopoietic cell transplant (HCT) because outcomes are generally better in individuals who do not have severe disease morbidities, but individuals without severe disease morbidities may have an unclear prognosis and may be less willing to accept the potential morbidities and mortality associated with HCT.

> According to an international consensus guideline, preschool age is the ideal age for HCT. This is based on improved outcomes in children in this age range (eg, improved survival, lower rates of graft-versus-host disease [GVHD]).

Compared with children, there is much less experience with HCT in older adolescents and adults with SCD. Overall survival rates are lower and transplant toxicity appear to be higher with increasing recipient age. When reduced-intensity conditioning regimens are used, there is also a greater concern for graft failure with autologous reconstitution. Decisions about HCT in older adolescents and adults are individualized according to comorbidities and other Factors.

Children who receive a related donor transplant can expect to have an overall survival of approximately 91 to 96 percent and an event-free survival (EFS) that is slightly lower. Experience is less with older adolescents and adults; increasing age appears to confer lower survival rates and higher transplant toxicity. Those who have good engraftment (donor chimerism of at least 20 percent) can expect to be cured of their disease, and in some cases, prior organ injury may be reversed. Infertility is common after transplant, although some individuals do have children. The risk of acute and chronic GVHD is approximately 15 percent.

NOTE: IL: Medicaid: HFS covers stem cell transplants for patients with Sickle Cell Disease with no age restrictions or limitations.

Procedure:

Criteria for Coverage:

Many factors affect the outcome of tissue transplantation; the selection process is designed to obtain the best result for each individual. Overall health, age, and disease stage are extremely important considerations in evaluating candidates.

As consideration for hematopoietic stem cell transplantation these guidelines MUST be met:

1. Cardiac function evaluation:
    a. Left ventricular ejection fraction equal or greater than 40 %26
    b. If present, coronary artery disease and cardiac arrhythmias must be controlled/stable
2. Pulmonary function evaluation:
    a. Forced vital capacity (FVC)/forced expiratory volume in 1 second (FEV1)/diffusion capacity of the lung for carbon monoxide (DLCO) equal to or greater than 50 % predicted.
3. Renal function with a serum creatinine < 2 mg/dl of Clcr > 50 ml/min
4. Liver function studies indicate no frank cirrhosis
5. No active infection must be present including any of the following:
    a. Human immunodeficiency virus (HIV)
    b. Hepatitis B virus (HBV)
    c. Hepatitis C virus (HCV)
    d. Human T-cell lymphotropic virus (HTLV)-1
6. Dental exam, x-rays and treatment completed to eliminate sources of infection in the Oral cavity.

a. Examples include, but are not limited to gum disease, tooth decay, tooth abscesses and poor oral hygiene.

7. Karnofsky rating 70% or greater and/or Eastern Cooperative Oncology Group (ECOG) performance status less than 2
8. Documentation of member's ability to understand the risks of the procedures.
9. Emotional and psychiatric stability, including a strong family or alternative support network (documented by formal social work evaluation)
10. Absence of psychiatric disease that would interfere with the member's ability to comply with the pre- or post-transplant therapeutic regimen

The rationale to proceed with transplantation, if a transplant candidate has sub-optimal organ function or a per-existing comorbid conditions (s) must be documented within the candidate's medical record by the BMT physician.

Criteria for allogeneic hematopoietic cell transplantation for members with sickle cell disease:

1. Medical Director to review current literature and special instructions regarding age restrictions AND
2. Member must have an HLA matched sibling donor or first-degree relative donor AND
3. One of the following must be present:
   - Stroke or central nervous system event lasting longer than 24 h
   - Acute chest syndrome (fever, chest pain, and appearance of a new infiltrate on chest radiograph) with recurrent hospitalizations or previous exchange transfusions
   - Recurrent vaso-occlusive pain (more than 2 episodes per year over several years) or recurrent priapism
   - Impaired neuropsychological function with abnormal cerebral MRI scan or an Abnormal transcranial Doppler study
   - Stage I or 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 major visual impairment in at least one eye
   - Osteonecrosis of multiple joints
   - Red-cell alloimmunization during long-term transfusion therapy

A standard myeloablative conditioning regimen will be used.

Meridian Health Plan does not cover non-myeloablative (NMA) allogeneic HSCT for this diagnosis. Nonmyeloablative (NMA) regimens typically do not ablate the recipient's bone marrow. Evidence regarding outcomes with Reduced-intensity conditioning (RIC) regimens in SCD is limited. Most of the available studies are small series in adults. The greatest concern with RIC regimens is that there is a greater risk that stable donor chimerism (engraftment) will not occur.

Meridian Health Plan does not cover HSCT for the treatment of sickle cell disease using stem

cells derived from:

Cord blood or peripheral blood
Matched unrelated donors
Non-sibling family donors

Experience with alternative donors is limited in SCD, but these approaches may be appropriate for selected individuals as part of a clinical trial.

Donor lymphocyte infusion (DLI) is used in hematologic malignancies as a means of increasing graft-versus-tumor effect. Experience with DLI to improve engraftment in nonmalignant diseases is extremely limited. This procedure might be useful in members with recurrence of SCD following allogeneic HCT.

Donor lymphocyte infusion (DLI), collection and cryopreservation may be authorized following a medically necessary allogeneic hematopoietic stem cell transplant:

- For incomplete chimerism and disease relapse in the setting of incomplete chimerism(defined as incomplete donor stem cell grafting in the recipient's bone marrow); and
- Donor lymphocytes must be collected from the original hematopoietic stem cell donor

II. It is the policy of health plans affiliated with Centene Corporation that the following are considered experimental/investigational:

A. Autologous hematopoietic cell transplant for sickle cell anemia;

B. Allogeneic hematopoietic cell transplants for the treatment of sickle cell anemia or homozygous β- Thalassemia for any other indications than those specified above.
* Powars et al. [6] found that the natural history of SCLD evolved through four Successive stages that could be differentiated by pulmonary function tests, chest radiographs, blood gas values and noninvasive cardiac studies. Patients with stage I disease, were usually free of respiratory symptoms (except during acute events) and exhibited only a moderate ventilator defect (which was not characterized as restrictive or obstructive)

Member Assessment of Compliance with Plan of Care (applicable for ages 10 and above):

- Alcohol screen- abstinence for the past 6 months prior to actual transplant approval, if member history includes use of alcohol. If no history exists then 1 negative alcohol screen must be submitted for members with no history of past alcohol use
- Drug screen-abstinence for the past 6 months prior to actual transplant approval if historyexists of drug use. If no history exists then 1 negative drug screen must be submitted for members with no history of positive drug screen.
- Nicotine screening- abstinence for the past 6 months prior to actual transplant approval If history of smoking. If no history exists then 1 negative cotinine level must be submitted

Refusal or failure to undergo monthly testing for those members with a history of alcohol, tobacco, and/or drug use will be interpreted as a positive test result.

Six month abstinence period may be shortened in cases where patient's condition is sufficiently advanced that mortality is reasonably expected before the full abstinence period can be completed. Patients granted a waiver of the six month abstinence period require documentation of participation in a formal outpatient treatment program, when practical, as well as serial blood or urine testing no less frequently than monthly. A positive test result at any time prior to the procurement phase will result in denial.

Absolute Contraindications:

Facilities performing stem cell transplants must be accredited by the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee and compliant with the FACT_JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration manual

Appendix – KPS and ECOG: One tool that assesses a patient's performance status is the Karnofsky Performance Scale. The scale ranges from 0 to 100%, with 100% representing patients without evidence of disease and 0% being dead. A status score of 70% denotes those patients that are able to care for themselves but may not be able to effectively work, shop, drive, or care for family members; patients with an irreversible score or less the 70% generally have a poor prognosis.

100% Normal, no complaints, no signs of disease
90% Capable of normal activity, few symptoms or signs of disease
80% Normal activity with some difficulty, some symptoms or signs
70% Caring for self, not capable of normal activity or work
60% Requiring some help, can take care of most personal requirements
50% Requires help often, requires frequent medical care
40% Disabled, requires special care and help
30% Severely disabled, hospital admission indicated but no risk of death
20% Very ill, urgently requiring admission, requires supportive measures or treatment
10% Moribund, rapidly progressive fatal disease processes
0% Death

The Eastern Cooperative Oncology Group (ECOG) developed a performance status tool. This tool assesses the patient's disease progression, the impact of the disease on daily living, and provides information used to determine proper treatment and prognosis. Patients are classified based on the following information:

0 Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1 Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2 Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3 Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4 Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed

or chair)
5 Death

Background

Hemoglobinopathies are a group of over 1,000 hematological disorders that result from deleterious molecular alterations to hemoglobin and are broadly classified into two categories based on the phenotypic characteristics of these variations.

The first of these categories includes disorders, such as sickle cell anemia, in which there is a structural defect in one of the
globin subunits.

Each of these physiological aspects of hemoglobin are deleteriously affected in the hemoglobinopathy disorders,

Sickle Cell Anemia
Sickle cell disease results from a synonymous mutation that exchanges glutamic acid with valine at position 6 in the β-globin subunit. Homozygous inheritance of this mutation results in the disease phenotype, whereas heterozygous carriers do not exhibit clinical disease symptoms; heterozygous carriers are also referred to as having sickle cell trait. This amino acid substitution causes deoxygenated hemoglobin to rigid polymers in red blood cells, which ultimately forms the classic sickle-shaped morphology. The sickle red blood cells occlude the microvasculature which leads to tissue hypoxia, infarction, and chronic hemolytic anemia.4

Thus, sickle cell anemia presents a heterogeneous range of clinical manifestations, including pain, strokes, vaso-occlusive episodes, multi-organ injury, reduced quality of life, and shortened lifespan.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is recognized as the only cure for sickle cell disease, and the success rate for specific pediatric groups has been shown to be 85 – 90%.4
In the United States, it is estimated that the number of children with homozygous sickle cell anemia is 70,000 – 100,000, of which 5,000 – 7,000 could be eligible for transplantation.6
A survey of the European Blood and Marrow Transplant and CIBMTR data files that ~1,200 patients in total
have received HCT for sickle cell disease, and the 3 year survival rate is ~90% regardless of the source of hematopoietic stem cells.

The establishment of complete donor-derived erythropoiesis can stabilize function in affected organs, such as the central nervous system and lungs. However, HCT related organ toxicities, graft vs. host disease, graft rejection, and donor availability are major limitations of this procedure. Infertility and gonadal failure are two specific morbidities with which HCT is associated.Also, use of fully matched sibling donors as potentially eligible donors is one of the limitations for HCT implementation. However, siblings are preferable HCT donors due to the

lowered risk of graft vs host disease.

Coding Implications

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CPT®* Codes	Description

HCPCS ®* Codes	Description

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

+ Indicates a code(s) requiring an additional character

ICD-10-CM Code	Description

Reviews, Revisions, and Approvals	Date	Approval Date
Original approval date		

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.