Protocol

Allogeneic Hematopoietic Stem-Cell Transplantation for Genetic Diseases and Acquired Anemias

(80122)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 01/15
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14	

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. ***Preauthorization is required and must be obtained through Case Management.*** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Description

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Allogeneic HSCT refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

Immunologic compatibility between infused stem cells and the recipient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the class I and class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Preparative Conditioning for Allogeneic HSCT

The conventional practice of allogeneic HSCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to cause bone marrow failure. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC allotransplantation. They represent a continuum in their intensity, from almost totally myeloablative to minimally myeloablative with lymphoablation.

Genetic Diseases and Acquired Anemias

<u>Hemoglobinopathies</u>

The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, reducing oxygen delivery. The supportive treatment of beta-thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic, and endocrine function. (1) The only definitive cure for thalassemia is to correct the genetic defect with allogeneic HSCT.

Sickle cell disease is caused by a single amino acid substitution in the beta chain of hemoglobin and, unlike thalassemia major, has a variable course of clinical severity. (1) Sickle cell disease typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for males and 48 for females. Three major therapeutic options are available: chronic blood transfusions, hydroxyurea, and HSCT, the latter being the only possibility for cure. (1)

Bone marrow failure syndromes

Aplastic anemia in children is rare and is most often idiopathic and less commonly due to a hereditary disorder. Inherited syndromes include Fanconi anemia, a rare, autosomal recessive disease characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently this disease terminates in a myelodysplastic syndrome or acute myelogenous leukemia. Most patients with Fanconi anemia succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age. (2) In Fanconi anemia, HSCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HSCT, with cure of the marrow failure and amelioration of the risk of leukemia. (2)

Dyskeratosis congenita is characterized by marked telomere dysregulation with clinical features of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia. (3) Early mortality is associated with bone marrow failure, infections, pulmonary complications, or malignancy. (3)

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia. (3) Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities, and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of myelodysplastic syndrome and malignant transformation, especially acute myelogenous leukemia. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow, with 30% of patients also having a variety of physical anomalies. (3)

Primary immunodeficiencies

The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes. (4) The most severe defects (collectively known as severe combined immunodeficiency, or SCID) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells. (4) Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the lifespan of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood. (4) Bone marrow transplant is the only definitive cure, and the treatment of choice for SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function. (5)

Inherited metabolic diseases

Lysosomal storage disorders consist of many different rare diseases caused by a single gene defect, and most are inherited as an autosomal recessive trait. (6) Lysosomal storage disorders are caused by specific enzyme deficiencies that result in defective lysosomal acid hydrolysis of endogenous macromolecules that subsequently accumulate as a toxic substance. Peroxisomal storage disorders arise due to a defect in a membrane transporter protein that leads to defects in the metabolism of long-chain fatty acids. Lysosomal storage disorders and peroxisomal storage disorders affect multiple organ systems, including the central and peripheral nervous systems. These disorders are progressive and often fatal in childhood due to both the accumulation of toxic

substrate and a deficiency of the product of the enzyme reaction. (6) Hurler syndrome usually leads to premature death by five years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs don't cross the blood-brain barrier, which results in ineffective treatment of the central nervous system. Stem-cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier. (6) The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells, for example microglial cells in the brain and Kupffer cells in the liver. (6)

Allogeneic HSCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in the Table. (6) The first stem-cell transplant for an inherited metabolic disease was performed in 1980 in a patient with Hurler syndrome. Since that time, more than 1,000 transplants have been performed worldwide. (6)

Table. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis (MPS)	MPS I	Hurler, Scheie, H-S
	MPS II	Hunter
	MPS III A-D	Sanfilippo A-D
	MPS IV A-B	Morquio A-B
	MPS VI	Maroteaux-Lamy
	MPS VII	Sly
Sphingolipidosis	Fabry's	
	Farber's	Lipogranulomatosis
	Gaucher's I-III	
	GM_1 gangliosidosis	
	Niemann-Pick disease A and B	
	Tay-Sachs disease	
	Sandhoff's disease	
	Globoid leukodystrophy	Krabbe disease
	Metachromatic leukodystrophy	MLD
Glycoproteinosis	Aspartylglucosaminuria	
	Fucosidosis	
	alpha-Mannosidosis	
	beta-Mannosidosis	
	Mucolipidosis III and IV	Sialidosis
Other lipidoses	Niemann-Pick disease C	
	Wolman disease	
	Ceroid lipofuscinosis	Type III-Batten disease
Glycogen storage	GSD type II	Pompe
Multiple enzyme deficiency	Galactosialidosis	
	Mucolipidosis type II	I-cell disease
Lysosomal transport defects	Cystinosis	
	Sialic acid storage disease	
	Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy	ALD
	Adrenomyeloneuropathy	AMN

Infantile malignant osteopetrosis

Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow. (7) Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis. Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately six months of age, and severe hematologic malfunction with bone marrow failure. (7) Seventy percent of these patients die before the age of six years, often of recurrent infections. (7) HSCT is the only curative therapy for this fatal disease.

Hematopoietic stem-cell transplantation for autoimmune disease, such as rheumatoid arthritis or multiple sclerosis, is considered in a separate Protocol.

Policy (Formerly Corporate Medical Guideline)

Allogeneic hematopoietic stem cell transplantation is considered **medically necessary** for selected patients with the following disorders:

Hemoglobinopathies

- Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage
- Homozygous beta-thalassemia (i.e., thalassemia major)

Bone marrow failure syndromes

- Aplastic anemia including hereditary (including Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond, Diamond-Blackfan) or acquired (e.g., secondary to drug or toxin exposure) forms

Primary immunodeficiencies

- Absent or defective T-cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
- Absent or defective natural killer function (e.g., Chediak-Higashi syndrome)
- Absent or defective neutrophil function (e.g., Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)

(See policy guideline # 1.)

Inherited metabolic disease

- Lysosomal and peroxisomal storage disorders *except* Hunter, Sanfilippo, and Morquio syndromes

(See policy guideline # 2.)

Genetic disorders affecting skeletal tissue

- Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease)

Policy Guideline

1. The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem-cell transplantation (HSCT) (4):

Lymphocyte immunodeficiencies

Adenosine deaminase deficiency

Artemis deficiency

Calcium channel deficiency

CD 40 ligand deficiency

Cernunnos/X-linked lymphoproliferative disease deficiency

CHARGE syndrome with immune deficiency

Common gamma chain deficiency

Deficiencies in CD 45, CD3, CD8

DiGeorge syndrome

DNA ligase IV

Interleukin-7 receptor alpha deficiency

Janus-associated kinase 3 (JAK3) deficiency

Major histocompatibility class II deficiency

Omenn syndrome

Purine nucleoside phosphorylase deficiency

Recombinase-activating gene (RAG) 1/2 deficiency

Reticular dysgenesis

Winged helix deficiency

Wiskott-Aldrich syndrome

X-linked lymphoproliferative disease

Zeta-chain-associated protein-70 (ZAP-70) deficiency

Phagocytic deficiencies

Chediak-Higashi syndrome

Chronic granulomatous disease

Hemophagocytic lymphohistiocytosis

Griscelli syndrome, type 2

Interferon-gamma receptor deficiencies

Leukocyte adhesion deficiency

Severe congenital neutropenias

Shwachman-Diamond syndrome

Other immunodeficiencies

Autoimmune lymphoproliferative syndrome

Cartilage hair hypoplasia

CD25 deficiency

Hyper IgD and IgE syndromes

ICF syndrome

IPEX syndrome

NEMO deficiency

NF-$_K$B inhibitor, alpha (I_KB-alpha) deficiency

Nijmegen breakage syndrome

2. In the inherited metabolic disorders, allogeneic HSCT has been proven effective in some cases of Hurler, Maroteaux-Lamy, and Sly syndromes, childhood onset cerebral X-linked adrenoleukodystrophy, globoid-cell leukodystrophy, metachromatic leukodystrophy, alpha-mannosidosis, and aspartylglucosaminuria. Allogeneic HSCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM_1, gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HSCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes. (8)

   The experience with reduced-intensity conditioning (RIC) and allogeneic HSCT for the diseases listed in this Protocol has been limited to small numbers of patients, and have yielded mixed results, depending upon the disease category. In general, the results have been most promising in the bone marrow failure syndromes and primary immunodeficiencies. In the hemoglobinopathies, success has been hampered by difficulties with high rates of graft rejection, and in adult patients, severe graft versus host disease (GVHD). Several Phase II/III trials are ongoing examining the role of this type of transplant for these diseases, as outlined in the clinical trial section under each disease type.

Benefit Application

Individual transplant facilities may have their own *additional* requirements or protocols that must be met in order for the patient to be eligible for a transplant at **their** facility.

Medicare Advantage

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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