Protocol

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

(80122)

Medical Benefit		**Effective Date**: 04/01/13	**Next Review Date**: 11/20
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17, 11/18, 11/19	

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. 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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With a hemoglobinopathy • With a bone marrow failure syndrome • With a primary immunodeficiency • With inherited metabolic diseases including Hunter, Sanfilippo, or Morquio • Syndromes • With inherited metabolic diseases excluding Hunter, Sanfilippo, or Morquio syndromes • With a genetic disorder affecting skeletal tissue	Interventions of interest are: • Allogeneic hematopoietic cell transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Quality of life • Treatment-related morbidity

DESCRIPTION

A number of inherited and acquired conditions have the potential for severe and/or progressive disease. For some conditions, allogeneic hematopoietic cell transplantation (allo-HCT) has been used to alter the natural history of the disease or potentially offer a cure.

SUMMARY OF EVIDENCE

For individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome disease (specifically those other than Hunter, Sanfilippo, or Morquio syndromes), or a genetic disorder affecting skeletal tissue who receive allo-HCT, the evidence includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in overall survival and other disease-specific outcomes. Allo-HCT is likely to improve health outcomes in select patients with certain inherited and acquired diseases. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have an inherited metabolic syndrome disease (specifically those including Hunter, Sanfilippo, and Morquio syndromes) who receive allo-HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. Use of allo-HCT to treat patients with Hunter, Sanfilippo, or Morquio syndromes does not result in improvements in neurologic, neuropsychologic, and neurophysiologic function. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Allogeneic hematopoietic cell transplantation is considered **medically necessary** for select 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 β-thalassemia (i.e., thalassemia major).

BONE MARROW FAILURE SYNDROMES

- Aplastic anemia including hereditary (including Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome) 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) or
- Absent or defective natural killer function (e.g., Chediak-Higashi syndrome) or
- Absent or defective neutrophil function (e.g., Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect).

(See policy guideline 1.)

INHERITED METABOLIC DISEASES

- Lysosomal and peroxisomal storage disorders *except* for 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 GUIDELINES

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.

1. The following guideline lists immunodeficiencies that have been successfully treated by allo-HCT (Gennery & Cant et al, 2008).

LYMPHOCYTE IMMUNODEFICIENCIES

- Adenosine deaminase deficiency
- Artemis deficiency
- Calcium channel deficiency
- CD40 ligand deficiency
- Cernunnos/X-linked lymphoproliferative disease deficiency
- CHARGE syndrome with immune deficiency
- Common gamma chain deficiency
- Deficiencies in CD45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV deficiency syndrome
- Interleukin-7 receptor alpha deficiency
- Janus-associated kinase 3 deficiency
- Major histocompatibility class II deficiency
- Omenn syndrome
- Purine nucleoside phosphorylase deficiency
- Recombinase-activating gene 1/2 deficiency
- Reticular dysgenesis
- Winged helix deficiency
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative disease
- Zeta-chain-associated protein-70 deficiency

PHAGOCYTIC DEFICIENCIES

- Chédiak-Higashi syndrome
- Chronic granulomatous disease
- Griscelli syndrome type 2
- Hemophagocytic lymphohistiocytosis
- 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

Immunodeficiency, centromeric instability, and facial dysmorphism syndrome

Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome

Nuclear factor-κ B (NF-κB) essential modulator deficiency

NF-κB inhibitor, NF-κB-α deficiency

Nijmegen breakage syndrome

2. For inherited metabolic disorders, allo-HCT 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 HCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galacto-sialidosis, GM_1, gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick disease, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes (Mehta, 2004).

The experience with reduced-intensity conditioning (RIC) and allo-HCT for the diseases listed in this protocol has been limited to small numbers of patients, and has 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 adults, severe graft versus host disease. Phase 2/3 trials are ongoing, or completed, examining the role of this type of transplant for these diseases.

MEDICARE ADVANTAGE

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

BACKGROUND

GENETIC DISEASES AND ACQUIRED ANEMIAS

Hemoglobinopathies

Thalassemias result from variants in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of b-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. 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 men and 48 for women.

Treatment

The only definitive cure for thalassemia is to correct the genetic defect with allogeneic hematopoietic cell transplantation (allo-HCT).

Three major therapeutic options are available for sickle cell disease: chronic blood transfusions, hydroxyurea, and allo-HCT, the latter being the only possibility for cure.[1]

Bone Marrow Failure Syndromes

Aplastic anemia in children is rare; most often, it is 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 myelodysplastic syndrome or acute myeloid 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]

Dyskeratosis congenitais 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.

Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan syndrome.[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 myeloid 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]

Treatment

In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of human leukocyte antigen (HLA)-matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

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) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells.[4]

Treatment

Without treatment, patients with severe combined immunodeficiency 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 transplantation is the only definitive cure, and the treatment of choice for severe combined immunodeficiency 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 defi-

ciencies 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.

Treatment

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs do not cross the blood-brain barrier, which results in the 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 (e.g., microglial cells in the brain and Kupffer cells in the liver).[6]

Allogeneic HCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1.[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 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis (MPS)	Mucopolysaccharidosis I H or HS	Hurler syndrome or Hurler-Scheie syndrome
	Mucopolysaccharidosis II	Hunter syndrome
	Mucopolysaccharidosis III A-D	Sanfilippo syndrome A-D
	Mucopolysaccharidosis IV A-B	Morquio syndrome A-B
	Mucopolysaccharidosis VI	Maroteaux-Lamy syndrome
	Mucopolysaccharidosis VII	Sly syndrome
Sphingolipidosis	Fabry disease	
	Farber disease	Lipogranulomatosis
	Gaucher disease types 1 and 3	
	GM_1 gangliosidosis	
	Niemann-Pick disease A and B	
	Tay-Sachs disease	
	Sandhoff disease	
	Globoid cell 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	Glycogen storage disease type II	Pompe disease
Multiple enzyme deficiency	Galactosialidosis	
	Mucolipidosis type II	I-cell disease

Category	Diagnosis	Other Names
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

Genetic Disorders Affecting Skeletal Tissue

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 (Albers-Schonberg disease or marble bone disease). 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]

Treatment

HCT is the only curative therapy for this fatal disease.

Hematopoietic Cell Transplantation

HCT 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 radiotherapy. Allo-HCT 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. Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic cells and the recipient is a critical factor in achieving a good outcome with allo-HCT. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (except umbilical cord blood).

Preparative Conditioning for Allo-HCT

The conventional practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. Reduced-intensity conditioning refers to chemotherapy regimens that seek to reduce adverse events secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo reduced-intensity conditioning with allo-HCT 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 reduced-intensity conditioning allogeneic transplantation. They represent a continuum in their intensity, from almost totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition.

HCT for autoimmune diseases, such as rheumatoid arthritis or multiple sclerosis, is considered separately in Hematopoietic Cell Transplantation for Autoimmune Diseases Protocol.

REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RELATED PROTOCOL

Hematopoietic Cell Transplantation for Autoimmune Diseases

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

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

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