



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Stem-Cell Transplantation for Myelofibrosis

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Coverage Policy

CIGNA covers allogeneic hematopoietic stem-cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched donor (i.e., at least five of six match of the HLA-A, HLA-B, or HLA-DRB1 antigens) as medically necessary for the treatment of myelofibrosis, for symptoms that persist, or worsen despite standard supportive care.

CIGNA does not cover autologous HSCT for the treatment of myelofibrosis because it is considered experimental, investigational or unproven.

General Background

Myelofibrosis is considered a myeloproliferative disorder, characterized by replacement of the bone marrow by fibrous scar tissue, which reduces the ability of the marrow to produce red blood cells. The disorder is also known as primary myelofibrosis, idiopathic myelofibrosis, agnogenic myeloid metaplasia, myeloid sclerosis with myeloid metaplasia, idiopathic myeloid metaplasia, and oteosclerosis. Myelofibrosis can be associated with other hematological disorders, including polycythemia vera and essential thrombocytopenia; however, the etiology of chronic idiopathic or primary myelofibrosis is unknown.

The presence of two or three of the following factors may signal adverse prognosis (NCI, 2010): older age, anemia, leukopenia, leukocytosis, circulating blasts, karyotype abnormalities, systemic B symptoms (i.e., fever, night sweats, and weight loss). Additionally, there are several schema used to predict prognosis that assign risk-

score (i.e., low-, intermediate-, and high-risk). Individuals with symptomatic disease have a median survival of <five years (Kroger, 2009).

Most therapeutic interventions are directed toward symptom palliation and supportive measures; current medical therapeutic options for patients with primary myelofibrosis, myelofibrosis after polycythemia, or essential thrombocytopenia have not demonstrated an impact on disease course (Kroger, 2009). Allogeneic hematopoietic stem-cell transplantation (HSCT) may be appropriate for selected individuals who have an appropriate donor and can tolerate a more aggressive treatment approach.

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSC transplantation (HSCT) can be either autologous (using the patient's own stem cells) or allogeneic (using stem cells from a donor).

In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. Alternative donor sources including matched-unrelated and unmatched-related donors (e.g., haploidentical donors) are being evaluated for individuals who do not have an HLA-identical donor. However, a study by Bacigalupo et al. (2010) found that use of alternate donor sources was an independent unfavorable factor for survival.

Myeloablative Allogeneic HSCT: Although randomized controlled clinical trial data are limited, allogeneic HSCT is considered a curative treatment option for selected individuals with myelofibrosis who have an acceptable donor (Robin, 2011). Engraftment can be obtained, and a complete and durable remission of the disease can be achieved in approximately 50% of patients (Hoffman, 2008; Kroger, 2007; Tanner, 2007; Barosi, 2006; Clark, 2004; Tefferi, 2008). Successful transplantation is associated with gradual resolution of marrow fibrosis and normalization of hematopoiesis (Hoffman, 2008). Several retrospective analyzes have demonstrated improved outcomes with the use of allogeneic HSCT, with estimated one-, three-, and five-year overall survival rates of 56–61%, 38.5–58%, and 31–61%, respectively. Toxicity of myeloablative therapy remains high with one- and three-year treatment-related mortality (TRM) rates of 35%–48.3% and 43%, respectively, in various studies (Bacigalupo, 2010; Patriarca, 2008; Karrabul, 2007; Ditschkowski, 2004; Deeg, 2003; Daly, 2003).

The utility of this approach is limited by the age and condition of many patients, the availability of suitable donors, and by the morbidity and mortality associated with this procedure (Faderl, 2005; Clark, 2004). Because the disease may remain stable for years in individuals who present without adverse prognostic factors, allogeneic HSCT should be reserved for symptomatic patients (Hoffman, 2008). It is usually employed as a therapy for patients who have failed standard treatment and who have relapsed or refractory disease. Definitive patient selection criteria for allogeneic HSCT in this disease have not been identified; however, allogeneic HSCT has been proposed for patients under the age of 45–50 years with intermediate and high-risk features, and for patients 50–60 years of age with an anticipated survival of less than five years (Robin, 2011; Tefferi, 2008; van Biesen, 2005).

Non-Myeloablative Allogeneic HSCT: The high TRM associated with the use of myeloablative allogeneic HSCT has led to the investigation of non-myeloablative and reduced-intensity conditioning regimens. Reduced-intensity conditioning is based on the concept that the induction of a graft-versus-myelofibrosis (GVM) effect may be sufficient to achieve disease eradication without the need for fully myeloablative treatment (Pappeorgiou, 2007). Non-myeloablative and reduced-intensity regimens have decreased the morbidity and TRM of allogeneic HSCT and allow for a broader application in elderly patients (Kroger, 2008; Barosi, 2006).

The effectiveness of nonmyeloablative allogeneic HSCT has been demonstrated in several prospective and retrospective clinical studies with three-, and five-year overall- and disease-free survival rates of 83% and 67%, respectively (Kroger, 2009; Kroger, 2007; Merup, 2006; Rondelli, 2005; Kroger, 2005). Five-year disease-free and overall survival rates were 51% and 67%, respectively.

Although longer-term follow-up data and larger studies are desirable, non-myeloablative conditioning with allogeneic transplantation appears to be an acceptable therapeutic option for patients with myelofibrosis (Hoffman, 2008).

Autologous Transplantation: Autologous HSCT has been investigated in a small number of patients in an effort to reverse advanced disease and ameliorate symptoms in patients who do not have a matched donor. Autologous HSCT may relieve disease-related symptoms such as splenomegaly, but the curative potential is very unlikely (van Beisen, 2005; Kroger, 2008). There are scarce data in the published peer-reviewed scientific literature regarding the safety and effectiveness of autologous transplantation for this indication. The role of this therapy in the treatment of myelofibrosis remains uncertain (Hoffman, 2007).

Contraindications

Many factors affect the outcome of a tissue transplant; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)
- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal), unless related to AML
- poor renal function (creatinine clearance < 50ml/min)
- poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
- active central nervous system involvement
- a pattern of demonstrated patient noncompliance which would place a transplant at serious risk of failure
- presence of human immunodeficiency virus OR an active form of any ONE of the following:
 - hepatitis B virus (HBV)
 - hepatitis C virus (HCV)
 - human T-cell lymphotropic virus (HTLV)-1
- Karnofsky rating < 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status > 2

Professional Societies/Organizations

National Marrow Donor Program (NMDP): The NMDP lists agnogenic myeloid metaplasia as a condition that is treatable by allogeneic HCST.

National Cancer Institute (NCI): The NCI (2010) notes that allogeneic peripheral stem cell or bone marrow transplantation is a treatment option for chronic idiopathic myelofibrosis.

Leukemia and Lymphoma Society: The Leukemia and Lymphoma Society (2007) notes that in certain circumstances, allogeneic stem cell transplantation is an accepted treatment for idiopathic myelofibrosis.

Summary

Although data are not robust, allogeneic hematopoietic stem-cell transplantation (HSCT) is an accepted treatment option for selected individuals with myelofibrosis. There is insufficient evidence in the published, peer-reviewed scientific literature to determine the safety and effectiveness of autologous HSCT for the treatment of myelofibrosis. The role of this therapy has not yet been established for this indication.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®*	Description
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Codes	
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150 [†]	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

ICD-9-CM Diagnosis Codes	Description
238.76	Myelofibrosis with myeloid metaplasia
289.83	Myelofibrosis

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
38206 [†]	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38241 [†]	Bone marrow or blood-derived peripheral stem cell transplantation; autologous

[†]**Note:** Experimental, investigational, unproven and not covered when used to report autologous stem cell transplant for the treatment of myelofibrosis.

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare			
Great-West Healthcare			

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