



Cigna Medical Coverage Policy

Subject Stem-Cell Transplantation for Myelofibrosis and Polycythemia Vera

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Coverage Policy

Cigna covers allogeneic hematopoietic stem-cell transplantation (HSCT) from an appropriately-matched human leukocyte antigen (HLA) donor 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.

Cigna does not cover hematopoietic stem-cell transplantation (HSCT) for the treatment of polycythemia vera (PV) because it is considered experimental, investigational or unproven.

General Background

Myelofibrosis and polycythemia vera are considered myeloproliferative neoplasms. Myelofibrosis is characterized by replacement of the bone marrow by fibrous scar tissue, which reduces the ability of the marrow to produce red blood cells. Polycythemia vera is characterized by an abnormal increase in the number of red and white blood cells as well as platelets, with red blood cell overproduction being predominant. There is an increase in total blood volume, as well as thrombocytosis and splenomegaly (Hoffman, 2012).

Myelofibrosis

This 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, 2013): 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) for primary myelofibrosis is potentially curative but dangerous; transplant-related death or severe morbidity occurs in about half of transplanted patients, regardless of the intensity of conditioning regimens used (Tefferi, 2011). 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.

Hematopoietic Stem-Cell Transplantation (HSCT) for Myelofibrosis

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

The selection of an appropriately-matched allogeneic donor source is dependent on several variables including the availability of a human leukocyte antigen (HLA)-identical sibling donor, and stage of disease. It is preferable for donors to have an HLA type that is identical to the recipient due to the potential for increased complications such as graft rejection and graft-versus-host disease; however, only about one-third of individuals who might otherwise be eligible for allogeneic HSCT have an HLA-matched sibling donor. Especially for individuals with high-risk disease, additional appropriate donor sources may include HLA-matched unrelated and HLA partially-matched related donors.

A boost of hematopoietic progenitor or stem cells, also referred to as a hematopoietic stem-cell infusion (HSCI) may be used to facilitate more rapid hematopoietic recovery, graft loss, or loss of chimerism following HSCT. The cell product used for a boost may be a previously cryopreserved cell product that contains stem cells or may alternatively require the donor to undergo additional evaluation, mobilization, and harvest. A boost is not preceded by a preparative regimen, and may be required when additional conventional chemotherapy is given to treat relapse and reestablish remission after transplantation. Prolonged cytopenias and immunosuppression may result, requiring additional HSCI which is typically given days to weeks after reinduction chemotherapy (LeMaistre, 2013).

Contraindications to HSCT

Many factors affect the outcome of hematopoietic stem-cell transplantation; 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 transplantation. 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

Allogeneic Hematopoietic Stem-Cell Transplantation (HSCT) for Myelofibrosis: The utility of myeloablative allogeneic HSCT 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 (Mascarenhas, 2012). 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). The use of this therapy is also noted to be a standard treatment option by the National Cancer Institute (2013) for the treatment of selected individuals with myelofibrosis.

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 (Mascarenhas, 2012; Kroger, 2007; Tanner, 2007; Barosi, 2006; Clark, 2004; Tefferi, 2008). Successful transplantation is associated with gradual resolution of marrow fibrosis and normalization of hematopoiesis (Mascarenhas, 2012). Several retrospective analyses have demonstrated improved outcomes with the use of allogeneic HSCT, with estimated one-, three-, and five-year overall survival rates of 56–61%, 41–58%, 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; Stewart, 2010; Patriarca, 2008; Karrabul, 2007; Ditschkowski, 2004; Deeg, 2003; Daly, 2003).

The high treatment-related mortality (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 (Papageorgiou, 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 disease-free- and three-year overall survival rates of 67% and 31–83%, respectively (Stewart, 2010; 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 hematopoietic stem-cell transplantation (HSCT) appears to be an acceptable therapeutic option for patients with myelofibrosis (Mascarenhas, 2012).

Autologous HSCT: 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 (Mascarenhas, 2012).

Professional Societies/Organizations

National Marrow Donor Program (NMDP): The NMDP (1996–2013) notes that agnogenic myeloid metaplasia as a condition that is treatable by allogeneic HSCT.

National Cancer Institute (NCI): The NCI (2013) notes that allogeneic peripheral stem cell or bone marrow transplantation is a treatment option for primary myelofibrosis.

Summary for Myelofibrosis: Although randomized controlled clinical trial data are limited allogeneic stem-cell transplantation is supported by professional organization guidelines and is considered an acceptable treatment option as a second-line therapy for the treatment of myelofibrosis.

Polycythemia Vera (PV)

This disorder which is also called polycythemia rubra vera, is a rare, acquired, chronic myeloproliferative neoplasm resulting from a mutation to a single hematopoietic stem cell in the marrow (Means, 2009). Less common synonyms include splenomegalic polycythemia, Osler disease, polycythemia with chronic cyanosis, and myelopathic polycythemia. It is the most common primary polycythemia.

Median duration of survival is fifteen years after diagnosis; life expectancy is nearly normal in the first decade of the disease. After a number of years, the disease frequently becomes inactive (i.e., spent phase); about 20% of individuals may no longer suffer from the sequelae of excessive red cell production. If the excessive production of red blood cells and platelets can be controlled, prolonged survival usually results; however, the natural history of the disorder is characterized by a lifelong propensity for thrombotic complications and late-onset disease transformation into both myelofibrosis and acute myeloid leukemia (AML) (Tefferi, 2008; Hoffman, 2012). Phlebotomy is the cornerstone of treatment for PV and is the only treatment modality that has improved survival in affected patients (Tefferi, 2008).

Hematopoietic Stem-Cell Transplantation (HSCT) for PV

HSCT has been proposed as a potential treatment for PV; however, transplantation during the polycythemic phase of the disease is rarely appropriate (Hoffman, 2012). For those patients in whom myeloid metaplasia with myelofibrosis develops or the disease evolves to acute myelogenous leukemia (AML), HSCT may be investigated as a possible treatment option at that time. For additional information regarding HSCT for AML please refer to the Cigna Coverage Policy Stem-Cell Transplantation for Acute Myelogenous Leukemia.

Literature Review

There are scarce data in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for PV. Available studies are limited by uncontrolled design, small participant populations, heterogeneous patient selection criteria, and a lack of long-term outcomes data.

Professional Societies/Organizations

Hematopoietic stem-cell transplantation is not mentioned as a treatment option for polycythemia vera by the National Cancer Institute Chronic Myeloproliferative Disorders Treatment PDQ®.

Summary for Polycythemia Vera: There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of polycythemia vera (PV). At this time the role of HSCT has not yet been established for this indication.

Use Outside of the US

No relevant information.

Summary

Although data are not robust, allogeneic hematopoietic stem-cell transplantation (HSCT) is an accepted treatment option for patients with myelofibrosis who have failed standard treatment and who have relapsed or refractory disease. At present there is insufficient evidence in the published, peer-reviewed scientific literature to determine the safety and effectiveness of autologous HSCT for myelofibrosis. There are scarce data regarding the safety and effectiveness of HSCT for the treatment of polycythemia vera and it is not considered a standard of care. Additionally, professional support in the form of published clinical guidelines are lacking for this indication.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.

- 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary when used to report allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of myelofibrosis:

CPT®* Codes	Description
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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

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

Experimental/Investigational/Unproven/Not Covered when used to report autologous hematopoietic stem-cell transplantation (HSCT) for the treatment of myelofibrosis:

CPT®* Codes	Description
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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

HCCPS 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

Experimental/Investigational/Unproven/Not Covered when used to report hematopoietic stem-cell transplantation (HSCT) for the treatment of polycythemia vera (PV):

CPT* Codes	Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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
38232	Bone marrow harvesting for transplantation, autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCCPS Codes	Description
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

*Current Procedural Terminology (CPT®) ©2013 American Medical Association: Chicago, IL.

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