



CIGNA MEDICAL COVERAGE POLICY

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

Subject Stem-Cell Transplantation for Amyloidosis

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Hyperlink to Related Coverage Policies

Stem-Cell Transplantation for Multiple Myeloma and POEMS Syndrome

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers autologous hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of primary systemic (i.e., amyloid light-chain [AL]) amyloidosis when ALL of the following criteria are met:

- Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (i.e., at a minimum, ambulatory and able to perform most, if not all, self-care)
- ≤ two organs significantly involved with amyloid
- asymptomatic or compensated cardiac function (i.e., absence of congestive heart failure, echocardiographic left ventricular ejection fraction > 30%, interventricular septal thickness < 15 mm)–
- adequate pulmonary status as noted on pulmonary function testing, oxygen saturation results on room air and a DLCO > 50% predicted
- adequate liver function (i.e., bilirubin < 3.0 mg/dL)
- adequate renal function (i.e., creatinine clearance > 51 ml/min, serum creatinine ≤ 2.0 ml/dL)
- absence of severe or multiple comorbidities that would increase risk of poor result or death

CIGNA does not cover second autologous HSCT for the treatment of recurrent or refractory AL amyloidosis because it is considered experimental, investigational or unproven.

CIGNA does not cover the following procedures for the treatment of AL amyloidosis because they are considered experimental, investigational or unproven (this list may not be all-inclusive):

- tandem autologous HSCT
 - allogeneic HSCT
-

General Background

Amyloidosis is a group of diseases characterized by the deposit of insoluble protein into peripheral nerves and visceral organs such as the kidney, heart, liver, and spleen, with related end-organ dysfunction. It is clinically classified as either systemic or localized; systemic amyloidosis is subclassified as primary (when associated with a plasma-cell dyscrasia), secondary (when it occurs as a result of a chronic inflammatory condition) or hereditary (familial). Patients with primary systemic amyloidosis (i.e., amyloid light-chain [AL] amyloidosis) not only have a hematologic malignancy, but also present with progressive dysfunction of one or more organs (Palladini, 2009).

Survival varies greatly depending on the dominant organ that is involved-with cardiac amyloid having the worst outcome-, and the number of major organs that are affected (Gertz, 2008). Untreated individuals have a median survival of 10 months to two years (Santhorawala, 2007; Lebowitz and Morris, 2003). The presence of symptomatic congestive heart failure is associated with a median survival of 4–6 months and is the single most important predictor of poor outcome (Gertz, 1999).

Most conventional strategies for AL amyloidosis remain unsatisfactory with conventional chemotherapy yielding only moderate efficacy (Frossard, 2008). Stem-cell transplantation has been proposed for the treatment of primary systemic AL amyloidosis.

Stem-Cell Transplantation

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

Autologous HSCT: Remission of the effects of amyloidosis on organs can be achieved with autologous HSCT in approximately 50%–75% of patients treated with such therapy (Rajikumar, 2008; Bird, 2006; Gertz, 2004). Median survival rates for individuals eligible for transplantation are 40 months compared with 18 months for those not eligible for transplantation (Gertz, 2008). One- and two-year overall survival (OS) rates are 69%–89%, and 62%–81%, respectively (Perz, 2006; Vesole, 2006; Skinner, 2004; Dispenzieri, 2001).

Several prospective case series and retrospective studies have demonstrated higher complete response rates in addition to improved outcomes after high-dose chemotherapy and autologous HSCT, in selected subgroups with AL amyloidosis (Santhorawala, 2007; Dispenzieri, 2006; Vesole, 2006; Gertz, 2004; Skinner, 2004); however, in a single randomized controlled trial involving 100 individuals (Jaccard, 2007), hematologic complete response rates were not improved with HSCT compared with conventional chemotherapy although results were not statistically significant (36% versus 52%). OS was higher in the conventional chemotherapy group (56.9 months versus 22.2 months, respectively). The authors noted that one explanation for the relatively poor results using high-dose melphalan was the high mortality rate before and after the intensive treatment. Additionally, the time required to collect stem cells for the transplantation procedure resulted in a delay of treatment of approximately one month for the patients in the transplantation group compared to the non-transplantation arm.

Autologous HSCT is associated with risks of higher morbidity and mortality than stem-cell transplantation for other disorders. Data in the peer-reviewed scientific literature are not robust; nonetheless, it is considered to be an accepted treatment option for rescue of high-dose chemotherapy for a highly selected subset of individuals with AL amyloidosis.

Use of tandem and second HSCT has also been proposed for the treatment of refractory or recurrent AL amyloidosis. These therapies involve performing multiple cycles of chemotherapy and HSCT, either as part of an established protocol of therapy; usually within three to six months of the initial transplantation, or as disease progression or relapse occurs. Data are lacking in the published, peer-reviewed scientific literature regarding the

safety and effectiveness of these therapies for AL amyloidosis. Although a research interest, the role of second or tandem autologous HSCT has not been established.

Allogeneic HSCT: Data are lacking in the peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic HSCT for AL amyloidosis. According to the UK Myeloma Forum AL Amyloidosis Guidelines Working Group (2004) this treatment is appropriate for use in clinical trials only, as it is likely to be associated with extremely high treatment-related mortality. Whether this therapy offers improved outcomes over conventional chemotherapy for patients with AL amyloidosis is unknown. The role for this therapy in the treatment of AL amyloidosis has not been established.

Contraindications

Although improved responses have been reported in the peer-reviewed scientific literature, autologous HSCT is not considered an appropriate therapy for every individual with AL amyloidosis. The presence of any significant comorbid condition which would significantly compromise clinical care and chances of survival is a contraindication to transplantation. Strict patient selection criteria are required to increase the chances for success in individuals with AL (Gertz, 2008; Rajikumar, 2008; Gono, 2004; British Committee for Standards in Haematology [BCSH], 2004). Individuals are highly selected on the basis of age, performance status, the number of organs involved with amyloidosis, absence of severe cardiomyopathy, and the presence of preserved renal function.

Several risk factors predicting outcome have been identified. The significant visceral organ dysfunction that occurs with amyloid puts patients at high risk for complications and the number of organs affected at the time of transplantation is an important predictor of outcome (Gertz, 2008). Persons with two affected organs have a median survival of 55 months while those with three or more affected organs have a median survival of 25.5 months. Cardiac involvement (i.e., congestive heart failure, left ventricular ejection fraction <30%, interventricular septal thickness >15 mm), poor renal function (i.e., reduced glomerular filtration rate, creatinine clearance < 51 ml/min, serum creatinine >2.0 mg/dL, high-proteinuria), advanced age, poor Eastern Cooperative Oncology Group (ECOG) performance status, multiorgan involvement and elevated liver function tests (i.e., bilirubin >3.0 mg/dL) are considered risk factors for poor outcome (Gertz, 2008; Bird, 2006). Poorer outcomes are also seen in individuals who are already dialysis-dependent (Comenzo, 2002). In addition, the presence of human immunodeficiency virus or an active form of hepatitis B or C, other human T-cell lymphotropic virus (HTLV)-1 is considered a relative contraindication to transplantation.

Causes of treatment-related mortality in AL include gastrointestinal tract bleeding, cardiac rhythm disturbances, and multiorgan failure (Gertz, 2008). Despite stringent patient-selection criteria; treatment-related mortality can range from 12% to 43% in certain subsets of patients (Leung, 2005; Dispenzieri, 2004).

Professional Societies/Organizations

National Cancer Institute: The NCI (2010) reviews the results of various studies of high-dose chemotherapy followed by autologous HSCT for patients with AL amyloidosis. It notes that a randomized trial confirming the benefit of autologous transplantation is not anticipated.

British Committee for Standards in Haematology (BCSH): Guidelines published on behalf of the BCSH by the Guidelines Working Group of the United Kingdom Myeloma Forum (2004) note that high-dose therapy and autologous peripheral blood stem-cell transplantation (PBSCT) can result in reversal of the clinical manifestations of AL amyloidosis in up to approximately 60% of patients who survive the procedure. This is associated with regression of AL deposits on scanning, reduction or elimination of the causative clonal plasma cell disorder and improved performance status and quality of life for patients. However, the efficacy of peripheral blood stem-cell transplantation in AL amyloidosis has not been investigated in any controlled comparative study, and procedure-related mortality has been consistently and substantially higher among patients with amyloid than those with multiple myeloma. The Guidelines note that high-dose therapy and peripheral blood stem cell transplantation is not recommended in patients with symptomatic cardiac amyloid, symptomatic autonomic neuropathy; history of GI bleeding due to amyloid; dialysis-dependent renal failure; age > 70 years; or more than two organ systems involved. The Guidelines also note that peripheral blood stem cell transplantation may be considered in other selected patients, including good-risk patients (no cardiac involvement, one to two organs involved and glomerular filtration rate >50 ml/min), patients treated with vincristine, doxorubicin, dexamethasone (VAD) or other initial therapy who have not responded; and patients with early relapse of plasma cell dyscrasia after VAD or other treatment. According to the Forum a small proportion of patients may derive significant

clinical benefit from allogeneic HSCT but at present it remains experimental and is likely to be associated with extremely high treatment-related mortality. According to the Forum, there are currently no data on the use of reduced-intensity conditioning in AL amyloidosis.

The National Comprehensive Cancer Network Network™ (NCCN™): NCCN guidelines (2010) note “Treatment of systemic light chain amyloidosis should be in a clinical trial because data are insufficient to identify optimal treatment of the underlying plasma cell disorder. Treatment options include intermediate or high-dose melphalan therapy with stem-cell transplantation.” The Guideline further notes “This option may not be applicable to all. Patients have to be carefully selected as it is associated with significant treatment-related mortality”

Summary

Although data are limited, a single autologous hematopoietic stem-cell transplantation (HSCT) is an accepted treatment option for a carefully selected subset of individuals with primary systemic (AL) amyloidosis. There is insufficient evidence to support the safety and effectiveness of allogeneic HSCT and at this time, the role of this therapy has not been established. Although second or tandem autologous HSCT for the treatment of AL amyloidosis remains a focus of ongoing research, there is insufficient evidence to support this therapy for the treatment of AL amyloidosis.

Coding/Billing Information

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

Covered when medically necessary:

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
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38211	Transplant preparation of hematopoietic progenitor cells; tumor 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
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous

HCPCS 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 or pre-and post-transplant care in the global definition

[†]**Note:** Covered when medically necessary when used to report autologous bone marrow or blood-derived stem cell procedures.

ICD-9-CM Diagnosis Codes	Description
277.30	Amyloidosis, unspecified
277.39	Other amyloidosis

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic

*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	11/15/2007	0241	Stem-Cell Transplant for Amyloidosis
Great-West Healthcare	4/23/2007	05.288.02	Bone Marrow Transplantation (BMT) for AL (Primary) Amyloidosis

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