



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 Multiple Myeloma and POEMS Syndrome

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- Umbilical Cord Blood Banking

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Coverage Policy

CIGNA covers an autologous hematopoietic stem-cell transplantation (HSCT) following high-dose chemotherapy as medically necessary for EITHER of the following conditions:

- stage II, stage III or refractory/recurrent multiple myeloma (MM)
- POEMS syndrome

CIGNA covers a second (tandem) autologous HSCT as medically necessary following a less than very good partial response (VGPR)* to the initial autologous HSCT.

*very good partial response includes the following:

- serum and urine M-protein detectable by immunofixation but not on electrophoresis or
- 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 hours

CIGNA covers myeloablative allogeneic HSCT from a human leukocyte antigen (HLA)-matched donor (i.e., at least five of six match of the HLA-A, HLA-B, and HLA-DRB1 antigens) as medically necessary for the treatment of stage II, stage III or refractory/recurrent MM.

CIGNA covers non-myeloablative allogeneic HSCT from an HLA-matched donor (i.e., at least five of six match of the HLA-A, HLA-B, and HLA-DRB1 antigens) as medically necessary when BOTH of the following conditions are met:

- stage II, stage III or refractory/recurrent MM
 - following less than complete response or progressive disease after a previous myeloablative HSCT
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General Background

Multiple Myeloma

Multiple myeloma (MM) is one of several types of plasma cell neoplasms, and is associated with a myeloma protein. Treatable, but rarely curable, this disease is usually progressive and is characterized by renal failure, lytic bone lesions, anemia and hypercalcemia. With standard dose chemotherapy, median survival is 24–30 months; 10-year survival is 3% (National Cancer Institute [NCI], 2011).

MM is staged by several systems, including the Durie-Salmon staging system, which is based on the amount of abnormal monoclonal immunoglobulin in the blood or urine; blood calcium levels; the amount of bone damage shown by x-ray; and blood hemoglobin levels, and the International Staging System which relies on the levels of albumin and beta-2-microglobulin in the blood (NCI, 2011; Reece, 2005).

Treatment is based on stage of disease and risk stratification. The failure of conventional therapy to cure MM has led to the study of dose intensification, with stem-cell support.

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells from a donor into a patient. 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).

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.

Initial Hematopoietic Stem-Cell Transplantation (HSCT)

Autologous HSCT: High-dose chemotherapy (HDC) with autologous HSCT remains the treatment for MM associated with the highest complete remission rate (Giralt, 2009). A number of randomized controlled trials (RCT), prospective nonrandomized comparisons and systematic reviews have shown improved overall survival (OS) and/or progression-free survival (PFS) for individuals who received HDC followed by an initial autologous HSCT compared with standard dose chemotherapy options (Barlogie, 2006 [a-c]; Lenhoff, 2006; Child, 2003; Attal, 1996). Although autologous HSCT is not curative, studies demonstrate an improvement in complete response rates and prolongation of median OS by approximately 12 months (Giralt, 2009; Rajkumar, 2008). Other studies have demonstrated variable benefit to high-dose therapy including two meta-analyses of over 3000 persons (Koreth, 2007; Femand, 2005, Levy, 2005, Seregren, 2003).

A number of studies have compared outcomes achieved with the use of HDC and autologous HSCT for individuals who are older versus younger than age 65 and determined that there is no difference in the time to progression or overall survival (Kumar, 2008; Jantunen, 2006) or progression-free survival (Jantunen, 2006) between these groups. According to the National Comprehensive Cancer Network® ([NCCN®]; 2011), advanced age is not a contraindication to transplantation.

Summary

Despite conflicting evidence regarding the benefit of autologous HSCT in various subgroups, an initial autologous HSCT is considered a standard treatment option for many patients with MM (Bensinger, 2006).

Myeloablative Allogeneic HSCT: The advantages of myeloablative allogeneic HSCT include a lack of graft contamination with tumor cells and the presence of a graft-versus-myeloma effect, which may provide long-term disease control and result in a cure rate of 10-20% (Rajkumar, 2008; Rotta, 2008; Bensinger, 2006). Unfortunately, only a small percentage of individuals are eligible for a fully ablative transplantation due to age, availability of an appropriate donor, and adequate organ function (Rajkumar, 2008; Rotta, 2008). For those

patients who have human leukocyte antigen (HLA)-matched donors and are without comorbidities, this therapy may be an appropriate treatment option.

Historically, single myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) for patients with multiple myeloma (MM) has been associated with a transplant-related mortality (TRM) between 10% and 60%; however, improved patient selection criteria and chemotherapy regimens have resulted in a decrease to approximately 20% (NCI, 2011; Vesole, 2009). In prospective case series and retrospective studies, two-, five-, and 10-year overall survival (OS) rates were 51%, 41-48%, and 39.9%, respectively, while two- and five-year event-free survival (EFS) rates were 35% and 33.3%, respectively (Kuruville, 2007; Crawley, 2006; Kennedy, 2006). Allogeneic HSCT has also been compared with autologous HSCT with no significant difference between TRM at one year for allogeneic and autologous transplantation ($p=0.21$) or cumulative incidence of relapse at ten years ($p=0.10$) (Kuruville, 2007).

Summary

Although TRM remains high, the published, peer-reviewed scientific literature supports the effectiveness of myeloablative allogeneic HSCT for selected individuals.

Non-Myeloablative Allogeneic HSCT: The high TRM associated with myeloablative allogeneic HSCT has been the impetus for investigation of reduced-intensity or non-myeloablative conditioning regimens designed to allow engraftment of allogeneic stem cells (Bensinger, 2006). Non-myeloablative conditioning is infrequently used as first-line therapy. Although the use of reduced-intensity conditioning compared with myeloablative conditioning is associated with lower nonrelapse mortality, it does not translate into improved OS due to the higher relapse rate associated with reduced-intensity conditioning (Gahrton, 2007).

Summary

Although promising, at this time the role of non-myeloablative allogeneic HSCT as first-line therapy has not been established for this indication.

Second Hematopoietic Stem-Cell Transplantation (HSCT)

Multi-institutional trials demonstrating that initial HSCT prolongs remission duration and survival but is not curative has led to the exploration of whether a second HSCT should be used early after diagnosis (i.e., tandem, generally within six-months after initial transplantation therapy) or its use delayed as a treatment for relapsed or progressive myeloma (Munshi, 2008). Evidence regarding the effectiveness of tandem autologous HSCT versus a single HSCT is conflicting. As a result, the timing of second transplantation is somewhat controversial (Kumar, 2009; Rajikumar, 2008).

Autologous HSCT: Several randomized controlled trials (RCTs) have demonstrated improved response rates (47% versus 33%, respectively) and OS rates (42% versus 21%, respectively) with the use of tandem compared with single autologous transplantation (Bruno, 2007; Cavo, 2007; Attal, 2003). However, the benefit of a second autologous HSCT was restricted to patients who failed to achieve a complete, or very good partial response (e.g., >90% reduction in M protein level) with the first procedure (Rajikumar, 2008; Attal, 2007). A subgroup of individuals who achieved a very good partial response or better response with the first transplantation did not significantly benefit from the second HSCT. OS and event-free survival rates in other studies were not improved (Abdelkelfi, 2008; Rosinol, 2008; Garbon, 2006).

In a meta-analysis and systematic review by Kumar et al. (2009), response rates were significantly increased with tandem autologous HSCT compared with single autologous HSCT ($p=.004$); however, patients treated with tandem autologous HSCT did not have better OS ($p=.533$) or EFS ($p=.14$) compared with single autologous HSCT. The use of tandem autologous HCT was also associated with a statistically significant increase in TRM ($p=0.03$). The authors noted that none of these studies stratified patients according to biologic and genomic risk factors that have been proposed to affect prognosis of patients with multiple myeloma (MM); therefore, it is not known whether a benefit in OS may exist for use of tandem HSCT in patient subgroups.

In a RCT by Abdelkelfi (2008), use of tandem autologous HSCT was noted to result in a significant increase in TRM. Individuals with de novo symptomatic MM were randomly assigned to receive either tandem transplantation upfront (i.e. planned second autologous HSCT followed within six months of first HSCT) or one autologous HSCT followed by six months of maintenance therapy beginning at three months after transplantation. Response rates were similar in both groups (40% and 41%, respectively) at three months after

transplantation. With a median follow-up of 33 months, three-year overall survival (OS) was 65% in the group receiving tandem hematopoietic stem-cell transplantation (HSCT) and 85% for the group receiving a single transplantation followed by maintenance therapy (p=0.04). Three-year progression-free survival was 57% and 85%, respectively (p=0.02).

Summary

Despite conflicting results regarding safety and effectiveness, the use of a second autologous HSCT is considered an accepted therapy for the treatment of selected individuals with MM who have a less than very good partial response (VGPR) to initial transplantation.

Non-Myeloablative Allogeneic HSCT: A graft-versus-myeloma effect has been identified with allogeneic HSCT. Allogeneic graft-versus-tumor effects can be used with some success in patients with hematologic malignancies who have exhausted other treatment options, including high-dose therapy with autologous stem-cell rescue. Non-myeloablative conditioning has been investigated as therapy for individuals who have previously received an initial or subsequent autologous HSCT or initial allogeneic HSCT. Several studies demonstrate an increase in response rate, and a trend toward improved OS (Vesole, 2009; Garban, 2006; Martino, 2006; Maloney, 2003); although relapse rates continue high post allogeneic HSCT (Rotta, 2008; Eom, 2006). Long-term disease control, graft-versus-host-disease, and relapse rates remain key issues.

Summary

Non-myeloablative allogeneic HSCT is an appropriate treatment option when used for selected patients with a less than complete response or progressive disease following a previous myeloablative HSCT. Several prospective controlled trials and retrospective studies demonstrated higher response rates, a trend toward longer progression-free survival, and improved OS (Rosinol, 2008; Bruno, 2007; Baron, 2006; Badros, 2002).

POEMS Syndrome

POEMS syndrome is an extremely rare plasma cell disorder associated with monoclonal gammopathy of undetermined significance; however, the exact etiology is unknown. The term 'POEMS' is an acronym of the most common symptoms: polyneuropathy, organomegaly, endocrinopathy, M proteins and skin changes. POEMS syndrome been variously referred to in the literature as osteosclerotic myeloma, Crow-Fukase syndrome, PEP (plasma cell dyscrasia, endocrinopathy, polyneuropathy) syndrome, and Takatsuki syndrome (Laurenti, 2008). With only several hundred cases documented it is likely that the incidence is higher because of undiagnosed cases. For patients with widespread osteosclerotic lesions, treatment is similar to that for multiple myeloma. Effective treatment of the underlying plasma cell disorder controls the disease and results in dramatic reversal of symptoms. In eligible patients, autologous HSCT has provided significant responses and have more recently been used to treat this disease (Dispenzieri, 2008; Rajkumar, 2008).

As POEMS syndrome is associated with plasma cell disorders, it may respond to high-dose chemotherapy and autologous HSCT. As the syndrome is rare, it is unlikely that randomized controlled trials of sufficient size will become available. In several small case series, slow, but progressive improvement of neurological involvement and performance status was noted after autologous HSCT (Laurenti, 2008; Dispenzieri, 2008; Kuwabara, 2006; Dispenzieri, 2004; Jaccard, 2002).

Summary

Although data are not robust, autologous HSCT has resulted in clinical improvement in patients with POEMS syndrome, and it is considered a reasonable option for selected patients.

Contraindications to HSCT

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 transplantation. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)

- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Professional Societies/Organizations

National Cancer Institute (NCI): The NCI (2011) discusses the results of various clinical trials and notes that while some prospective randomized trials such as the U.S. Intergroup trial (i.e., SWOG-9321), have shown improved survival for patients who received autologous peripheral stem cell or bone marrow transplantation after induction chemotherapy versus chemotherapy alone, other trials have not shown any survival advantage. The NCI also notes that another approach to high-dose therapy has been the use of two sequential episodes of high-dose therapy with stem cell support (tandem transplant). Regarding the use of allogeneic HSCT, the NCI notes that a definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes. Allogeneic stem-cell transplantation has highly toxic effects with 15%–40% mortality; however, the possibility of a graft-versus-myeloma reaction makes this therapy attractive. Non-myeloablative allogeneic stem-cell transplantation is under development.

National Comprehensive Cancer Network Guidelines™ (NCCN Guidelines™) (2011): Published guidelines note all types of stem-cell transplantations are appropriate in different clinical settings. Regarding allogeneic HSCT, the Guidelines do not distinguish between myeloablative and non-myeloablative conditioning for allogeneic hematopoietic stem-cell transplantation (HSCT). “Allogeneic HSCT may be an accepted option in the setting of a clinical trial in patients with responsive or primary progressive disease, or as salvage therapy in patients with progressive disease following an initial autologous HSCT.” Regarding the use of autologous HSCT, the Guidelines note that “Autologous HSCT results in high response rates and remains the standard of care following induction therapy for eligible patients. Autologous HSCT results in high response rates and remains the standard of care following induction therapy for eligible patients.” The guidelines indicate autologous HSCT is an option for treatment of primary progressive or refractory disease post induction treatment. The algorithms also identify two situations where a repeat salvage autologous HSCT is recommended: “ In patients initially treated with induction therapy alone, followed by an autologous HSCT when the disease relapsed, who now have progressive disease following a first autologous HSCT” and “ In patients with initial CR or near CR to an initial single autologous HSCT who develop progressive disease.”

National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow

Transplantation (ASBMT) (2009): Transplantation referral guidelines note that referral for evaluation for HSCT should take place after initiation of therapy and at first progression.

International Myeloma Working Group (IMWG) (2009): On behalf of the IMWG, Durie et al. (2006) published uniform response criteria to assess clinical outcomes in myeloma. The International Response Criteria for multiple myeloma, also known as the International Myeloma Working Group uniform response criteria includes categories for stringent complete response (sCR), complete response (CR), very good partial response (VGPR), and partial response (PR). According to the IMWG, failure to achieve VGPR correlates with inferior outcome. Criteria for this category include serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours.

A consensus statement published by Giralt (2009) notes that high-dose melphalan is still recommended for eligible patients, stem cell collection early in the course of therapy should be attempted in all transplant eligible patients, and that double autologous transplantation has a place in clinical trials, primarily in younger patients. The guidelines also note that allografting should continue to be explored in the context of clinical trials in carefully selected patients as frontline therapy or as salvage therapy.

United Kingdom Myeloma Forum, the Nordic Myeloma Study Group, and the British Committee for Standards in Haematology (2005): On behalf of these professional societies, Smith et al. published guidelines for the diagnosis and management of multiple myeloma (MM). Regarding use of autologous HSCT, the guidelines note that high-dose chemotherapy with autologous HSCT should be part of the primary treatment strategy in newly diagnosed patients with adequate performance status and organ function. Allogeneic HSCT with human leukocyte antigen-matched sibling donors may also be considered in patients up to the age of 50 years who have achieved at least a partial remission after initial therapy. Reduced-intensity conditioning followed by allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered in patients up to age

70 years with a human leukocyte antigen-matched sibling donor. The procedure would usually follow an initial autologous HSCT, be done early in the disease phase, and should always be done as part of a clinical trial.

Summary

The published, peer-reviewed medical literature supports the effectiveness of autologous and allogeneic hematopoietic stem-cell transplantation (HSCT) in the treatment of multiple myeloma for selected individuals.

POEMS syndrome is a rare plasma disease which is unlikely to be studied in large, randomized controlled clinical trials. Resulting in clinical improvement in patients with POEMS syndrome, autologous HSCT is a reasonable treatment option for selected individuals.

Coding/Billing Information

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

Covered when medically necessary:

CPT®*	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
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
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
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
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
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
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

ICD-9-CM Diagnosis Codes	Description
203.00	Multiple myeloma without mention of remission
203.01	Multiple myeloma in remission
273.1	Monoclonal paraproteinemia
273.9	Unspecified disorder of plasma protein metabolism

*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	4/15/2008	0294	Stem-Cell Transplant for Multiple Myeloma and POEMS Syndrome
Great-West Healthcare	7/19/2007	05.290.03	Bone Marrow Transplantation (BMT) for Multiple Myeloma

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