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MEDICAL POLICY – 8.01.17

Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

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Introduction

Plasma cells are a special type of white blood cell. They are made in the bone marrow, and they make antibodies to fight viral and bacterial infections. Multiple myeloma and POEMS syndrome are two types of bone marrow cancer that affect the plasma cells. These cancers may be treated with various medications and chemotherapy. Sometimes a person may be given a very high dose of chemotherapy followed by a hematopoietic cell transplant. This policy describes when a hematopoietic cell transplant may be medically necessary as part of the treatment of multiple myeloma and POEMS syndrome.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Transplant	Medical Necessity
Multiple Myeloma	
A single or second (salvage) autologous hematopoietic cell transplantation	A single or second (salvage) autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma.
Tandem autologous hematopoietic cell transplantation	Tandem autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma in individuals who fail to achieve at least a near-complete or very good partial response (see Additional Information below) after the first transplant in the tandem sequence. Tandem transplantation with an initial autologous hematopoietic cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered medically necessary to treat individuals with newly diagnosed multiple myeloma.
POEMS Syndrome	
Autologous hematopoietic cell transplantation	Autologous hematopoietic cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome (see Additional Information below).

Transplant	Investigational
Multiple Myeloma	
Initial allogeneic hematopoietic cell transplantation	Allogeneic hematopoietic cell transplantation, myeloablative or nonmyeloablative, as initial therapy of newly diagnosed multiple myeloma or as salvage therapy, is considered investigational.
POEMS Syndrome	
Allogeneic and tandem hematopoietic cell transplantation	Allogeneic and tandem hematopoietic cell transplantation are considered investigational to treat POEMS syndrome.

Additional Information

- The International Working Group on Myeloma has updated the European Group for Blood and Marrow Transplant criteria to describe a complete response to multiple myeloma therapy. The criteria include negative immunofixation on the serum and urine; disappearance of soft tissue plasmacytomas; and 5% or fewer plasma cells in bone marrow aspiration.
- Very good partial response is described as serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
- Individuals with disseminated POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes) may have diffuse sclerotic lesions or disseminated bone marrow involvement.

Documentation Requirements

The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- Prior treatment (if any) individual has received

Coding

Code	Description
CPT	
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. POEMS syndrome, characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes, is a rare, paraneoplastic disorder secondary to a plasma cell dyscrasia. Plasma cell dyscrasias are treatable but rarely curable. In some cases, autologous or allogeneic hematopoietic cell transplantation (HCT) is considered as therapy.

Background

Multiple Myeloma

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 18% of all hematologic cancers in the United States. It is treatable but rarely curable. At diagnosis, most individuals have generalized disease, and the selection of treatment is influenced by the individual's age, general health, prior therapy, and the presence of disease complications.[1-4]

The disease is staged by estimating tumor mass, based on various clinical parameters such as hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure. MM usually evolves from an asymptomatic premalignant stage (termed monoclonal gammopathy of undetermined significance). Treatment is usually reserved for individuals with symptomatic disease (usually progressive myeloma), whereas asymptomatic individuals are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival when compared with therapy delivered at the time of symptoms or end-organ damage.[1,2] In some individuals, an intermediate asymptomatic but more advanced premalignant stage is recognized and referred to as smoldering MM. The overall risk of disease progression from smoldering to symptomatic MM is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% for the next 10 years.[1,2]

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takatsuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma-cell dyscrasia.[5,6] This complex, multiorgan disease was first described in 1938, but the acronym POEMS was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.[7] No single test establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence has suggested it is mediated by an imbalance of proinflammatory cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved.[6,8] However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in **Table 1**.[9] Both mandatory major criteria, at least one of the other major criteria, and at least one of the minor criteria are necessary for diagnosis.

Table 1: Criteria and Associations for POEMS Syndrome

Mandatory Major Criteria	Other Major Criteria	Minor Criteria	Other Symptoms and Signs
Polyneuropathy	Castleman disease	Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)	Pulmonary hypertension/restrictive lung disease
Monoclonal plasma-proliferative disorder	Sclerotic bone lesions	Extravascular volume overload (edema, pleural effusion, ascites)	Clubbing
	Vascular endothelial growth factor elevation	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)	Thrombotic diatheses
		Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)	Weight loss
		Papilledema	Low vitamin B_{12}levels
		Thrombosis/polycythemia	Diarrhea
			Hyperhidrosis

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.[10] Other large series had been described in the United States, France, China, and India.[9] In general, individuals with POEMS have superior overall survival compared with that of MM (nearly 14 years in a large series).[8] However, given the rarity of POEMS, there is a paucity of randomized controlled trial (RCT) evidence for POEMS therapies.[9] Numerous approaches have been tried, including ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, corticosteroids, alkylating agents, tamoxifen, trans-retinoic acid, and high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) support. Optimal treatment involves eliminating the plasma cell clone (e.g., by surgical excision or local radiotherapy for an isolated plasmacytoma), or systemic chemotherapy in individuals with disseminated disease (e.g., medullary disease or multiple plasmacytomas). Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, have also been investigated.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect in this procedure is

due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to individuals who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and an individual's condition. Individuals who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this policy, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

Multiple Myeloma Treatment Overview

In the prechemotherapy era, the median survival for an individual diagnosed with MM was approximately 7 months. After the introduction of chemotherapy (e.g., the alkylating agent melphalan in the 1960s), prognosis improved, with a median survival of 24 to 30 months and 10-year survival of 3%. In a large group of individuals with newly diagnosed MM, there was no difference in overall survival reported during a 24-year period from 1971-1994, with a trend toward improvement during 1995-2000, and a statistically significant benefit in overall survival during 2001-2006.[2] These data suggested that autologous HCT was responsible for the trends during 1994-2000, while novel agents have contributed to the improvement since 2001.

The introduction of novel agents and better prognostic indicators has been the major advances in the treatment of this disease.[11] Novel agents such as the proteasome inhibitors (e.g., bortezomib), the monoclonal antibody daratumumab, and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed and refractory myeloma and now have been integrated into first-line regimens.[11-13] With the introduction of these novel treatments, it is now expected that most individuals with MM will respond to initial therapy, and only a small minority will have refractory disease.[14]

Summary of Evidence

Newly Diagnosed Multiple Myeloma (MM)

For individuals who have newly diagnosed multiple myeloma who receive autologous hematopoietic cell transplantation (HCT) as initial treatment, the evidence includes reviews, a retrospective study, several prospective, RCTs that compared high-dose chemotherapy plus autologous HCT to standard chemotherapy regimens or regimens containing newer MM agents, and systematic reviews. The relevant outcomes are overall survival and treatment-related morbidity. In general, the evidence has suggested overall survival rates are improved with autologous HCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes, and inconsistency in reporting or collecting outcomes. Recent RCTs comparing high-dose chemotherapy plus autologous HCT to regimens that include novel MM agents have also shown that high-dose chemotherapy plus autologous HCT improves progression-free survival (PFS). Likewise, a systematic review found that autologous HCT plus novel triplet therapy (bortezomib, lenalidomide, and dexamethasone or carfilzomib, lenalidomide and dexamethasone) significantly improves PFS in newly diagnosed MM when compared to triplet therapy alone for

consolidation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have newly diagnosed MM who receive tandem autologous HCT, the evidence includes several RCTs and a systematic review. The relevant outcomes are overall survival and treatment-related morbidity. Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improves overall survival and recurrence-free survival in newly diagnosed MM. Two recent RCTs found conflicting results on the benefit of tandem autologous HCT versus single autologous HCT; however, the study that found no additional benefit with tandem autologous HCT had a higher rate of nonadherence to the second planned HCT. Differences in initial therapy regimens between trials may also have led to conflicting results. In a systematic review, tandem autologous HCT was associated with a significantly higher complete response rate compared to single autologous HCT; however, no significant differences were observed between the groups in PFS, OS, or overall response rate. Several RCTs and one retrospective study compared reduced-intensity conditioning (RIC) allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on genetic randomization (i.e., patients with a human leukocyte antigen-identical sibling were offered RIC allo-HCT following autologous HCT, whereas other individuals underwent either one or two autologous transplants). Although the body of evidence has shown inconsistencies regarding overall survival and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allo-HCT, although at the cost of higher transplant-related mortality compared with conventional treatments. Factors across studies that may account for differing trial results include different study designs, nonuniform preparative regimens, different patient characteristics (including risk stratification), and criteria for advancing to a second transplant. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have newly diagnosed MM who receive allo-HCT as initial or salvage treatment, the evidence includes nonrandomized studies. The relevant outcomes are overall survival and treatment-related morbidity. Studies have reported on individuals with both myeloablative conditioning and RIC. Limitations of the published evidence include patient sample heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes, and inconsistency in reporting or collecting outcomes. Nonmyeloablative allo-HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allo-HCT improves survival better than autologous HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Relapsed or Refractory Multiple Myeloma

For individuals who have relapsed MM after failing an autologous HCT who receive autologous HCT, the evidence includes RCTs, retrospective studies, and reviews summarizing recent studies on a second autologous HCT in relapsed myeloma. The relevant outcomes are overall survival and treatment-related morbidity. Despite some limitations of the published evidence, including patient sample heterogeneity, variability in treatment protocols, and short follow-up periods, the available trial evidence has suggested overall survival rates are improved with autologous HCT compared with conventional chemotherapy or continuous lenalidomide plus dexamethasone in this setting. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have refractory MM after failing a first HCT who receive tandem autologous HCT, the evidence includes systematic reviews and a retrospective study. The relevant outcomes are overall survival and treatment-related morbidity. The evidence has shown tandem autologous HCT improves overall survival rates in this setting. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome

For individuals who have POEMS syndrome who receive HCT, the evidence includes retrospective cohort studies, case reports and case series. The relevant outcomes are overall survival and treatment-related morbidity. No RCTs of HCT of any type have been performed in individuals with POEMS syndrome of any severity, nor is it likely such studies will be performed because of the rarity of this condition. Available case reports and series are subject to selection bias and are heterogeneous concerning treatment approaches and peritransplant support. However, for individuals with disseminated POEMS syndrome, a chain of evidence and contextual factors related to the disease and MM would suggest improvement in health outcomes with autologous HCT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in **Table 2**.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01208662[a]	A Randomized Phase III Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib, and Dexamethasone (RVD) to High-dose Treatment With Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients up to 65 Years of Age	660	Sep 2025
NCT05675319	Allogeneic Stem Cell Transplantation vs. Conventional Therapy as Salvage Therapy for Relapsed / Progressive Patients With Multiple Myeloma After First-line Therapy	482	Mar 2033
Unpublished			
NCT02322320	Continued, Long-Term follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 (BMT CTN #Q07LT)	273 (actual enrollment)	Jun 2019 (Completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate

reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

In response to requests, input was received from one specialty medical society, one academic medical center, and two Blue Distinction Centers for Transplant while this policy was under review in 2017. There was consensus that allogeneic HCT is investigational for newly diagnosed MM and as salvage therapy after primary graft failure and for primary progressive disease.

2013 Input

In response to requests, input was received from three academic medical centers and six Blue Distinction Centers for Transplant while this policy was under review in 2013. There was near-consensus that autologous HCT is medically necessary for POEMS syndrome, and near-consensus that allogeneic and tandem HCT are investigational for POEMS syndrome.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2019, the American Society of Clinical Oncology (ASCO) published practice guidelines for the treatment of MM.[69] The guidelines recommend offering up-front transplant to all eligible individuals, although delayed HCT may be considered in select individuals. Salvage or delayed HCT may be used as consolidation at first relapse in individuals who choose not to proceed with

HCT initially. Tandem autologous HCT and allogeneic HCT (allo-HCT) should not be routinely recommended. However, up-front tandem autologous HCT can be considered for select high-risk individuals or those with a suboptimal response to the initial transplant; allo-HCT may be considered in select high-risk individuals in the context of a clinical trial. For relapsed MM, autologous HCT, if not received after primary induction therapy, should be offered to transplant-eligible individuals. Repeat HCT may be considered in relapsed MM if progression-free survival after the first transplant was 18 months or greater.

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT; now referred to as the American Society for Transplantation and Cellular Therapy) published evidence-based guidelines on the use of HCT in individuals with MM.[70] The ASBMT recognized that much of the evidence from RCTs summarized in the 2015 guidelines came from trials that predated the novel triple-therapy induction regimens. Furthermore, advances in supportive care and earlier disease detection have increasingly influenced decision making and allow individual tailoring of therapy. The ASBMT guidelines did not address POEMS or other plasma cell dyscrasias besides MM.

The ASTCT updated guidance for transplantation and cellular therapies in MM in 2022.[71] The panel endorsed continued use of autologous HCT for individuals with newly diagnosed MM as a standard-of-care option and did not recommend front-line use of allo-HCT and CAR-T outside the setting of a clinical trial. For individuals not undergoing autologous HCT upfront, the panel recommended its use in first relapse. The panel also encouraged allo-HCT in relapsed/refractory MM setting only in the context of a clinical trial.

The ASBMT, and three other groups (2015) published joint guidelines based on an expert consensus conference.[72] These guidelines contained the following recommendations for HCT as salvage therapy:

> … autologous HCT: (1) In transplantation-eligible individuals relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with HCT as part of salvage therapy should be considered standard; (2) High-dose therapy and autologous HCT should be considered appropriate therapy for any individuals relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months; (3) High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT; (4) The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors; (5) Autologous HCT

consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in individuals with short remission (less than 18 months remissions) after primary therapy and (6) Prospective randomized trials need to be performed to define the role of salvage autologous HCT in individuals with MM [multiple myeloma] relapsing after primary therapy comparing to 'best non-HCT' therapy.

Regarding allogeneic HCT… (1) Allogeneic HCT should be considered appropriate therapy for any eligible individual with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or with high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Allogeneic HCT should be performed in the context of a clinical trial if possible; (3) The role of post allogeneic HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in individuals with MM relapsing after primary therapy.

In 2020, the ASTCT published a guideline on indications for HCT and immune effector cell therapy.[73] Regarding plasma cell dyscrasias, the guideline states that MM remains the most common indication for autologous HCT. For rarer plasma cell dyscrasias like POEMS syndrome, autologous HCT may be considered a clinical option on the basis of single-center and registry data. Detailed recommendations in adults can be found in **Table 3**.

Table 3. Summary of Recommendations for Hematopoietic Cell Transplantation in Plasma Cell Disorders Including Multiple Myeloma and POEMS Syndrome

Indication	Allogeneic HCT	Autologous HCT
Myeloma, initial response	D	S
Myeloma, sensitive relapse	S	S
Myeloma, refractory	C	C
POEMS syndrome	N	C
Relapse after autologous transplant	C	C

C: standard of care, clinical evidence available; D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care

International Myeloma Working Group

The 2010 conclusions and recommendations of the International Myeloma Working Group consensus statement on the current status of allo-HCT for MM are as follows: myeloablative allo-HCT may cure a minority of individuals but is associated with a high transplant-related mortality, but could be evaluated in well-designed prospective clinical trials.[74] Nonmyeloablative allo-HCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse, and convincing evidence is lacking that allo-HCT improves survival compared with autologous HCT.

National Comprehensive Cancer Network

Autologous Hematopoietic Cell Transplantation

The National Comprehensive Cancer Network (NCCN) guideline for multiple myeloma (v.1.2025) states that autologous HCT is the preferred option after induction therapy in transplant-eligible individuals, but a delayed HCT after early stem cell collection and storage is appropriate as well (category 1 recommendation).[4] A repeat HCT can be considered for refractory/progressive disease after primary treatment in individuals with prolonged response to initial HCT.

Tandem Hematopoietic Cell Transplantation

The NCCN guideline for multiple myeloma (v.1.2025) recommends collecting enough stem cells for two transplants in younger individuals if tandem transplant or salvage transplant would be considered.[4] A tandem transplant with or without maintenance therapy can be considered for all individuals who are candidates for HCT and is an option for individuals who do not achieve at least a very good partial response after the first autologous HCT and those with high-risk features.

Allogeneic Hematopoietic Cell Transplantation

The NCCN guideline for multiple myeloma (v.1.2025) states the following for allo-HCT: "Allogeneic HCT includes either myeloablative or nonmyeloablative (i.e., "mini" transplant) transplants. Allogeneic HCT has been investigated as an alternative to autologous HCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a

suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population".[4]

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin abnormalities (POEMS) Syndrome

The NCCN guideline for multiple myeloma (v.1.2025) recommends autologous HCT in individuals with POEMS syndrome who are eligible as sole therapy or as consolidation therapy after induction therapy.[4]

Medicare National Coverage

Medicare has the following national coverage determination for the use of HCT for MM.[75]

"Effective … January … 2016, allogeneic HSCT [hematopoietic stem cell transplantation] for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma and participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of preparative/conditioning regimen, graft vs. host disease (GVHD) prophylaxis, donor type and cell source.

A prospective clinical study seeking Medicare coverage for allogeneic HSCT for multiple myeloma pursuant to CED must address the following question:

Compared to individuals who do not receive allogeneic HSCT, do Medicare beneficiaries with multiple myeloma who receive allogeneic HSCT have improved outcomes as indicated by:

- Graft vs. host disease (acute and chronic);
- Other transplant-related adverse events;
- Overall survival; and
- (optional) Quality of life?"

Regulatory Status

The US 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.

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History

Date	Comments
06/12/12	New policy, add to Therapy section. Policy replaces 8.01.507.
09/10/12	Update coding section – ICD-10 codes are now effective 10/01/2014.
11/15/12	Reviewed and recommended by OAP, November 2012.
02/01/13	Update Related Policies, change title of policy 8.01.21.
02/12/13	Update Related Policies, change title of policy 8.02.02.
03/20/13	The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.
07/25/13	Update Related Policies. Change title to 8.01.35 and add 8.01.520.
10/14/13	Replace policy. Policy title changed. Policy updated with literature search through mid-March 2013; no change in multiple myeloma policy statements. POEMS syndrome added, with a medically necessary statement for autologous HCT for disseminated disease; allogeneic and tandem HCT for POEMS are investigational. Reference numbers 1, 6-9, 43 were removed, references 3-11, 47 were added and all were renumbered.
11/20/13	Update Related Policies. Add 2.01.91 and removed 8.01.31 as it was archived.
02/27/14	Update Related Policies. Change title to 8.01.29 and 8.01.30.
03/21/14	Update Related Policies. Add 8.01.15 and delete 8.01.514.
04/18/14	Update Related Policies. Delete 8.01.20 and add 8.01.529.

Date	Comments
06/24/14	Update Related Policies. Delete 8.01.42 and add 8.01.530
11/20/14	Annual Review. Policy updated with literature review through June 15, 2014; no change in policy statements. Reference numbers 2 and 3 were removed; numbers 1, 32, 42, 47, 48, and 50 were added. ICD-9 and ICD-10 diagnosis and procedure codes removed; they do not relate to adjudication of the policy.
10/13/15	Annual Review. Policy updated with literature review through July 14, 2015; references 2-3 were removed, references 16, 32, and 54 were added. Policy statements unchanged. Coding update: CPT codes 38320-21 and 86812-16, 86821-22 removed; these are informational and not reviewed in the scope of this policy.
08/01/16	Annual Review, approved July 12, 2016. No changes to policy statement.
01/01/17	Interim Review, approved December 13, 2016. Policy paragraphs restructured and wording edited for more specific restrictions of HCST for POEMS to autologous transplant only and excluding allogeneic including RIC allogeneic, RIC autologous, and tandem transplantations. HCT for myeloma clarified to explicitly require induction chemotherapy achieving partial response or better prior to HCT for initial treatment sequence. Remainder of policy statements unchanged.
04/01/17	Annual Review, approved March 14, 2017. Policy updated with literature review through July 13, 2016 and results of clinical input; references 21, 48, and 55 added; reference 59 updated. Policy statements became less restrictive in regard to treatment of multiple myeloma.
06/09/17	Coding update; updated description for CPT codes 38230, 38240, and 38241.
10/24/17	Policy moved to new format; no change to policy statements.
04/01/18	Annual Review, approved March 20, 2018. Policy updated with literature review through November 2017; references 21, 50-51, 53, 56-58, 61, and 68 added; reference 67 updated. Policy statements unchanged.
11/01/18	Minor update, removed 8.02.02 from related policies as it was archived.
01/15/19	Minor update, removed 12.04.97 from Related Policies as it was archived.
04/01/19	Annual Review, approved March 5, 2019. Policy updated with literature review through November 2018; reference 34 added. Policy statements unchanged.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020 and replaced with InterQual criteria for dates of service on or after July 2, 2020. Approved March 19, 2020, policy updated with literature review through November 2019; references added. Policy statements unchanged. Removed CPT code 38242, does not match criteria.
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.

Date	Comments
08/01/20	Annual Review, approved July 2, 2020. Policy updated with literature review through November, 2019; references added. Policy statements unchanged
09/01/20	Coding update. . Removed CPT codes 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232 and HCPCS S2140, S2142, S2150.
04/01/21	Annual Review, approved March 2, 2021. Policy updated with literature review through November 16, 2020; references added. Policy statements unchanged.
5/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
04/01/22	Annual Review, approved March 7, 2022. Policy updated with literature review through November 17, 2021; references added. Policy statements unchanged.
04/01/23	Annual Review, approved March 20, 2023. Policy updated with literature review through November 17, 2022; references added. Minor editorial refinements to policy statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Annual Review, approved March 25, 2024. Policy updated with literature review through November 29, 2023; references added. Policy statements unchanged.
04/01/25	Annual Review, approved March 10, 2025. Policy updated with literature review through November 25, 2024; references added. Policy statements unchanged.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.