



MASSACHUSETTS

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Medical Policy

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

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BCBSA Reference Number: 8.01.17 (For Plans internal use only)

Related Policies

- Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia, [#322](#)
- Placental/Umbilical Cord Blood as a Source of Stem Cells, [#285](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

MULTIPLE MYELOMA

A single or second (salvage) autologous hematopoietic cell transplantation may be **MEDICALLY NECESSARY** to treat multiple myeloma.

Tandem autologous-autologous hematopoietic cell transplantation may be **MEDICALLY NECESSARY** to treat multiple myeloma in patients who fail to achieve at least a near-complete or very good partial response after the first transplant in the tandem sequence.

Definition of near-complete response and very good partial response

- A near complete response, as defined by the European Group for Blood and Marrow Transplant (EBMT) is the disappearance of M protein at routine electrophoresis, but positive immunofixation.
- A very good partial response has been defined as a 90% decrease in the serum paraprotein level.

Tandem transplantation with an initial round of 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 **MEDICALLY NECESSARY** to treat newly diagnosed multiple myeloma patients.

Allogeneic hematopoietic cell transplantation, myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy, is **INVESTIGATIONAL**.

POEMS syndrome

Autologous hematopoietic cell transplantation may be considered **MEDICALLY NECESSARY** to treat disseminated POEMS syndrome.*

*Patients with disseminated POEMS syndrome may have diffuse sclerotic lesions or disseminated bone marrow involvement.

Allogeneic and tandem hematopoietic cell transplantation are **INVESTIGATIONAL** to treat POEMS syndrome.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|---------------------------------------|--|
| Commercial Managed Care (HMO and POS) | Prior authorization is required . |
| Commercial PPO and Indemnity | Prior authorization is required . |

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above **medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

CPT Codes

| CPT codes: | Code Description |
|------------|---|
| 38241 | Bone marrow or blood-derived peripheral stem-cell transplantation; autologous |

HCPCS Codes

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

ICD-10-PCS Procedure Codes

| ICD-10-PCS procedure codes: | Code Description |
|-----------------------------|------------------|
| | |

| | |
|---------|--|
| 30233G0 | Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach |
| 30233X0 | Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach |
| 30233Y0 | Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach |
| 30243G0 | Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach |
| 30243X0 | Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach |
| 30243Y0 | Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach |
| 30263G0 | Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach |
| 30263X0 | Transfusion of Autologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach |
| 30263Y0 | Transfusion of Autologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach |
| 3E04305 | Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach |

The following CPT, HCPCS and ICD Procedure codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

| CPT codes: | Code Description |
|------------|---|
| 38240 | Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic |

HCPCS Codes

| HCPCS codes: | Code Description |
|--------------|--|
| S2142 | Cord blood-derived stem-cell transplantation, allogeneic |

ICD-10-PCS Procedure Codes

| ICD-10-PCS procedure codes: | Code Description |
|-----------------------------|---|
| 30233G1 | Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach |
| 30233X1 | Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach |
| 30233Y1 | Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach |
| 30243G1 | Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach |
| 30243X1 | Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach |
| 30243Y1 | Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach |
| 30263G1 | Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach |
| 30263X1 | Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach |

| | |
|---------|--|
| 30263Y1 | Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach |
|---------|--|

Description

Multiple Myeloma

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable. At diagnosis, most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of disease complications.^{1,2,3}

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. Multiple myeloma usually evolves from an asymptomatic premalignant stage (termed *monoclonal gammopathy of undetermined significance*). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed because there is little evidence that early treatment of asymptomatic MM prolongs survival compared with therapy delivered at the time of symptoms or end-organ damage.^{1,2} In some patients, 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}

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.^{4,5} 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.⁶ 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)-1 β , IL-6, and tumor necrosis factor α ; vascular endothelial growth factor may also be involved.^{5,7} However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in Table 1.⁸ Both mandatory major criteria, at least 1 of the other major criteria, and at least 1 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 | Edema (edema, pleural effusion, ascites) | Clubbing |
| | Vascular endothelial growth factor elevation | Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) | Thrombotic diatheses |
| | | Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomas, white nails) | Weight loss |
| | | Papilledema | Low vitamin B ₁₂ levels |

| Mandatory Major Criteria | Other Major Criteria | Minor Criteria | Other Symptoms and Signs |
|--------------------------|----------------------|-------------------------|--------------------------|
| | | Thrombosis/polycythemia | Diarrhea |
| | | | Hyperhidrosis |

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.⁹ Other large series have been described in the United States, France, China, and India.⁸ In general, patients with POEMS have superior overall survival compared with that of MM (nearly 14 years in a large series).⁷ However, given the rarity of POEMS, there is a paucity of RCT evidence for POEMS therapies.⁸ 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 (eg, by surgical excision or local radiotherapy for an isolated plasmacytoma) or systemic chemotherapy in patients with disseminated disease (eg, medullary disease or multiple plasmacytomas). Given the underlying plasma cell dyscrasia of POEMS syndrome, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, have also been investigated.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation 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. Cord blood transplantation is discussed in detail in policy #285

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 antigens (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 of 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 patients 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 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 patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients

who undergo autologous HCT are also 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. Reduced-intensity conditioning regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients 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 review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

In the prechemotherapy era, the median survival for a patient diagnosed with MM was approximately 7 months. After the introduction of chemotherapy (eg, 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 patients with newly diagnosed MM, there was no difference in OS reported during a 24-year period from 1971 to 1994, with a trend toward improvement from 1995 to 2000, and a statistically significant benefit in OS from 2001 to 2006.² These data suggested that autologous HCT was responsible for the trends from 1994 to 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.¹⁰ Novel agents such as the proteasome inhibitors (eg, 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.^{10,11,12} With the introduction of these novel treatments, it is now expected that most patients with MM will respond to initial therapy, and only a small minority will have refractory disease.¹³

Summary

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.

Newly Diagnosed Multiple Myeloma

For individuals who have newly diagnosed MM who receive autologous HCT as initial treatment, the evidence includes several prospective randomized controlled trials (RCTs) that compared high-dose chemotherapy plus autologous HCT to standard chemotherapy regimens or regimens containing newer MM agents. Relevant outcomes are overall survival (OS) and treatment-related morbidity. In general, the evidence has suggested OS 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. 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. Relevant outcomes are OS and treatment-related morbidity. Compared with single autologous HCT, RCTs have generally found that tandem autologous HCT improves OS 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. Several RCTs compared reduced-intensity conditioning allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on genetic randomization (ie, patients with a human leukocyte antigen-identical sibling were offered reduced-intensity conditioning allo-HCT following autologous HCT, whereas other patients underwent either 1 or 2 autologous transplants). Although the body of evidence has shown inconsistencies regarding OS and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by reduced-intensity conditioning 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. Relevant outcomes are OS and treatment-related morbidity. Studies have reported on patients with both myeloablative conditioning and reduced-intensity conditioning. 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. Relevant outcomes are OS 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 OS 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 multiple myeloma after failing a first HCT who receive tandem autologous HCT, the evidence includes systematic reviews and a retrospective study. Relevant outcomes are OS and treatment-related morbidity. The evidence has shown tandem autologous HCT improves OS rates in this setting. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

POEMS Syndrome

For individuals who have POEMS syndrome who receive HCT, the evidence includes retrospective cohort studies, case reports, and case series. Relevant outcomes are OS and treatment-related morbidity. No RCTs of HCT of any type have been performed in patients 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 patients 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.

Policy History

| Date | Action |
|----------------|---|
| 2/2022 | Annual review. Description, summary, and references updated. Policy statements unchanged. |
| 3/2021 | Annual review. Description, summary, and references updated. Policy statements unchanged. |
| 1/2021 | Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference. |
| 4/2020 | Bone marrow harvesting codes were removed. Outpatient prior authorization is not required. |
| 3/2020 | Annual review. Description, summary, and references updated. Policy statements unchanged. |
| 6/2019 | Clarified coding information |
| 3/2019 | Annual review. Description, summary, and references updated. Policy statements unchanged. |
| 1/2019 | Outpatient prior authorization is required for all commercial products. Effective 1/1/2019. |
| 2/2018 | Annual review. New references added. Title clarified. |
| 1/2018 | Clarified coding information. |
| 11/2015 | Annual review. New references added |
| 4/2015 | Annual review. New references added |
| 1/2015 | Clarified coding information. |
| 5/2014 | Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015. |
| 2/2014 | Annual review. New medically necessary and investigational indications described; policy title changed. Effective 2/1/2014. |
| 12/2012 | Updated to add new CPT code 38243. |
| 11/2011-4/2012 | Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements. |
| 12/2011 | Minor change to policy statements (added phrase "in the tandem sequence" to the medically necessary tandem autologous-autologous statement). |
| 7/2011 | Medical Policy Group – Hematology and Oncology. No changes to policy statements. |
| 9/2010 | Medical Policy Group – Hematology and Oncology. No changes to policy statements. |
| 9/1/2010 | Medical Policy 075 effective 9/1/2010. |

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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