MEDICAL POLICY – 8.01.17
Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome

BCBSA Ref. Policy: 8.01.17

Effective Date: April 1, 2019
Last Revised: March 5, 2019
Replaces: 8.01.507

RELATED MEDICAL POLICIES:
2.01.91 Peroral Endoscopic Myotomy for Treatment of Esophageal Achalasia
7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Myeloma</strong></td>
</tr>
<tr>
<td>A single or second (salvage) autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma.</td>
</tr>
<tr>
<td>Tandem autologous hematopoietic cell transplantation may be considered 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. Tandem transplantation with an initial round of autologous hematopoietic cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic cell transplantation (ie, reduced-intensity conditioning transplant) may be considered medically necessary to treat newly diagnosed multiple myeloma patients.</td>
</tr>
</tbody>
</table>

### POEMS Syndrome

<table>
<thead>
<tr>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POEMS Syndrome</strong></td>
</tr>
<tr>
<td>Autologous hematopoietic cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome (see Additional Information below).</td>
</tr>
</tbody>
</table>

### Additional Information

- The International Working Group on Myeloma has updated the European Group for Blood and
Additional Information

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.

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

Documentation Requirements

The patient’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) patient has received

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
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</tr>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
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<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
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</table>

**HCPCS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood derived stem cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived 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</td>
</tr>
</tbody>
</table>

**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, hematopoietic cell transplantation (HCT) is considered as therapy.

Background

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.\(^1\)-\(^3\)

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. MM 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 when 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)-1β, IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved.\textsuperscript{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. Both major criteria and at least 1 of the minor criteria are necessary for diagnosis.\textsuperscript{7}

**Table 1: Criteria and Associations for POEMS Syndrome**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Known Associations</th>
<th>Possible Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Monoclonal plasma-proliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
</tr>
<tr>
<td></td>
<td>Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
</tr>
<tr>
<td></td>
<td>Edema (edema, pleural effusion, or ascites)</td>
<td>Polycythemia</td>
<td>Arthralgias</td>
</tr>
<tr>
<td></td>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Papilledema</td>
<td></td>
<td>Low vitamin B\textsubscript{12} values</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.\textsuperscript{8} Other large series had been described in the United States\textsuperscript{5,7,9} and India.\textsuperscript{10} In general, patients with POEMS have a superior overall survival compared with that of MM (nearly 14 years in a large series).\textsuperscript{7} However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported.\textsuperscript{11} Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) support.\textsuperscript{5,7} 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, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.\textsuperscript{5,12}

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow 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 from a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in greater detail in a separate medical policy (see Related Policies).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (except umbilical cord blood).

\textit{Conditioning for HCT}

\textbf{Conventional Conditioning}

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to
minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

**Reduced-Intensity Conditioning Allo-HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less-intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of non-relapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally 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, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For our purposes, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

**MM Treatment Overview**

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 a 10-year survival of 3%. In a large group of patients 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. 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. Novel agents such as the proteasome inhibitor bortezomib and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed and refractory myeloma and now have been integrated into first-line regimens. 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.

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 several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy with high-dose chemotherapy plus autologous HCT. The relevant outcomes include 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have newly diagnosed multiple myeloma who receive tandem autologous HCT, the evidence includes several RCTs. The relevant outcomes include overall survival and treatment-related morbidity. Compared with single autologous HCT, a number of RCTs have demonstrated tandem autologous HCT improved overall survival and recurrence-free survival in newly diagnosed multiple myeloma. The available RCTs compare RIC 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 who were offered an RIC allo-HCT following autologous HCT), whereas other patients underwent either 1 or 2 autologous transplants. Although the body of evidence has shown inconsistencies in terms of 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 a meaningful improvement in the net health outcome.

For individuals who have newly diagnosed multiple myeloma who receive allo-HCT with initial or salvage treatment, the evidence includes nonrandomized studies. The relevant outcomes include overall survival and treatment-related morbidity. Studies have reported on patients 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 the effects of the technology on health outcomes.

**Relapsed or Refractory Multiple Myeloma**

For individuals who have relapsed MM after failing an autologous HCT who receive autologous HCT, the evidence includes an RCT, a retrospective study, and a systematic review summarizing data from 4 series of patients who relapsed after a first autologous HCT, and a review summarizing recent studies on a second autologous HCT in relapsed myeloma. The relevant outcomes include 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 in this setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have refractory MM after failing the first HCT who receive tandem autologous HCT, the evidence includes 3 RCTs and a review. Relevant outcomes include 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 a meaningful improvement in the net health outcome.
**POEMS Syndrome**

For individuals who have POEMS syndrome who receive HCT, the evidence includes case reports and series. Relevant outcomes include overall survival 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 a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

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

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01208662</td>
<td>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</td>
<td>660</td>
<td>Sep 2018</td>
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<tr>
<td>NCT02322320</td>
<td>Continued, Long-Term follow-Up and Lenalidomide Maintenance Therapy for Patients on BMT CTN 0702 (BMT CTN #Q07LT)</td>
<td>450</td>
<td>Dec 2018</td>
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<tr>
<td>NCT00177047</td>
<td>Autologous Transplantation for Multiple Myeloma</td>
<td>363</td>
<td>Jan 2020</td>
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<tr>
<td>NCT01109004</td>
<td>A Trial of Single Autologous Transplant With or Without Consolidation Therapy Versus Tandem Autologous Transplant With Lenalidomide Maintenance for Patients With Multiple Myeloma (BMT CTN 0702)</td>
<td>750</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT01191060</td>
<td>Randomized Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide,</td>
<td>700</td>
<td>Sep 2020</td>
</tr>
</tbody>
</table>
Clinical Input from Physician Specialty Societies and Academic Medical Centers

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 1 specialty medical society, 1 academic medical center, and 2 Blue Distinction Centers for Transplant while this policy was under review in 2017. There was consensus that allogeneic hematopoietic cell transplantation (HCT) is investigational for newly diagnosed multiple myeloma and as salvage therapy after primary graft failure and for primary progressive disease.

2013 Input

In response to requests, input was received from 3 academic medical centers and 6 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.

2010 Input

In response to requests, input was received from 2 academic medical centers while this policy was under review in 2010. One reviewer agreed with the current policy statement related to tandem autologous HCT followed by reduced-intensity conditioning allogeneic HCT and the other disagreed. Those providing input agreed with the other policy statements. (The conclusion that allogeneic HCT is investigational for salvage therapy was a late addition to the policy and was not sent for clinical input.)

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

The American Society for Blood and Marrow Transplantation (ASBMT) (2015) published evidence-based guidelines on the use of HCT in patients with multiple myeloma (MM). ASBMT recognized that much of the evidence from randomized controlled trials 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. ASBMT guidelines did not address POEMS or other plasma cell dyscrasias besides MM.

The ASBMT, and 3 other groups (2015) published joint guidelines based on an expert consensus conference. These guidelines contained the following recommendations for HCT as salvage therapy:

... autologous HCT: (1) In transplantation-eligible patients 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 patients 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 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 patients 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 patients 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 patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or with high-risk features (ie, 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 patients with MM relapsing after primary therapy.

**International Myeloma Working Group**

The 2010 conclusions and recommendations of the International Myeloma Working Group consensus statement on the current status of allogeneic HCT (allo-HCT) for MM are as follows: Myeloablative allogeneic HCT may cure a minority of patients but is associated with a high transplant-related mortality, but could be evaluated in well-designed prospective clinical trials. 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 HCT**

The National Comprehensive Cancer Network (NCCN) guidelines (v.3.2018) consider autologous HCT a category 1 recommendation as follow-up to induction therapy for newly diagnosed MM and as a category 1 recommendation for relapsed or progressive disease if the patient is considered a transplant candidate.
Tandem HCT

The NCCN recommends collecting enough stem cells for 2 transplants in all eligible patients.66

Allo-HCT

The NCCN recommends the following for allo-HCT: “Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably on a clinical trial. Current data do not support miniallografting alone” (category 2A).66

POEMS Syndrome

The NCCN guidelines do not address the treatment of POEMS syndrome.66

Medicare National Coverage

Medicare has the following national coverage determination for the use of HCT for MM.67

“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 patients 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 U.S. 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.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/12/12</td>
<td>New policy, add to Therapy section. Policy replaces 8.01.507.</td>
</tr>
<tr>
<td>09/10/12</td>
<td>Update coding section – ICD-10 codes are now effective 10/01/2014.</td>
</tr>
<tr>
<td>11/15/12</td>
<td>Reviewed and recommended by OAP, November 2012.</td>
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<tr>
<td>02/01/13</td>
<td>Update Related Policies, change title of policy 8.01.21.</td>
</tr>
<tr>
<td>02/12/13</td>
<td>Update Related Policies, change title of policy 8.02.02.</td>
</tr>
<tr>
<td>03/20/13</td>
<td>The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.</td>
</tr>
<tr>
<td>07/25/13</td>
<td>Update Related Policies. Change title to 8.01.35, and add 8.01.520.</td>
</tr>
<tr>
<td>10/14/13</td>
<td>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.</td>
</tr>
<tr>
<td>11/20/13</td>
<td>Update Related Policies. Add 2.01.91, and removed 8.01.31 as it was archived.</td>
</tr>
<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.29 and 8.01.30.</td>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Add 8.01.15 and delete 8.01.514.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and add 8.01.529.</td>
</tr>
<tr>
<td>06/24/14</td>
<td>Update Related Policies. Delete 8.01.42 and add 8.01.530</td>
</tr>
<tr>
<td>11/20/14</td>
<td>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 related to adjudication of the policy.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>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.</td>
</tr>
<tr>
<td>08/01/16</td>
<td>Annual Review, approved July 12, 2016. No changes to policy statement.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>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</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/01/17</td>
<td>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 regards to treatment of multiple myeloma.</td>
</tr>
<tr>
<td>06/09/17</td>
<td>Coding update; updated description for CPT codes 38230, 38240, and 38241.</td>
</tr>
<tr>
<td>10/24/17</td>
<td>Policy moved to new format; no change to policy statements.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, removed 8.02.02 from related policies as it was archived.</td>
</tr>
<tr>
<td>01/15/19</td>
<td>Minor update, removed 12.04.97 from Related Policies as it was archived.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Annual Review, approved March 5, 2019. Policy updated with literature review through November 2018; reference 34 added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

**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). ©2019 Premera All Rights Reserved.

**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.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

When you believe that Premera has failed to provide these services or discriminate in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
- Civil Rights Coordinator - Complaints and Appeals
  PO Box 91102, Seattle, WA 98111
  Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5537
  Email AppealsDepartmentInquiries@Premera.com

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5537).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ikloko (Illoko):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impomarson. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impomarson maipanggep iti aplikasyonno yenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakkay dagiti partikulak a naistung nga adda aldaw tapno mapagtalaineyo ti coverage ti salun-atyo yenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impomarson ken tulong iti bukodyo a pagasasoa nga awi ti bayaddanyo. Tumawagi iti numero nga 800-722-1471 (TTY: 800-842-5537).

Italiano (Italian):
Japanese (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている可能性がある重要な日目をご確認ください。健康保険や費用サポートを維持するには、特定の期日までに行動を取らなければなりません。お彼女の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에
관하여 그리고 Premera Blue Cross를 통한 커버리지를 관할 정보를
포함하고 있는 것입니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수
있습니다. 귀하의 귀하의 건강 커버리지를 계속 유지하시거나 비용을 절감하기 위함에 일정한 마감일까지 조치를 취해야 할 필요가 있을 것입니다.
귀하의 이러한 정보와 도움을 귀하의 만드는 비용 부담없이 얻을 수 있는
권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하시오.

Polski (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może
zawierać ważne informacje odnośnie Polski wniosku lub zakresu
świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na
kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie
przekroczyć terminów w przypadku utraty ubezpieczenia lub
pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter
informações importantes a respeito de sua aplicação ou cobertura por meio
do Premera Blue Cross. Poderão existir dados importantes neste aviso.
Talvez seja necessário que você tome providências dentro de
determinados prazos para manter sua cobertura de saúde ou ajuda de
custos. Você tem o direito de obter esta informação e ajuda em seu idioma

Română (Romanian):
Prezentă notificare conține informații importante. Această notificare
poate conține informații importante privind cererea sau acoperirea asigurărilor
dunneavoastră de sănătate prin Premera Blue Cross. Poți exista date cheie
în această notificare. Este posibil să fie nevoie să acționați până la anumite
termini limita pentru a vă menține acoperirea asigurării de sănătate sau
asistența privitoare la costuri. Aveți dreptul să o obțineți gratuit aceste

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это
уведомление может содержать важную информацию о вашем
заявлении или страховом покрытии через Premera Blue Cross. В
настоящем уведомлении могут быть указаны ключевые даты. Вам,
возможно, потребуется принять меры к определенным предельным
срокам для сохранения страхового покрытия или помощи с расходами.
Вы имеете право на бесплатное получение этой информации
и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso
contenga información importante acerca de su solicitud de cobertura a
através de Premera Blue Cross. Es posible que haya fechas claves en este
aviso. Es posible que deba tomar alguna medida antes de determinadas
fechas para mantener su cobertura médica o ayuda con los costos. Usted
tiene derecho a recibir esta información y ayuda en su idioma sin costo

Tagalog (Tagalog):
Ang Pagawa na ito ay naglalaman ng mahalagang impormasyon. Ang
pagawa na ito ay maaring nagagtanghal ng mahalagang impormasyon
tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue
Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring

ไทย (Thai):
ประกาศนี้มีข้อมูลที่สำคัญ คุณสามารถขอข้อมูลเหล่านี้ได้โดยไม่คิดค่าใช้จ่าย
ในภาษาของคุณโดยไม่มีค่าใช้จ่าย. ติดต่อ 800-722-1471 (TTY: 800-842-5357).