Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

RELATED PROTOCOL

None

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • With newly diagnosed multiple myeloma</td>
<td>Interventions of interest are: • Autologous hematopoietic cell transplantation as initial treatment</td>
<td>Comparators of interest are: • Conventional chemotherapy with or without novel therapies</td>
<td>Relevant outcomes include: • Overall survival • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With newly diagnosed multiple myeloma</td>
<td>Interventions of interest are: • Tandem autologous hematopoietic cell transplantation</td>
<td>Comparators of interest are: • Conventional chemotherapy with or without novel therapies</td>
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</tr>
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<td>Individuals: • With newly diagnosed multiple myeloma</td>
<td>Interventions of interest are: • Allogeneic hematopoietic cell transplantation as initial or salvage treatment</td>
<td>Comparators of interest are: • Conventional chemotherapy with or without novel therapies</td>
<td>Relevant outcomes include: • Overall survival • Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: • With relapsed multiple myeloma after failing an autologous hematopoietic cell transplantation</td>
<td>Interventions of interest are: • Autologous hematopoietic cell transplantation</td>
<td>Comparators of interest are: • Conventional chemotherapy with or without novel therapies</td>
<td>Relevant outcomes include: • Overall survival • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With refractory multiple myeloma after failing a first hematopoietic cell transplant</td>
<td>Interventions of interest are: • Tandem autologous hematopoietic cell transplantation</td>
<td>Comparators of interest are: • Conventional chemotherapy with or without novel therapies</td>
<td>Relevant outcomes include: • Overall survival • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With POEMS syndrome</td>
<td>Interventions of interest are: • Hematopoietic cell transplantation</td>
<td>Comparators of interest are: • Conventional chemotherapy with or without novel therapies</td>
<td>Relevant outcomes include: • Overall survival • Treatment-related morbidity</td>
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</tbody>
</table>
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.

SUMMARY OF EVIDENCE

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 (i.e., patients with a human leukocyte antigen-identical sibling were offered reduced-intensity conditioning allo-HCT following autologous HCT, whereas other patients underwent either one or two 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 autolo-
gous 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

MULTIPLE MYELOMA

A single or second (salvage) autologous hematopoietic cell transplantation may be considered medically necessary to treat multiple myeloma.

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. (For definitions of near-complete response and very good partial response, see Policy Guidelines.)

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 considered 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 considered investigational.

POEMS SYNDROME

Autologous hematopoietic cell transplantation may be considered medically necessary to treat POEMS syndrome (See Policy Guidelines).
Allogeneic and tandem hematopoietic cell transplantation are considered investigative to treat POEMS syndrome.

POLICY GUIDELINES

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

The International Working Group on Myeloma has updated the European Group for Blood and Marrow Transplant (EBMT) 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.

MEDICARE ADVANTAGE

If a transplant is needed, we arrange to have the transplant center review and decide whether the patient is an appropriate candidate for the transplant.

BACKGROUND

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 five years, approximately 3% per year for the next five years, and 1% for the next ten 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.5,7 However, specific criteria have been estab-
lished, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in Table 1. 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

<table>
<thead>
<tr>
<th>Mandatory Major Criteria</th>
<th>Other Major Criteria</th>
<th>Minor Criteria</th>
<th>Other Symptoms and Signs</th>
</tr>
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<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Castleman disease</td>
<td>Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)</td>
<td>Pulmonary hypertension/restrictive lung disease</td>
</tr>
<tr>
<td>Monoclonal plasma-</td>
<td>Sclerotic bone lesions</td>
<td>Vascular endothelial growth factor (endocardial, thyroid, parathyroid, pancreatic)</td>
<td>Clubbing</td>
</tr>
<tr>
<td>proliferative disorder</td>
<td></td>
<td>Endocrinopathy (adrenal, thyroid, parathyroid, pancreatic)</td>
<td>Thrombotic diatheses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangioma, white nails)</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Papilledema</td>
<td>Low vitamin B12 levels</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Thrombosis/polycythemia</td>
<td>Hyperhidrosis</td>
<td></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. Other large series have been described in the United States, France, China, and India. In general, patients with POEMS have superior overall survival compared with that of MM (nearly 14 years in a large series). However, given the rarity of POEMS, there is a paucity of RCT evidence for POEMS therapies. 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 patients with disseminated disease (e.g., 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 the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

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.

MULTIPLE MYELOMA TREATMENT OVERVIEW

In the prechemotherapy era, the median survival for a patient diagnosed with MM was approximately seven 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 ten-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 to 1994, with a trend toward improvement during 1995 to 2000, and a statistically significant benefit in overall survival during 2001 to 2006. These data suggested that autologous HCT was responsible for the trends during 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. 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. With the introduc-
tion 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.14

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES
We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


