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

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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 section.)

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 is considered investigational.

POEMS Syndrome
Autologous hematopoietic cell transplantation may be considered medically necessary to treat disseminated POEMS syndrome (see Policy Guidelines).

Allogeneic and tandem hematopoietic cell transplantation is considered investigational to treat POEMS syndrome.

Related Policies

2.01.91 Peroral Endoscopic Myotomy (POEM) for Treatment of Esophageal Achalasia
Policy Guidelines

The International Working Group on Myeloma has updated the European Group for Blood and Marrow Transplant (EBMT) criteria to describe a complete response to MM 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.

Coding

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<td>38207</td>
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HCPCS

| S2140 | Cord blood harvesting for transplantation, allogeneic |
| S2142 | Cord blood derived stem cell transplantation, autologous |
| S2150 | 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 |

Description

Multiple myeloma 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.
Newly Diagnosed Multiple Myeloma

For individuals who have newly diagnosed multiple myeloma who receive autologous HCT as initial treatment, the evidence includes several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy to high-dose chemotherapy plus autologous HCT. 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. Relevant outcomes include overall survival and treatment-related morbidity. Compared with single autologous HCT, a number of RCTs demonstrated tandem autologous HCT improved OS and recurrence-free survival in newly diagnosed multiple myeloma. The available RCTs compare RIC allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on "genetic randomization," i.e., patients with a human leukocyte antigen–identical sibling 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 allogeneic HCT, although at a 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 allogeneic HCT (allo-HCT) with as initial or salvage treatment, the evidence includes nonrandomized studies. Relevant outcomes include overall survival and treatment-related morbidity. Studies have reported on patients with both myeloablative and RIC 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 the effects of the technology on health outcomes.

Relapsed or Refractory Multiple Myeloma

For individuals who have relapsed multiple myeloma who receive autologous HCT after failing an autologous HCT, the evidence includes 1 RCT and a systematic review summarizing data from 4 series of patients who relapsed after a first autologous HCT. 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 multiple myeloma who receive tandem autologous HCT after failing the first transplant, the evidence includes 3 RCTs. 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 with respect to treatment approaches and peritransplant support. However, for patients with disseminated POEMS syndrome, a chain of evidence and contextual factors related to the disease and multiple
myeloma 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.

Background
Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic 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 cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic 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 cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in a separate medical policy (see Related Policies).

Immunologic compatibility between infused hematopoietic 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 allogeneic 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 Class I and Class II 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 (with the exception of umbilical cord blood).

Conditioning For HCT

Conventional Conditioning
The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., 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 (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic cells within the patient’s bone marrow space. While the slower GVM 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 allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, 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 GVHD.

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 but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM 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 allogeneic 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.
**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 the time of diagnosis, most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease.(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, as 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 suggests it is mediated by 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 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.(7)

**Table 1: Criteria and Associations**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Known Associations</th>
<th>Possible Associations</th>
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<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
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<tr>
<td>Monoclonal plasmaproliferative disorder</td>
<td>Castleman disease</td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
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<td></td>
<td>Organomegaly (spleenomegaly, hepatomegaly, or lymphadenopathy)</td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
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<tr>
<td></td>
<td>Edema (edema, pleural effusion, or ascites)</td>
<td>Polycythemia</td>
<td>Arthralgias</td>
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<td></td>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
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<td></td>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)</td>
<td></td>
<td>Fever</td>
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<tr>
<td></td>
<td>Papilledema</td>
<td>Low vitamin B_{12} values</td>
<td>Diarrhea</td>
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The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.(8) Other large series have been described in the United States(5,7, 9) and in India.(10) In general, patients with POEMS have a superior OS compared with that of MM, nearly 14 years in a large series from Mayo Clinic.(7) However, given the rarity of POEMS, no randomized controlled trials (RCTs) of therapies have been reported.(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 HCT support.(5,7) Optimal treatment involves eliminating the plasma cell clone, for example, by surgical excision or local radiotherapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasias of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.(5,12)
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 cells are included in these regulations.

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.

Benefit Application
The following considerations may supersede this policy:
- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for patients participating in NIH-approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.

Rationale
The earliest versions of policy were based on two 1996 and two 1998 TEC Assessments. Since 1999, the treatment of multiple myeloma (MM) has changed radically. POEMS syndrome was added to this review in 2013.

The literature search for this evidence review was updated through July 13, 2016. No new evidence was identified that would support a change in any of the review conclusions on MM.

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

The introduction of novel agents and better prognostic indicators has been the major advances in the treatment of this disease.(13,14) Novel agents such as the proteasome inhibitor bortezomib and the immunomodulatory derivatives thalidomide and lenalidomide first showed efficacy in relapsed/refractory myeloma and now have been integrated into first-line regimens.(13-15) With the introduction of these novel treatments, it is now expected that most patients with MM will have responsive disease with initial therapy, and only a small minority will have refractory disease.(16)
Newly Diagnosed Multiple Myeloma

Risk-Adapted Therapy

The approach to the treatment of newly diagnosed MM (symptomatic) is dictated by eligibility for autologous hematopoietic cell transplantation (HCT) and risk-stratification.(17) Risk stratification, using fluorescent in situ hybridization and conventional karyotyping divides patients into standard- or high-risk categories.

High-risk patients, which comprise approximately 25% of patients with MM, are defined by any of the following cytogenetic findings: 17p deletion, translocations of chromosomes 4 and 14, chromosomes 14 and 16, chromosomes 14 and 20, deletion 13, or hypodiploidy.(17) Standard-risk patients are those with hyperdiploidy (translocations of chromosomes 11 and 14 and chromosomes 6 and 14).

High-risk patients are generally treated with a bortezomib-based induction followed by autologous HCT and then bortezomib-based maintenance.(17) Standard-risk patients are typically treated with non-alkylator-based therapy (eg, lenalidomide plus low-dose dexamethasone) followed by autologous HCT; however, if the patient is tolerating the induction regimen well, an alternative strategy would be to continue the initial therapy after hematopoietic cell collection, reserving the transplant for first relapse.

Recent reviews highlight the treatment of newly diagnosed myeloma (2011),(18) relapsed, and refractory myeloma (2011).(19) A review of the literature highlights advances in the use of autologous and allogeneic HCT (allo-HCT). (20)

Autologous HCT Versus Standard Chemotherapy

Randomized Controlled Trials

One 2015 randomized controlled trial (RCT) compared autologous HCT to standard chemotherapy plus lenalidomide, a newer agent for treatment of MM.(21) The open-label RCT from 59 centers in Europe and Australia used a 2x2 factorial design to compare 4 groups (1) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide alone, (2) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide and prednisone, (3) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide alone, and (4) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide plus prednisone. The primary outcome was progression-free survival (PFS). Mean follow-up at the time of publication was 52 months. Median PFS was superior for the HCT group plus standard consolidation (43.3 months; 95% confidence interval [CI], 33.2 to 52.2 months) compared to chemotherapy plus lenalidomide (28.6 months; 95% CI, 20.6 to 36.7 months; p<0.0001). The rate of grade 3 or 4 adverse events was higher for the HCT group than for the chemotherapy groups (hematologic events, 84% vs 26%; gastrointestinal complications, 20% vs 5%; infections, 19% vs 5%; all respectively).

Based on several prospective, randomized trials comparing conventional chemotherapy to high-dose therapy plus autologous HCT for patients with MM, autologous HCT has become the treatment of choice in patients younger than 65 years of age. Data from 7 randomized studies are available.(22-28) In all but 1 study,(24) the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HCT arm: this study published final results of the S9321 trial, which was initiated in 1993 and randomized 516 patients with MM to receive either standard therapy or myeloablative conditioning with melphalan 140 mg/m2 plus total body irradiation followed by autologous HCT.(24) The authors reported virtually no difference in outcomes, including response rates, progression-free survival (PFS), and OS.

In 5 of the 7 studies, the superior CR rate translated into a significant increase in PFS. However, in the 2 studies that did not show an improved PFS with autologous HCT, randomization was not performed at diagnosis but only after induction treatment, possibly introducing selection bias.(22) Three of the 7 studies showed superior OS in the autologous HCT group.(23,26,28)

The Intergroupe Francophone du Myélome (IFM) showed the superiority of high-dose chemotherapy plus autologous HCT compared with conventional chemotherapy in a 1996 randomized trial of 200 patients younger than 65 years of age.(23) The group that underwent autologous HCT had significantly improved response rates, event-free survival (EFS), and OS. Seven years later, the British Medical Research Council published similar results.(26)
**Systematic Reviews**

A 2007 systematic review of 2411 patients enrolled in RCTs compared standard-dose chemotherapy to myeloablative chemotherapy plus single autologous HCT.(29) Meta-analysis concluded that myeloablative therapy with autologous HCT increased the likelihood of PFS (hazard ratio [HR] of progression, 0.75; 95% CI, 0.59 to 0.96) but not OS (HR of death, 0.92; 95% CI, 0.74 to 1.13); in this group, the odds ratio for treatment-related mortality (TRM) was 3.01 (95% CI, 1.64 to 5.50). However, the effects of myeloablative chemotherapy and autologous HCT may have been underestimated because up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HCT as salvage therapy when MM progressed. This could account for the lack of a significant difference in OS between the 2 groups.

**Subsection Summary**

For individuals with newly diagnosed MM, evidence from multiple RCTs has suggested that high-dose chemotherapy with autologous HCT is superior to standard chemotherapy in PFS, and possibly OS.

**Tandem HCT**

A tandem transplant involves an autologous transplant followed by a preplanned second transplant, either another autologous or a RIC allogeneic transplant. A tandem transplant differs from a second salvage transplant in that a tandem transplant involves prospective planning for a second transplant at the time the first transplant is being planned.

**Tandem Autologous- HCT**

The first randomized trial of autologous tandem transplants (IFM-94) was published in December 2003 by Attal et al. and randomized patients with newly diagnosed myeloma to single or tandem autologous transplants.(30) Outcomes were analyzed by intention-to-treat at 75 month median follow-up. Among those randomized to single transplants (n=199), 148 relapsed: 33 were salvaged with a second autotransplant, 13 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Among those randomized to tandem autotransplants (n=200), 129 patients experienced disease relapse: 34 received salvage therapy with another (third) transplant, 12 received no salvage, and the remainder received conventional chemotherapy plus thalidomide. Seven years after diagnosis, patients randomized to tandem transplants had higher probabilities than those randomized to single transplants for EFS (20% vs. 10%, respectively; p=0.03), relapse-free survival (RFS; 23% vs. 13%, respectively; p<0.01), and OS (42% vs. 21%, respectively; p=0.010). TRM was 6% and 4% after tandem and single transplants, respectively (p=0.40). Second transplants apparently extended survival only for those who failed to achieve a CR or very good partial response (VGPR) after one transplant (OS at 7 years: 43% vs. 11%, respectively; p<0.001).

An accompanying editorial by Stadtmauer(31) raised concerns that these results might be specific to the regimens used for myeloablative therapy in IFM-94. Patients in the single transplant arm received 140 mg/m2 melphalan plus total-body irradiation (TBI), while those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. The editorial cites an IFM-95 study as evidence, suggesting 140 mg/m2 melphalan plus TBI may be less effective and more toxic than myeloablative therapy than 200 mg/m2 melphalan and no TBI. Based on this, the author hypothesizes increased survival in the IFM-94 tandem arm may have resulted from greater cumulative exposure to melphalan (280 mg/m2 vs. 140 mg/m2).

The Bologna 96 clinical study (2007) compared single and double autologous HCT (N=321).(32) Patients undergoing tandem autologous HCT were more likely than those with a single autologous HCT to attain at least a near CR (47% vs 33%; p=0.008), to prolong RFS (median, 42 months vs 24 months; p<0.001), and extend EFS (median, 35 months vs 23 months; p=0.001), all respectively. There was no significant difference between groups in TRM (3%-4%). There was a trend for improved OS among patients in the double transplant group (7-year rate, 60%) compared with the single transplant group (7-year rate, 47%; p=0.10). Conversely, among patients achieving CR or near CR after 1 transplant, EFS and OS estimates did not differ significantly according to transplant(s) received by study randomization. A subgroup analysis of outcomes of patients assigned to the 2 treatment arms, conducted by treatment response, showed that the benefit of a second transplant was particularly evident in patients who failed to achieve at least near CR after the first autologous transplant.
**Subsection Summary**

Compared with single autologous HCT, a number of RCTs have demonstrated tandem autologous RCTs improved OS and recurrence-free survival in newly diagnosed MM.

**Tandem Autologous-HCT Followed by RIC Allo-HCT**

Several RCTs have been published comparing RIC-allogeneic HCT following a first autologous HCT with autologous transplants, single or in tandem. These studies were based on “genetic randomization,” that is, patients with an HLA-identical sibling were offered an RIC-allogeneic HCT following the autologous HCT, whereas the other patients underwent either one or two autologous transplants.

The first published study by Garban et al. included high-risk patients (including deletion of chromosome 13). Sixty-five patients were in the autologous/RIC-allogeneic group and 219 in the autologous/autologous group. (33) Based on the intention-to-treat analysis, there was better median EFS and OS in the autologous/autologous group (35 months vs. 31.7 months, p=NS; 47.2 months vs. 35 months, p=0.07, respectively). If results for only those patients who actually received the autologous/RIC-allogeneic (n=46) or tandem autologous transplants (n=166) were analyzed, the superior OS was again seen in the tandem autologous group (median, 47.2 months vs. 35 months; p=0.07). Updated results of this population were reported with a reference date of July 2008 by Moreau et al. (34) Comparing the results of the 166 patients who completed the tandem autologous HCT protocol to the 46 patients who underwent the entire autologous/RIC-allogeneic program, no difference was seen regarding EFS (median, 25 months vs. 21 months, respectively; p=0.88), with a trend toward superior OS in favor of double autologous HCT (median OS, 57 months vs. 41 months, respectively; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

One study by Bruno et al. included 80 patients with an HLA-identical sibling and who were allowed to choose autografts or autografts for the second transplant (58 completed an autograft/autograft sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence). (35) The results among those completing tandem transplantation showed a higher CR rate at the completion of the second transplant for the autograft/autograft group (55%) than for the autograft/autograft group (26%; p=0.004). EFS and OS were superior for the patients who underwent autologous-allogeneic transplantation (35 months vs 29 months; p=0.02 and 80 months vs. 54 months; p=0.01, respectively). Analyzing the group with HLA-identical siblings versus those without, in a pseudo intention-to-treat analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The TRM rate at 2 years was 2% in the double autograft group and 10% in the autograft/autograft group; 32% of the latter group had extensive, chronic GVHD.

Rosinol et al. reported the results of a prospective study of 110 patients with MM who failed to achieve at least near CR after a first autologous HCT and were scheduled to receive a second autologous transplant (n=85) or an RIC-allogeneic transplant (n=25), depending on the availability of an HLA-identical sibling donor. (36) The autologous/RIC-allogeneic group had a higher CR rate (40% vs. 11%, respectively; p=0.001) and a trend toward a longer PFS (median, 31 months vs. not reached, respectively; p=0.08). There was no statistical difference in EFS or OS between the two groups. The autologous/RIC-allogeneic group experienced a higher transplantation-related mortality rate (16% vs. 5%, respectively; p=0.07) and a 66% chance of chronic GVHD.

Although the results differ among the Garban/Moreau study (33,34) and the other two studies, (35,36) this may be due to different study designs. The Moreau et al. study focused on patients with high-risk disease and involved a conditioning regimen before the RIC-allogeneic transplant that may have eliminated some of the graft-versus-myeloma effect. Other contributing factors may have been non-uniform preparative regimens, different patient characteristics and criteria for advancing to a second transplant (i.e., only patients who failed to achieve a CR or near CR after the first autologous transplant underwent a second), and a small population in the allogeneic group in the Moreau et al. study. The authors suggest that the subgroup of high-risk patients with de novo MM may have equivalent or superior results with a tandem autologous/autologous transplant versus a tandem autologous/RIC-allogeneic transplant and that in patients with standard-risk and/or chemosensitive MM, RIC allograft may be an option.

Interim results of 2 prospective Phase III trials that compared double autologous with single autologous followed by RIC-allogeneic transplant have been published. (37,38) The HOVON Group study at 36 months of follow-up found no significant difference between the groups that received autologous/RIC-allogeneic transplants or tandem autologous transplants in EFS (median, 34 months and 28 months, respectively) or OS (80% and 75%, respectively) at 36 months. (37)
An interim analysis of an EBMT study presented somewhat different inclusion criteria. (38) Previously untreated patients received vincristine, doxorubicin, dexamethasone (VAD) or VAD-like induction treatment, and had a response status of at least stable disease (i.e., complete or partial remission or stable disease) at the time of autologous transplantation, which was also the time point for study inclusion. Patients with an HLA-identical sibling proceeded to RIC-allogeneic transplantation, while those without a matched sibling received no further treatment or a second autologous cell transplant (if treated within a tandem program). A total of 356 patients were included, with a median follow-up of 3.5 years. Of these, 108 patients were allocated to the RIC-allogeneic transplant group and 248 to the autologous transplant group. Of the patients allocated to the allogeneic group, 98 received an RIC-allogeneic transplant. At interim publication, no significant difference in PFS or OS was noted between the double autologous and autologous/RIC-allogeneic transplant recipients.

At 96 months in the EBMT trial, PFS and OS were 22% and 49% versus 12% (p=0.027) and 36% (p=0.030) with autologous/RIC-allogeneic and autologous HCT, respectively. (39) The corresponding relapse/progression rate (RL) was 60% versus 82% (p<0.001). Nonrelapse mortality at 36 months was 13% versus 3% (p<0.001). In patients with the del(13) abnormality, corresponding PFS and OS were 21% and 47% versus 5% (p=0.026), and 31% (p=0.154). (39) Long-term outcome in patients with MM was better with autologous/RIC-allogeneic HCT compared with autologous only, and the autologous/RIC-allogeneic approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation.

Krishnan et al (2011) conducted a phase 3 trial comparing tandem autologous HCT versus tandem autologous HCT plus RIC allo-HCT (tandem auto-allo group) in patients from 37 transplant centers in the United States, who, between 2003 and 2007, had received an autologous HCT (n=710). (40) Of these patients, 625 had standard-risk disease, and 156 (83%) of 189 patients in the tandem auto-allo group and 366 (84%) of 436 in the tandem autologous group received a second transplant. Patients were eligible for transplantation if they were younger than 70 years of age and had completed at least 3 cycles of systemic therapy for myeloma within the past 10 months. Patients were assigned to receive a second autologous or allo-HCT based on the availability of an HLA-matched sibling donor. Patients in the tandem autologous group subsequently underwent random assignment to observation (n=219) or to maintenance therapy with thalidomide plus dexamethasone (n=217). Kaplan-Meier estimates of 3-year PFS were 43% (95% CI, 36% to 51%) in the tandem auto-allo group and 46% (42% to 51%) in the tandem autologous group (p=0.67). OS also did not differ at 3 years (77% [95%, CI, 72% to 84%] vs 80% [CI, 77% to 84%]; p=0.19). Grade 3, 4, or 5 morbidity rates between the 2 groups were 46% and 42%, respectively. The data suggested nonmyeloablative tandem auto-allo-HCT was no more effective than tandem autologous HCT for patients with standard-risk myeloma.

Section Summary
Although the body of evidence has shown inconsistencies in terms of OS and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC allo-HCT, although at a cost of higher TRM compared with conventional treatments.

Allo HCT
Although myeloablative allogeneic HCT may be the only curative treatment in MM (due to its graft-versus-myeloma effect), its use has been limited to younger patients. Even with the limited indications, the toxic death rate related to infections and GVHD is high, and this strategy has been almost completely abandoned. (41)

In an approach to reduce NRM associated with allogeneic HCT, Nonmyeloablative conditioning (RIC) methods have been investigated. Most studies are Phase II studies with no comparison with other treatment modalities. One retrospective study compared myeloablative and non-myeloablative conditioning. (42) This study, conducted by EBMT, found that transplant-related mortality was significantly reduced with RIC but because of a higher relapse or progression rate, there was no significant improvement in OS.

When RIC-allogeneic transplant alone is used in patients with a high tumor burden or with chemotherapy-resistant disease, the immunologic effect of the graft is not sufficient to preclude relapses. (43) Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HCT. (41)

The role of allogeneic HCT remains controversial, in particular because of conflicting data from cooperative group trials, but also because of improvement in outcomes that have been observed with proteasome inhibitors, new
immune modulatory agents, and the use of post-transplant maintenance therapy. These issues have recently been reviewed and summarized.(50,51,55)

**Section Summary**
The role of allo-HCT remains controversial, in particular because of conflicting data from cooperative group trials, but also because of improvement in outcomes with proteasome inhibitors, new immune modulatory agents, and the use of posttransplant maintenance therapy. These issues were reviewed and summarized in 2013, 2014, and 2015.(44,45,55) The evidence for allo-HCT following failed auto-HCT is sufficient to conclude there is likely in some situations a net health benefit.

**Relapsed or Refractory MM**

**Salvage Autologous HCT for Relapsed MM**

Despite the success in improved survival with autologous HCT versus conventional chemotherapy, nearly all patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HCT include novel biologic agents (e.g., thalidomide, lenalidomide, bortezomib, as single agents, in combination with dexamethasone, and in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HCT.(46)

In a multicenter, randomized, open-label, Phase III study from 51 centers across the United Kingdom, between April 16, 2008, and November 19, 2012, Cook et al. recruited patients aged at least 18 years with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT [NCT00747877] and EudraCT (2006-005890-24). (47) Before randomization, eligible patients received bortezomib, doxorubicin, and dexamethasone (PAD) induction therapy and then underwent peripheral blood stem cell mobilization and harvesting, if applicable. Eligible patients were randomly assigned (1:1) to receive either high-dose melphalan 200 mg/m2 plus salvage autologous HCT or oral cyclophosphamide (400 mg/m2/wk for 12 weeks). The primary end point was time to disease progression, analyzed by intention to treat. A total of 297 patients were enrolled, of whom 293 received PAD reinduction therapy. Among the latter, 174 patients with sufficient harvest of peripheral blood stem cells were randomly allocated to undergo salvage HCT (n=89) or receive cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HCT group than in the cyclophosphamide group (19 months [95% CI: 16 to 25] vs. 11 months [95% CI: 9 to 12]; hazard ratio, 0.36 [95% CI: 0.25 to 0.53]; p<0.001). Frequently reported (>10% of patients) grade 3-4 morbidity with PAD induction, salvage HCT, and cyclophosphamide were: neutropenia (125 [43%] of 293 patients after PAD and 63 [76%] of 83 patients in the salvage HCT group vs. 11 [13%] of 84 patients in the cyclophosphamide group), thrombocytopenia (150 [51%] after PAD, 60 [72%] vs. 4 [5%], respectively), and peripheral neuropathy (35 [12%] after PAD, and none vs. none, respectively).

Final survival data for the Myeloma X Relapse trial were reported in 2016.(48) The HCT group had superior median OS (67 months; 95% CI, 55 months to not estimable) compared to the chemotherapy group (52 months; 95% CI, 42 to 60 months; p<0.001). Time to disease progression continued to favor the HCT group at the longer follow-up (19 months [95% CI, 16 to 26 months] vs 11 months [95% CI, 9 to 12 months]; p=0.02). There were no further adverse events related to the HCT procedure reported during longer follow-up. The cumulative incidence of second malignancies was 5.2% (95% CI, 2.1% to 8.2%).

Tandem Autologous HCT for Relapse After First Autologous HCT A 2003 evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation summarized data from 4 relevant clinical series. (49) Reviewers reported that some myeloma patients who relapsed after a first autotransplant achieved durable complete or partial remissions after a second autotransplant as salvage therapy. Factors found to increase the likelihood of durable remissions and extend survival included a chemosensitive relapse, younger age, a long disease-free or progression-free interval since the initial autotransplant, and fewer chemotherapy regimens before the initial autotransplant. Olin et al (2009) reported their experience with 41 patients with MM who received a second salvage autologous HCT for relapsed disease. (46) Median time between transplants was 37 months (range, 3-91 months). Overall response rate in assessable patients was 55%. TRM was 7%. Median follow-up time was 15 months, with median PFS of 8.5 months and median OS 20.7 months. In a multivariate analysis of OS, the number of prior lines of therapy (≥5) and time to progression after initial transplant were the strongest predictors of OS.
**Allo-HCT for Relapse After Initial Autologous HCT**

Qazilbash et al. reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant.(50) Fourteen patients (median age, 52 years) received a second autologous transplant, and 26 patients (median age, 51 years) underwent a reduced-intensity allogeneic transplant. Median interval between first and second transplant was 25 and 17 months for the autologous and allogeneic groups, respectively. After a median follow-up of 18 months (range, 2-69 months) for the autologous group, median PFS was 6.8 months and OS was 29 months, respectively. After a median follow-up of 30 months (range, 13-66 months) for the allogeneic group, median PFS was 7.3 months and OS was 13 months. On univariate analysis, in the allogeneic group, an interval of greater than 1 year between the first and salvage transplants predicted a significantly better OS (p=0.02). None of the prognostic factors that were evaluated for the allogeneic group was found to have a significant impact on survival in the autologous group (which included age, cytogenetics, type of donor, and chronic graft-versus-host disease [GVHD], among others).

EBMT (2013) analyzed 413 MM patients who received a related or unrelated RIC allo-HCT for the treatment of relapse or disease progression after a prior autologous HCT.(51) Median age at RIC allo-HCT was 54 years, and 45% of patients had undergone 2 or more prior autologous transplants. Median OS and PFS from the time of allogeneic transplantation for the entire population were about 25 months and 10 months, respectively. Cumulative NRM at 1 year was about 22%. In a multivariate analysis, cytomegalovirus (CMV) seronegativity of both patient and donor was associated with significantly better PFS, OS, and NRM. Patient-donor sex mismatch was associated with better PFS; fewer than 2 prior autologous transplants was associated with better OS; and shorter time from the first autologous HCT to the RIC allo-HCT was associated with lower NRM. These results suggested patient and donor CMV seronegativity represent key prognostic factors for outcome after RIC allo-HCT for MM that relapses or progresses following 1 or more autologous transplants.

**POEMS Syndrome**

**Systematic Reviews**

A 2012 Cochrane review published provides a comprehensive source on the treatment of POEMS syndrome.(11) Reviewers performed a broad literature search and identified no RCTs, no quasi-RCTs, no historically controlled trials, and no trials with concurrent controls that met selection criteria. Reviewers selected 6 small series (total N=57 patients) evaluating autologous HCT. Two-year survival rates ranged from 94% to 100%. Pooled results suggested that TRM with autologous HCT would be 3 (2.7%) of 112. The reviewers cautioned that long-term outcomes with autologous HCT have not been evaluated and require continuing study.

A second 2012 review article indicates case series suggest most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m2.(5) Responses have been reported as durable but relapse occurs. Symptomatic progression has typically been reported as rare, with most progressions identified as rising vascular endothelial growth factor (VEGF) and radiographic. This author also reports that long-term outcomes with autologous HCT are unclear given the sparse numbers.

**Case Series**

A single-center series published in 2012 from Mayo Clinic reported a 5-year OS of 94% and a PFS of 75% among 59 patients entered between 1999 and late 2011.(52) A second recent series included 9 advanced POEMS syndrome patients who had an Eastern Cooperative Oncology Group performance status score of 3 or 4 and were treated with high-dose melphalan therapy followed by autologous stem cell-transplantation from 2004 to 2011.(53) Eight patients achieved an initial hematologic response, 4 of whom had complete responses. At a median follow-up of 44 months (range, 8-94 months), 7 patients were alive, with 3-year OS rate of 78%. There were no hematologic relapses in the survivors. One patient died of disease progression; the other died of pneumonia, despite a hematologic response 3 months after autologous HCT. All survivors achieved improvement in general performance status and in clinical response.

**Section Summary**

There is a lack of RCT evidence for POEMS syndrome, but cohort studies and case series have reported improvement in symptoms and disease progression after HCT. POEMS syndrome is rare and treatment options are few. In addition, the natural history of POEMS does not suggest that spontaneous improvement will occur in the absence of treatment.
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>
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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT00998270</td>
<td>A Prospective, Randomized Trial of Autologous Bone Marrow Transplantation Compare With Allogenic Bone Marrow Transplantation in Multiple Myeloma</td>
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<td>Oct 2017</td>
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<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>
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<td>Sep 2018</td>
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<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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<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>
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<td>May 2020</td>
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<td>NCT01191060</td>
<td>Randomized Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone to High-Dose Treatment With ASCT in the Initial Management of Myeloma in Patients up to 65 Years of Age</td>
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<td>Sep 2020</td>
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<td>NCT01208766</td>
<td>A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone (VMP) With High Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma</td>
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<td>NCT00747877</td>
<td>Myeloma X Relapse (Intensive): A Phase III Study to Determine the Role of a Second Autologous Stem Cell Transplant as Consolidation Therapy in Patients With Relapsed Multiple Myeloma Following Prior High-dose Chemotherapy and Autologous Stem Cell Rescue</td>
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<td>NCT00670631</td>
<td>Tandem Autotransplantation for Multiple Patients With Less Than 12 Months of Preceding Therapy, Incorporating Bortezomib With the Transplant Chemotherapy and During Maintenance</td>
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<td>Apr 2014</td>
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</table>

NCT: national clinical trial.

Summary of Evidence

**Newly Diagnosed Multiple Myeloma**
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 to high-dose chemotherapy plus autologous HCT. 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. Relevant outcomes include overall survival and treatment-related morbidity. Compared with single autologous HCT, a number of RCTs demonstrated tandem autologous HCT improved OS and recurrence-free survival in newly diagnosed multiple myeloma. The available RCTs compare RIC allogeneic HCT (allo-HCT) following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on "genetic randomization," i.e., patients with a human leukocyte antigen–identical sibling 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 allogeneic HCT, although at a 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 allogeneic HCT (allo-HCT) with as initial or salvage treatment, the evidence includes nonrandomized studies. Relevant outcomes include overall survival and treatment-related morbidity. Studies have reported on patients with both myeloablative and RIC 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 the effects of the technology on health outcomes.

Relapsed or Refractory Multiple Myeloma
For individuals who have relapsed multiple myeloma who receive autologous HCT after failing an autologous HCT, the evidence includes 1 RCT and a systematic review summarizing data from 4 series of patients who relapsed after a first autologous HCT. 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 multiple myeloma who receive tandem autologous HCT after failing the first transplant, the evidence includes 3 RCTs. 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 with respect to treatment approaches and peritransplant support. However, for patients with disseminated POEMS syndrome, a chain of evidence and contextual factors related to the disease and multiple myeloma 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.

Clinical Input Received 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.

2016 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 2016. 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 is investigational for POEMS syndrome.

2009 Input
In response to requests, input was received from 2 academic medical centers while this policy was under review in 2009. One reviewer agreed with the current policy statement related to tandem autologous/RIC-allogeneic 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
In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published evidence-based guidelines on the use of hematopoietic cell transplantation (HCT) in patients with multiple myeloma (MM).(54) 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.

In 2015, ASBMT, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group published joint guidelines based on an expert consensus conference.(55) 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, -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 (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Allogeneic HCT should be performed in the context of a clinical trial if possible; (3) The role of post allogeneic HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.

Mayo Stratification of Myeloma and Risk-Adapted Therapy

Treatment of Newly Diagnosed Multiple Myeloma(55)
The 2013 consensus guideline on the management of newly diagnosed symptomatic multiple myeloma, updating the Mayo Stratification of Myeloma and Risk Adapted Therapy (mSMART), stated there is a greater emphasis on delayed high-dose therapy and autologous cell transplant (ACT).(56) With improved induction therapies resulting in deeper responses, many patients are opting to collect their stem cells and delay ACT while undergoing prolonged induction. Recent evidence has supported this strategy, demonstrating the ongoing benefit of ACT even when delayed.
Treatment of Relapsed Multiple Myeloma
Based on the 2012 mSMART multiple myeloma update, if the patient is considered transplant eligible (off-study), risk status should be determined.\(^{(57)}\) If the patient is standard risk and relapsed after autologous transplant, repeat autologous transplant is an option, after a bortezomib or immunomodulatory derivative-containing regimen. If the standard-risk patient is relapsed after conventional chemotherapy, the recommendation is to proceed to autologous HCT or to repeat the previous regimen to maximum response or 1 year. If the patient is high risk and relapses after an autologous transplant, an autologous followed by an allogeneic transplant is an option in selected patients. If a high-risk patient relapses after bortezomib or immunomodulatory-based initial therapy, autotransplant (followed by allogeneic in selected patients), is recommended.

International Myeloma Working Group
The 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 (TRM), but could be evaluated in well-designed prospective clinical trials.\(^{(58)}\) Nonmyeloablative allo-HCT as first-line therapy is associated with lower TRM but a greater risk of relapse, and convincing evidence is lacking that allo-HCT improves survival compared with autologous HCT.

National Comprehensive Cancer Network\(^{(58)}\)

Autologous HCT
The National Comprehensive Cancer Network (NCCN) guidelines (v.3.2017) 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.\(^{(59)}\)

Tandem HCT
NCCN recommends collecting enough stem cells for 2 transplants in all eligible patients.\(^{(59)}\)

POEMS Syndrome
NCCN guidelines do not address the treatment of POEMS syndrome.\(^{(59)}\)

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


50. Qazilbash MH, Saliba R, De Lima M, et al. Second autologous or allogeneic transplantation after the


Appendix

N/A

History

<table>
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<td>Update coding section – ICD-10 codes are now effective 10/01/2014.</td>
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<td>11/15/12</td>
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02/27/14 Update Related Policies. Change title to 8.01.29 and 8.01.30.
03/21/14 Update Related Policies. Add 8.01.15 and delete 8.01.514.
04/18/14 Update Related Policies. Delete 8.01.20 and add 8.01.529.
06/24/14 Update Related Policies. Delete 8.01.42 and add 8.01.530
11/20/14 Annual Review. Policy updated with literature review through June 15, 2014; no change in policy statements. Reference numbers 2 and 3 were removed; numbers 1, 32, 42, 47, 48, and 50 were added. ICD-9 and ICD-10 diagnosis and procedure codes removed; they do not related to adjudication of the policy.
10/13/15 Annual Review. Policy updated with literature review through July 14, 2015; references 2-3 were removed, references 16, 32, and 54 were added. Policy statements unchanged. Coding update: CPT codes 38320-21 and 86812-16, 86821-22 removed; these are informational and not reviewed in the scope of this policy.
07/12/16 Annual Review. No changes to policy statement.
12/13/16 Interim review. Policy paragraphs restructured and wording edited for more specific restrictions of HCST for POEMS to autologous transplant only and excluding allogeneic including RIC allogeneic, RIC autologous, and tandem transplantations. HCT for myeloma clarified to explicitly require induction chemotherapy achieving partial response or better prior to HCT for initial treatment sequence. Remainder of policy statements unchanged.
03/14/17 Annual review. 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.
06/09/17 Coding update; updated description for CPT codes 38230, 38240, and 38241.

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).
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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.

If you believe that Premera has failed to provide these services or discriminated 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 800-537-7697 (TDD)
  Complaint forms are available at
  https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
  U.S. Department of Health and Human Services
  200 Independence Avenue SW, Room 509F, HHH Building
  Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
  This Notice has Important Information.
  You can 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.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Email AppealsDepartmentInquiries@Premera.com

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

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, using the Federal Civil Rights Complaint Form, available at:
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Email AppealsDepartmentInquiries@Premera.com

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: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalbin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyon wounded coverage babaen iti Premera Blue Cross. Daytoy ket mabalbin dagiti importante a pelta iti daytoy a pakdaar. Mabalbin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga adda aldwag tapno mapagalingasyon nga coverage iti salun-atyo wounded kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tuil nga bukodyo a pasagsao nga awan ti bayadanyon. Tumawig ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso, potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請接電話 800-722-1471 (TTY: 800-842-5357)。
한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에
관하여 그리고 Blue Cross를 통해 커버리지에 관한 정보를
포함하고 있습니다. 본 통지서에는 특이가 되는 날짜들이 있을 수
있습니다. 귀하의 신청 건강 커버리지를 제외 유지하거나 비용을 절감하기
위해서 일정한 마감기까지 조치를 취해야 할 필요가 있을 수 있습니다.
귀하의 이와 같은 정보와 귀하의 만족도 비용 부담없이 얻을 수 있는
업무가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하시오.

România (Romanian):
Prezentă notificarea conține informații importante. Această notificare
poate conține informații importante privind cererea sau acoperirea asigurărilor
dumneavoastră de sănătate prin Blue Cross. Po există date cheie
în această notificare. Este posibil să fie nevoie să acționăm până la anumite
terme limițate pentru a vă menține acoperirea asigurării de sănătate sau
asistența privată la costuri. Aveți dreptul de a obține gratuit aceste
informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471
(TTY: 800-842-5357).

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 clave 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

Тагалог (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang imposaryon. Ang
paunawa na ito ay maaring maglaganang ng mahalagang imposaryon
tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue
Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring
mayroong mahalagang petsa dito sa appikasyon o pag-akom sa pamamagitan
ng Premera Blue Cross. Maaaring mayroong mahalagang petsa dito sa
paunawa. 800-722-1471 (TTY: 800-842-5357).

泰语 (Thai):
ประกาศนี้อาจมีข้อมูลที่สําคัญเกี่ยวกับการการสมัครหรือขอบเขตประกัน
สุขภาพของคุณผ่าน Premera Blue Cross แม้คุณจะต้องไม่เกี่ยวกับ
การประกันสุขภาพของคุณการประกันสุขภาพที่มีอยู่ที่ไม่มีสิทธิ์ใดๆ
ที่จะรับซื้อ คุณมีสิทธิ์ที่จะได้รับข้อมูลและรายละเอียดเพิ่มเติมในภาษาของคุณได้ที่ โทร
800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення
може містити важливу інформацію про Ваше звернення щодо
страхувального покриття через Premera Blue Cross. Зверніть увагу на
ключові дати, які можуть бути вказані у цьому повідомленні. Існує
імовірність того, що Вам треба буде здійснити певні кроки у конкретні
кінцеві строки для того, щоб зберегти Ваше медичне страхування або
отримати фінансову допомогу. У Вас є право на отримання цієї
інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніть
за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông
tin quan trọng về đơn xin tham gia hoặc đơn xin bảo hiểm của quý vị qua
chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông
báo này. Quý vị có thể phải thực hiện một số bước để hoàn thành
điều này, hãy chơi trò chơi để giúp mình thêm về chi phí. Quý vị có
quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình