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

Policy # 00060
Original Effective Date: 01/28/2002
Current Effective Date: 03/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Multiple Myeloma

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider a single or second (salvage) autologous hematopoietic stem-cell transplantation (HSCT) to treat multiple myeloma to be eligible for coverage.

Based on review of available data, the Company may consider tandem** autologous-autologous hematopoietic stem-cell transplantation (HSCT) to treat multiple myeloma be eligible for coverage.

**Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant, and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Based on review of available data, the Company may consider tandem transplantation with an initial round of autologous hematopoietic stem-cell transplantation (HSCT) followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic stem-cell transplantation (HSCT) (i.e., reduced-intensity conditioning transplant) to treat newly diagnosed multiple myeloma patients to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic stem-cell transplantation (HSCT), myeloablative or nonmyeloablative, as upfront therapy of newly diagnosed multiple myeloma or as salvage therapy to be investigational.*
POEMS Syndrome

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider autologous hematopoietic stem-cell transplantation (HSCT) to treat disseminated POEMS syndrome to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic and tandem hematopoietic stem-cell transplantation (HSCT) to treat POEMS syndrome to be investigational.*

Background/Overview
Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (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).

Conventional Preparative Conditioning for HSCT
The conventional (“classical”) practice of allogeneic HSCT 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 stem cells.
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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 pre transplant 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 HSCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT 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 stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT
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 HSCT 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 the purposes of this Policy, the term “RIC” 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.

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” or MGUS). Treatment is usually reserved for patients with symptomatic disease...
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(usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic multiple myeloma prolongs survival when compared to therapy delivered at the time of symptoms or end-organ damage. 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.

POEMS Syndrome
POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma-cell dyscrasia. 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. 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-1β (IL-1β), IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved. However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in the Table. Both major criteria and at least one of the minor criteria are necessary for diagnosis.

Criteria for the Diagnosis of POEMS syndrome

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
<th>Known Associations</th>
<th>Possible Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Monoclonal plasma-proliferative disorder</td>
<td></td>
<td>Weight loss</td>
<td>Restrictive lung disease</td>
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<tr>
<td>Castleman disease</td>
<td></td>
<td>Thrombocytosis</td>
<td>Thrombotic diatheses</td>
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<tr>
<td>Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)</td>
<td></td>
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<tr>
<td>Edema (edema, pleural effusion, ascites)</td>
<td></td>
<td>Polycythemia</td>
<td>Arthralgias</td>
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<tr>
<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)</td>
<td></td>
<td>Hyperhidrosis</td>
<td>Cardiomyopathy (systolic dysfunction)</td>
</tr>
<tr>
<td>Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomatosa, white nails)</td>
<td></td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Papilledema</td>
<td></td>
<td>Low vitamin B12 values</td>
<td>Diarhhea</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. Other large series have been described in the United States and in India. In general, patients with POEMS have a superior overall survival compared with that of MM, nearly 14 years in a large series from the Mayo Clinic. However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported. Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HSCT support. Optimal treatment involves
eliminating the plasma cell clone, for example, by surgical excision or local radiation therapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.

### Rationale/Source

#### 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 24–30 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. These data suggested that autologous SCT was responsible for the trends during 1994–2000, while novel agents have contributed to the improvement since 2001.

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

#### NEWLY DIAGNOSED MM

**Risk-adapted therapy**

The approach to the treatment of newly diagnosed MM (symptomatic) is dictated by eligibility for autologous HSCT and risk-stratification. 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, t(4;14), t(14;16), t(14;20), deletion 13 or hypodiploidy. Standard-risk patients are those with hyperdiploidy, t(11;14) or t(6;14).

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

Recent reviews highlight the treatment of newly diagnosed myeloma, relapsed, and refractory myeloma. A review of the literature highlights advances in the use of autologous and allogeneic HSCT.
Autologous HCT vs 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. The open-label RCT from 59 centers in Europe and Australia used a 2×2 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. In all but 1 study, the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HSCT 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 HSCT. 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 HSCT, randomization was not performed at diagnosis but only after induction treatment, possibly introducing selection bias. Three of the 7 studies showed superior OS in the autologous HSCT group.

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

Systematic Reviews

A 2007 systematic review of 2411 patients enrolled in RCTs compared standard-dose chemotherapy to myeloablative chemotherapy plus single autologous HCT. 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: Autologous HCT vs Standard Chemotherapy**

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**

Tandem HCT 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 tandem autologous transplants (IFM-94) was published in 2003 by Attal et al. This trial randomized patients with newly diagnosed myeloma to single or tandem autologous transplants. Outcomes were analyzed by intention to treat (ITT) at 75-month 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%; p=0.03), relapse-free survival (RFS; 23% vs 13%; p<0.01), and OS (42% vs 21%; p=0.010), all respectively. TRM was 6% and 4% after tandem and single transplants, respectively (p=0.40). Second transplants extended survival only for those who failed to achieve a CR or without a very good partial response after 1 transplant (OS at 7 years, 43% vs 11%, respectively; p<0.001).

An accompanying editorial by Stadtmauer (2003) raised concerns that IFM-94 results might be specific to the regimens used for myeloablative therapy. Patients in the single transplant arm received melphalan 140 mg/m² 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 cited the IFM-95 study as evidence, suggesting melphalan 140 mg/m² plus TBI may be less effective and more toxic than myeloablative therapy plus melphalan 200 mg/m² and no TBI. Based on this, the editorialist hypothesized that increased survival in the IFM-94 tandem arm may have resulted from greater cumulative exposure to melphalan (280 mg/m² vs 140 mg/m²).
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The Bologna 96 clinical study (2007) compared single and double autologous HCT (N=321). 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: Tandem Autologous HCT
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 trials have compared RIC allo-HCT following single or tandem autologous HCT. These trials were based on “genetic randomization,” ie, patients with an human leukocyte antigen (HLA)-identical sibling who were offered RIC allo-HCT following the autologous HCT, whereas the other patients underwent either single or tandem autologous transplants.

The first published, by Garban et al (2006), included high-risk patients. Sixty-five patients were in the autologous followed by RIC allo-HCT group and 219 in the tandem autologous (autologous plus autologous) HCT group. Based on the ITT analysis, there was better median EFS and OS in the tandem autologous HCT group than in the RIC allo-HCT 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 received autologous HCT followed by RIC allo-HCT (n=46) or tandem autologous HCT (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 from this population were reported in 2008 by Moreau et al. Comparing the results of the 166 patients who completed the tandem autologous HCT protocol to the 46 patients who underwent the entire autologous followed by RIC alloengeneic program, no difference was seen in median EFS (25 months vs 21 months, respectively; p=0.88), with a trend toward superior median OS in favor of double autologous HCT (57 months vs 41 months, respectively; p=0.08), due to longer survival after relapse in the tandem autologous transplant arm.

A study by Bruno et al (2007) included 80 patients with an HLA-identical sibling who were allowed to choose allografts or autografts for the second transplant (58 completed an autograft or autolograf sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence). Results among those completing tandem transplantation showed a higher CR rate after the second transplant for the autologous plus allo-HCT group (55%) than for the tandem autologous HCT group (26%; p=0.004). EFS and OS were superior for patients who underwent autologous plus
allogeneic transplantation than for the tandem autologous transplantation (35 months vs 29 months; p=0.02; 80 months vs 54 months; p=0.01, respectively). Comparing the group with HLA-identical siblings and those without, in a pseudo-ITT analysis, EFS and OS were significantly longer in the group with HLA-identical siblings. The TRM rate at 2 years was 2% in the tandem autologous group and 10% in the autologous plus allogeneic group; 32% of the latter group had extensive, chronic GVHD.

Rosinol et al (2008) 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. The autologous followed by RIC allogeneic group had a higher CR rate (40% vs 11%, respectively; p=0.001) and a trend toward a longer median PFS (31 months vs not reached, respectively; p=0.08). There were no statistical differences in EFS or OS estimates between groups. The autologous followed by RIC allogeneic group experienced a higher TRM rate (16% vs 5%, respectively; p=0.07) and had a 66% chance of chronic GVHD.

Although results differed between the Garban (2006) and the Moreau (2008) studies and the Bruno (2007) and the Rosinol (2008) studies, these differences may have been due to study designs. The Moreau 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 nonuniform preparative regimens, different patient characteristics, and criteria for advancing to a second transplant (ie, 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 study. Reviewers suggested that the subgroup of high-risk patients with de novo MM may have had equivalent or superior results with a tandem autologous HCT versus a tandem autologous plus RIC allo-HCT and that, in patients with standard-risk and/or chemosensitive MM, RIC allograft may be an option.

Interim meeting abstracts for 2 prospective phase 3 trials comparing double autologous with single autologous followed by RIC allogeneic transplant have been published. The HOVON Group study (2008) at 36-month follow-up, found no significant differences between groups that received autologous followed by RIC allogeneic transplants or tandem autologous transplants in median EFS (34 months and 28 months, respectively) or in OS (80% and 75%, respectively). The other interim analysis of an European Group for Blood and Marrow Transplant (EBMT) study (2008) presented different inclusion criteria. Previously untreated patients received vincristine, doxorubicin, and dexamethasone (VAD) or VAD-like induction treatment, and had a response status of at least stable disease (ie, 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 allo-HCT, 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 allo-HCT group and 248 to the autologous transplant group. Of patients allocated to the allogeneic group, 98 received an RIC allogeneic transplant. At interim reporting, no significant differences in PFS or OS estimates were noted between the tandem autologous HCT recipients and tandem autologous plus allo-HCT recipients.
At 96 months in the EBMT trial (2013), PFS and OS rates were 22% and 49% versus 12% (p=0.027) and 36% (p=0.030) for tandem autologous plus RIC allo-HCT versus autologous HCT, respectively. The corresponding relapse or progression rates were 60% and 82% (p<0.001), respectively. Nonrelapse mortality rates at 36 months were 13% versus 3% (p<0.001), respectively. In patients with the chromosome 13 deletion (del[13]), corresponding PFS and OS estimates were 21% versus 5% (p=0.026) and 47% versus 31% (p=0.154), respectively. Long-term outcomes in patients with MM were better with autologous HCT followed by RIC allo-HCT than with autologous HCT only, and the autologous followed by 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). 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.

Subsection Summary: Tandem Autologous HCT Followed by RIC Allo-HCT
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 allo-HCT may be the only curative treatment in MM (due to its graft-versus-myeloma effect), its use has been restricted to younger patients. Even with the limited indications, the toxicity-related death rate for infections and GVHD is high, and this strategy has been almost completely abandoned.

In an approach to reduce NRM associated with allo-HCT, nonmyeloablative conditioning (RIC) methods have been investigated. Most studies are phase 2, with no comparison with other treatment modalities. One retrospective study compared myeloablative and nonmyeloablative conditioning. This study, conducted by EBMT, found that TRM was significantly reduced with RIC but, because of a higher relapse or progression rate, there was no significant improvement in OS.
When RIC allo-HCT 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. Therefore, RIC allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HCT.

Section Summary: Allo-HCT

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 and 2014. The evidence for allo-HCT is insufficient to draw conclusions.

RELAPSED OR REFRACTORY MM

Salvage Autologous HCT for Relapsed MM

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

The Myeloma X Relapse trial was a multicenter, randomized, open-label, phase 3 study involving 51 centers across the United Kingdom, with enrollment occurring between April 2008 and November 2012. Inclusion criteria were patients at least 18 years and with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT (NCT00747877; EudraCT 2006-005890-24). 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 randomized (1:1) to high-dose melphalan 200 mg/m² plus salvage autologous HCT or to oral cyclophosphamide 400 mg/m²/wk for 12 weeks. The primary end point was time to disease progression, analyzed by ITT. 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 randomized to salvage HCT (n=89) or cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HCT group (19 months; 95% CI, 16 to 25 months) than in the cyclophosphamide group (11 months; 95% CI, 9 to 12 months; HR=0.36, 95% CI, 0.25 to 0.53; p<0.001). Frequently reported (>10% of patients) grade 3 or 4 morbidity with PAD induction, salvage HCT, and cyclophosphamide were: neutropenia (43% [125/293] patients receiving PAD vs 76% [63/83] patients receiving salvage HCT vs 13% [11/84] patients receiving cyclophosphamide), thrombocytopenia (51% [150] after PAD, 72% [60] vs 5% [4]), and peripheral neuropathy (12% [35] after PAD, and none vs none), all respectively.

Final survival data for the Myeloma X Relapse trial were reported in 2016. 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];
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. 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. 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 (2006) reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant. Fourteen patients (median age, 52 years) received a second autologous transplant and 26 patients (median age, 51 years) underwent a RIC allo-HCT. Median interval between first and second transplant was 25 months for the autologous group and 17 months for the allogeneic group. 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. 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. Univariate analysis in the allogeneic group found that an interval of more than 1 year between the first and salvage transplants predicted a significantly better OS (p=0.02). None of the prognostic factors evaluated for the allogeneic group had a significant impact on survival in the autologous group (eg, age, cytogenetics, type of donor, chronic GVHD).

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. 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. 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 found that case series suggested most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m\(^2\). 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 and radiographic. The reviewer also reported that long-term outcomes with autologous HCT are unclear given the sparse numbers.

Case Series
A single-center series published in 2012 reported a 5-year OS rate of 94% and a PFS rate of 75% among 59 patients entered between 1999 and late 2011. A second series (2014) included 9 patients with advanced POEMS syndrome who had Eastern Cooperative Oncology Group Performance Status scores of 3 or 4 and were treated with high-dose melphalan therapy followed by autologous HCT from 2004 to 2011. Eight patients achieved an initial hematologic response, 4 of whom had CRs. At a median follow-up of 44 months (range, 8-94 months), 7 patients were alive, with a 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 improved in general performance status and in clinical response.

Section Summary: POEMS Syndrome
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.

SUMMARY OF EVIDENCE
Newly Diagnosed Multiple Myeloma
For individuals who have newly diagnosed multiple myeloma who receive autologous HCT as initial treatment, the evidence includes several prospective, 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,
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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 allo-HCT following a first autologous HCT with single or tandem autologous transplants. The RCTs were based on “genetic randomization,” ie, patients with a human leukocyte antigen—identical sibling who were offered an RIC allo-HCT following autologous HCT, whereas other patients underwent either 1 or 2 autologous transplants. Although the body of evidence has shown inconsistencies in terms of overall survival and disease-free survival rates, some studies have shown a survival benefit with tandem autologous HCT followed by RIC 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 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.

**References**

14. Food and Drug Administration (FDA). Tissue and Tissue Products
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01/28/2002 Managed Care Advisory Council approval
12/06/2006 Medical Policy Committee approval. Coverage eligibility unchanged.
09/09/2008 Medical Director review

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09/09/2010 Medical Policy Committee approval.
09/09/2010 Medical Policy Committee approval.

09/16/2009 Medical Policy Committee approval.
09/16/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.

09/15/2010 Medical Policy Committee approval.

09/15/2009 Medical Policy Committee approval.
09/15/2009 Medical Policy Implementation Committee approval. No change to coverage eligibility.

09/03/2009 Medical Policy Committee approval.
09/03/2009 Medical Policy Implementation Committee approval.

09/03/2010 Medical Policy Committee implementation.
09/03/2010 Medical Policy Committee implementation.

09/01/2011 Medical Policy Committee review
09/01/2011 Medical Policy Implementation Committee approval. Title changed. Coverage for POEMS syndrome added.

09/06/2012 Medical Policy Committee review
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09/14/2011 Medical Policy Committee review
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10/03/2013 Medical Policy Committee review
10/16/2013 Medical Policy Implementation Committee approval. Title changed. Coverage for POEMS syndrome added.

03/05/2015 Medical Policy Committee review
03/05/2015 Medical Policy Implementation Committee approval. No change to coverage eligibility.

03/03/2016 Medical Policy Committee review
03/03/2016 Medical Policy Implementation Committee approval. No change to coverage.

03/19/2015 Medical Policy Implementation Committee approval. Tandem autologous-autologous hematopoietic stem-cell transplantation to treat multiple myeloma clarified.
03/19/2015 Medical Policy Committee review

03/02/2017 Medical Policy Committee review
03/02/2017 Medical Policy Implementation Committee approval. No change to coverage.

03/15/2017 Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 03/2018

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  B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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  A. In accordance with nationally accepted standards of medical practice;
  B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
  C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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