Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

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

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for hematopoietic stem cell transplantation for multiple myeloma when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Multiple myeloma

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

Tandem autologous-autologous hematopoietic stem-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 Considerations).

Tandem transplantation with an initial round of autologous hematopoietic stem-cell transplantation followed by a non-marrow-ablative conditioning regimen and allogeneic hematopoietic stem-cell transplantation (i.e., reduced-intensity conditioning transplant) may be considered **medically necessary** to treat newly diagnosed multiple myeloma patients.

POEMS syndrome

Autologous hematopoietic stem-cell transplantation may be considered **medically necessary** to treat disseminated POEMS syndrome.

When Policy Topic is not covered

Multiple myeloma

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

POEMS syndrome

Allogeneic and tandem hematopoietic stem-cell transplantation are considered **investigational** to treat POEMS syndrome.

Considerations

A near complete response, as defined by the European Group for Blood and Marrow Transplant (EBMT) is the disappearance of M protein at routine electrophoresis, but positive immunofixation. (4) A very good partial response has been defined as a 90% decrease in the serum paraprotein level. (5)

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

Coverage will **not** be provided for:
- Transplant services when the cost is covered by government, foundation or charitable grants
- The purchase price of organs which are sold rather than donated to the recipient.
- An artificial organ

Reimbursement for Stem Cell collection and storage are considered payable under the Transplant Benefit when billed as a one-time, all-inclusive charge.

Transplant Benefit
The date on which the Transplant Benefit starts accumulating is determined by the transplant coordinator. The Transplant Benefit ends when the Transplant Lifetime Maximum benefit (if applicable) has been exhausted.

Benefits include:
- hospitalization of the recipient for medically recognized transplants from a donor to a transplant recipient;
- evaluation tests requiring hospitalization to determine the suitability of both potential (member's benefits must be verified with regard to the potential donor who does not turn out to be the actual donor) and actual donors, when such tests cannot be safely and effectively performed on an outpatient basis (**Note:** The member's benefits must be verified with regard to the **potential** donor who does not turn out to be the **actual** donor.);
- hospital room, board and general nursing in semi-private rooms;
- special care units, such as coronary and intensive care;
- hospital ancillary services;
- physicians' services for surgery, technical assistance, administration of anesthetics, and medical care;
- acquisition, preparation, transportation, and storage of organ / tissue / cells;
- diagnostic services;
- drugs which require a prescription by federal law;
- medical and surgical care of the donor (related to the procurement of the organ / tissue / cells) if coverage is not available to the donor from any other source. (Covered services provided to a donor will be applied against the recipient's transplant maximum benefit, if applicable)

If the donor and recipient are both listed on the same (family) policy, BCBSKC charges only one deductible and one coinsurance, if applicable.

In addition to the specific organ criteria, transplant candidates must also meet the following general criteria, including, but not limited to:
- Since compliance is a major factor in transplant graft survival, the patient (or legal guardian) must have the ability to accept and understand the transplant procedure and to maintain compliance with long-term medical management and immunosuppression.
- If applicable, patients with a history of malignancy must have passed the recommended length of time to be considered cured for that specific cancer. A complete metastatic evaluation must be performed before a patient will be considered an acceptable transplant candidate.
- Patients with a history of alcohol or substance abuse must have a six month history of abstinence as evidenced by negative urine or serum drug screens taken randomly.
- The patient must have adequate cardiopulmonary status.
- The patient must be free from active infection.

A covered person is eligible for retransplantation as deemed medically necessary and appropriate by BCBSKC. Review of a retransplantation request will include review of the covered person’s compliance with relevant transplant selection criteria including, but not limited to, adherence to medication regimens, follow-up examinations and abstinence from the use of alcohol and drugs.

Clinical trials for conditions other than those allowed in this policy may be available in the research setting. However, these trials are considered investigational and/or experimental and therefore contract exclusions.

Note: There are some state mandates in place that require insurance carriers to cover certain clinical trials under very specific guidelines. Please contact your BCBSKC representative for more information.

Description of Procedure or Service

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) 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). Cord blood is discussed in greater detail in a separate policy.

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 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 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 “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 is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable, with estimated new cases and deaths in 2008 in the United States 19,920 and 10,690, respectively. (1) 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)

The disease is staged by estimating tumor mass, based on various clinical parameters like hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure. (1) 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 (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. (1,2) In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized, and referred to as smoldering multiple myeloma. (3) The overall risk of disease progression from smoldering to symptomatic multiple myeloma 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. (2)

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. (3, 4) 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. (5) 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. (4, 6) 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. (6)

Criteria for the diagnosis of POEMS syndrome (4**,** 6**)**

Major Criteria	**Minor Criteria**	**Known Associations**	**Possible Associations**
Polyneuropathy	Sclerotic bone lesions	Clubbing	Pulmonary hypertension
Monoclonal plasmaproliferative	Castleman disease	Weight loss	Restrictive lung disease

disorder			
	Organomegaly	Thrombocytosis	
	(splenomegaly, hepatomegaly, or lymphadenopathy)		Thrombotic diatheses
		Polycythemia	
			Arthralgias
	Edema		
		Hyperhidrosis	
	(edema, pleural effusion, or ascites)		
			Cardiomyopathy (systolic dysfunction)
	Endocrinopathy		
	(adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)		Fever
			Low vitamin B12 values
	Skin changes		
	(hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)		Diarrhea
	Papilledema		

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.(7) Other large series have been described in the United States (4, 6, 8) and in India.(9) 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. (6) However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported. (10) 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. (4, 6) 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. (4, 11)

Rationale

The earliest versions of this policy were based on two 1996 and two 1998 TEC Assessments. Since 1999, the treatment of multiple myeloma (MM) has changed radically.

The literature search for this Policy was updated through mid-March 2013. No new evidence was identified that would support a change in any of the Policy statements on multiple myeloma. New information on POEMS syndrome has been added to the Policy.

Multiple Myeloma

Treatment Overview

In the prechemotherapy era, the median survival for a patient diagnosed with multiple myeloma (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 multiple myeloma, 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 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. (14, 15) 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. (14, 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)

Risk-adapted therapy

The approach to the treatment of newly diagnosed MM (symptomatic) is dictated by eligibility for autologous hematopoietic stem-cell transplantation (HSCT) 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, t(4;14), t(14;16), t(14;20), deletion 13 or hypodiploidy. (17) Standard-risk patients are those with hyperdiploidy, t(11;14) or t(6;14).

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. High-risk patients are generally treated with a bortezomib-based induction followed by autologous HSCT and then bortezomib-based maintenance. (17)

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

Single autologous HSCT versus standard chemotherapy

As a result of several prospective, randomized trials that were conducted comparing conventional chemotherapy with high-dose therapy and autologous HSCT for patients with multiple myeloma, autologous HSCT has become the treatment of choice in patients younger than 65 years of age.

Data from 7 randomized studies are available. (21-27) In all but 1 study, (23) 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. (23) 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. (21) Three of the 7 studies showed superior OS in the autologous HSCT group. (22, 25, 27)

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. (22) 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. (25)

The reasons for the discrepant results among these randomized studies are uncertain but may be related to the conditioning regimens or patient age.

A meta-analysis of 2,411 patients enrolled in randomized controlled trials (RCTs) compared standard-dose chemotherapy versus myeloablative chemotherapy with single autologous HSCT. (28) The authors of the meta-analysis concluded that myeloablative therapy with autologous HSCT increased the likelihood of PFS (hazard of progression: 0.75; 95% confidence interval [CI]: 0.59–0.96) but not OS (hazard of death: 0.92; 95% CI: 0.74–1.13); the odds ratio for treatment-related mortality (TRM) was 3.01 (95% CI: 1.64–5.50) in the group with autologous HSCT. However, the effects of myeloablative chemotherapy and autologous HSCT may have been diluted by the fact that up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HSCT as salvage therapy when the multiple myeloma progressed. This could account for the lack of a significant difference in OS between the two groups in the study.

These randomized trials of autologous HSCT following induction therapy were designed and implemented prior to the availability of thalidomide, lenalidomide, and bortezomib. The introduction of these agents has dramatically changed the treatment paradigm of MM. Ongoing trials incorporating these newer agents into induction regimens are ongoing. Preliminary results have shown CRs in a substantial proportion of these patients, opening the question as to what role autologous HSCT will continue to play. However, it will require further follow-up to determine if these newer induction regimens will translate into improved survival. (29)

Salvage HSCT

Despite the success in improved survival with autologous HSCT versus conventional chemotherapy, nearly all patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed MM after a prior autologous HSCT include novel biologic agents (e.g., thalidomide, lenalidomide, and bortezomib, as single agents, in combination with dexamethasone, and in combination with cytotoxic agents or with each other), traditional chemotherapy, or a second HSCT. (30)

Repeat Autologous HSCT for Relapse After Initial Autologous HSCT

An evidence-based systematic review (31) sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from 4 relevant clinical series. Investigators 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 that apparently increased the likelihood of durable remissions and extended survival included a chemosensitive relapse, younger age, a long disease-free or progression-free interval since the initial autotransplant, and fewer chemotherapy regimens prior to the initial autotransplant. Thus, clinical judgment plays an important role in selecting patients for this treatment with a reasonable likelihood that potential benefits may exceed harms.

Olin and colleagues reported their experience with 41 patients with MM who received a second salvage autologous HSCT for relapsed disease. (30) Median time between transplants was 37 months (range 3–91 months). Overall response rate in assessable patients was 55%. Treatment-related mortality 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.

Allogeneic HSCT for Relapse After Initial Autologous HSCT

Qazilbash and colleagues reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant. (32) 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 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 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).

Tandem HSCT

A tandem transplant involves an autologous transplant followed by a preplanned second transplant, either another autologous or a reduced-intensity conditioning (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-autologous HSCT

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. (33) Outcomes were analyzed by intention-to-treat at 75 months' 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 event-free (EFS; 20% vs. 10%, respectively; p=0.03), relapse-free (RFS; 23% vs. 13%, respectively; p<0.01), and overall (OS; 42% vs. 21%, respectively; p=0.010) survival. Treatment-related mortality 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 (34) 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 vs. 140 mg/m2).

The Bologna 96 clinical study, (35) compared single with double autologous HSCT (n=321). Patients undergoing tandem autologous HSCT were more likely than those with a single autologous HSCT to attain at least a near CR (47% vs. 33%, respectively; p=0.008), to prolong RFS (median, 42 vs. 24 months, respectively; p<0.001), and extend EFS (median, 35 vs. 23 months, respectively; p=0.001). There was no significant difference between the groups in TRM (3–4%). There was a trend for improved OS among patients in the double-transplantation group (7-year rate of 60%), as compared with the single-transplantation group (7-year rate of 47%; p=0.10). Conversely, among patients achieving CR or near CR after one transplantation, EFS and OS were not significantly different according to transplantation(s) received by study randomization. A subgroup analysis of outcomes of patients assigned to the two treatment arms was evaluated according to response and showed similar

results to the Attal et al. study, (32) in that the benefit of a second transplant was seen only in patients who did not achieve at least a very good partial response (PR) with the first transplant.

Tandem Autologous/Reduced-intensity Conditioning (RIC) Allogeneic HSCT
Several RCTs have been published comparing RIC-allogeneic HSCT following a first autologous HSCT to autologous transplants, single or in tandem. These studies were based on "genetic randomization," that is, patients with a human leukocyte antigen (HLA)-identical sibling were offered an RIC-allogeneic HSCT following the autologous HSCT, whereas the other patients underwent either one or two autologous transplants.

The first published study by Garban and colleagues 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. (36) Based on the intention-to-treat analysis, there was better median EFS and OS in the autologous/autologous group (35 months versus 31.7; p=NS and 47.2 months versus 35; 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 vs. 35 months; p=0.07). Updated results of this population were reported with a reference date of July 2008 by Moreau and colleagues.(37) Comparing the results of the 166 patients who completed the whole tandem autologous HSCT protocol to the 46 patients who underwent the entire autologous/RIC-allogeneic program, no difference was seen regarding EFS (median 25 vs. 21 months, respectively; p=0.88), with a trend toward superior OS in favor of double autologous HSCT (median OS 57 vs. 41 months, respectively; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

One study by Bruno and colleagues included 80 patients with an HLA-identical sibling and who were allowed to choose allografts or autografts for the second transplant (58 completed an autograft/allograft sequence) and 82 without an HLA-identical sibling who were assigned to tandem autografts (46 completed the double autograft sequence). (38) The results among those completing tandem transplantation showed a higher complete response (CR) rate at the completion of the second transplant for the autograft/allograft 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; p=0.02 and 80 months vs. 54; 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 treatment-related mortality rate at 2 years was 2% in the double autograft group and 10% in the autograft/allograft group; 32% of the latter group had extensive, chronic GVHD.

Rosinol and colleagues reported the results of a prospective study of 110 patients with MM who failed to achieve at least near-complete remission after a first autologous HSCT 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. (39) 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 (36, 37) and the other two studies, (38, 39) the authors of the Moreau et al. study suggest that this is 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 get 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.

The final results of 2 completed prospective Phase III trials comparing double autologous with single autologous followed by RIC-allogeneic transplant are awaited. (40, 41) Interim results of the study by the HOVON Group 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. (40) An interim analysis of a European Group for Blood and Marrow Transplant (EBMT) study was recently presented with somewhat different inclusion criteria. (41) 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 stem-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. As of now, there is no significant difference in PFS or OS between the double autologous and autologous/RIC-allogeneic transplant recipients. However, the follow-up is too short for firm conclusions to be drawn and the study is still ongoing.

An important variable in these studies is the use of different conditioning regimens. (42)

Krishnan and colleagues conducted a Phase 3 trial comparing tandem autologous-autologous HSCT (auto-auto group) versus tandem autologous-RIC allogeneic HSCT (auto-allo group) in patients from 37 transplant centers in the U.S., who between 2003 and 2007, had received an autologous HSCT (n=710). (43) Of these patients, 625 had standard-risk disease, and 156 of 189 patients (83%) in the auto-allo group and 366 of 436 (84%) in the auto-auto group received a second transplant. Patients were eligible 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 allogeneic HSCT based on the availability of an HLA-matched sibling donor. Patients in the auto-auto group subsequently underwent random assignment to observation (n=219) or maintenance therapy with thalidomide plus dexamethasone (n=217). Kaplan-Meier estimates of 3-year PFS were 43% (95% CI: 36-51) in the auto-allo group and 46% (42-51) in the auto-auto group (p=0.67). OS also did not differ at 3 years (77% [95%, CI: 72-84] versus 80% [CI: 77-84]; p=0.19). Grade 3-5 adverse events between the two groups were 46% and 42%, respectively. The authors concluded that non-myeloablative allogeneic HSCT after autologous HSCT is not more effective than tandem autologous HSCT for patients with standard-risk myeloma.

Allogeneic HSCT

Even though myeloablative allogeneic HSCT 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 considered too high, and this strategy has been almost completely abandoned. (44)

Nonmyeloablative conditioning (RIC) methods have since been used. Most studies are Phase II studies with no comparison to other treatment modalities. One retrospective study compared myeloablative and non-myeloablative conditioning. (45) This study, conducted by the EBMT, found that transplant-related mortality was significantly reduced with RIC but because of a higher relapse/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 avoid relapses.

(42) Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HSCT. (44)

Future direction
Despite recent advances in the treatment of MM, with new drugs and drug combinations, autologous HSCT, and reduced-intensity allografts, it remains an incurable disease. Future challenges will be how to integrate the best combinations of new and old drugs for initial induction treatments, conditioning regimens, and postinduction maintenance.

Summary
Several prospective, randomized trials have been conducted comparing conventional chemotherapy with high-dose therapy and autologous hematopoietic stem-cell transplantation (HSCT) for patients with newly diagnosed multiple myeloma, and superior complete response rates and prolongation of progression-free and overall survival has been demonstrated with autologous HSCT.

A systematic review that summarized data from 4 clinical series found that some myeloma patients who relapsed after a first autologous HSCT achieved durable partial or complete remissions after a second autologous HSCT as salvage therapy.

Randomized trials comparing a single autologous to a tandem autologous HSCT have shown improved survival with the use of tandem HSCT but that the benefit of the second HSCT appears to be limited to patients who did not achieve at least a very good partial response with the first transplant.

The results of trials comparing tandem autologous-reduced-intensity conditioning (RIC) allogeneic HSCT to tandem autologous-autologous have shown conflicting results, although most studies have not shown a survival benefit with tandem autologous-RIC allogeneic, and have shown higher transplant-related mortality. Factors across studies that may account for differing trial results include different study designs, non-uniform preparative regimens, different patient characteristics (including risk stratification) and criteria for advancing to a second transplant. The future of the use of tandem autologous-RIC allogeneic in treating myeloma will depend on additional trials with longer follow-up data.

The use of allogeneic HSCT with myeloablative conditioning may cure a minority of patients, but is associated with a high transplant-related mortality. Nonmyeloablative allogeneic HSCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse, and convincing evidence is lacking that allogeneic HSCT improves survival as compared to autologous HSCT. Therefore, allogeneic HSCT in treating myeloma is considered investigational (except as a component of a tandem autologous-RIC allogeneic HSCT).

Practice Guidelines and Position Statements

Treatment of Newly Diagnosed Multiple Myeloma Based onMayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART):
If the patient is considered transplant eligible (off-study), risk status should be determined. If the patient is standard risk, after induction therapy, autologous HSCT is recommended (with the option to continue induction therapy if response is good). If patient is not in CR or very good PR after the first autologous HSCT, a second autologous HSCT may be considered. In patients considered high risk, if after 4 cycles of bortezomib, lenalidomide, and dexamethasone, (especially if the patient is not in CR), autologous HSCT is recommended.

Available online at: http://www.msmart.org/newly%20diagnosed%20myeloma.pdf.

Treatment of Relapsed Multiple Myeloma Based onMayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART):

If the patient is considered transplant eligible (off-study), risk status should be determined. 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 HSCT 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.

Available online at: http://msmart.org/relapsed%20myeloma.pdf.

International Myeloma Working Group Consensus Statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma (46):
The conclusions and recommendations are as follows: Myeloablative allogeneic HSCT 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. Nonmyeloablative allogeneic HSCT as first-line therapy is associated with lower TRM but a greater risk of relapse, and convincing evidence is lacking that allogeneic HSCT improves survival as compared to autologous HSCT.

2013 National Comprehensive Cancer Network (NCCN) Practice Guidelines
Autologous HSCT:
Autologous HSCT is considered 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.

Repeat autologous HSCT as salvage therapy may be considered for:
- patients initially treated with primary therapy alone followed by the 1st autologous HSCT when the disease relapsed, who now have progressive disease following the first autologous HSCT (category 2A); and,
- patients who have progressive disease after the first autologous HSCT (category 2A).

Tandem autologous-autologous HSCT:
The NCCN Myeloma panel recommends collecting enough stem cells for two transplants in all eligible patients. A tandem transplant can be considered for all patients who are candidates for HSCT, and is an option for patients who do not achieve at least a VGPR after the first autologous HSCT. (category 2A)

Allogeneic HSCT:
Myeloablative allogeneic HSCT is an accepted option in the setting of a clinical trial (category 2A) in patients with responsive or primary progressive disease or as salvage therapy in patients with progressive disease following an initial autologous HSCT. Allogeneic HSCT may include nonmyeloablative allogeneic HSCT following an autologous HSCT (category 2A) or myeloablative allogeneic HSCT on a clinical trial (off trial category 3). Current data do not support nonmyeloablative allogeneic HSCT alone.

Ongoing trials
National Cancer Institute PDQ® Clinical Trial Database
A search of the National Cancer Institute's database of clinical trials identified the following Phase III trials addressing HSCT and a comparator in the treatment of myeloma:
- Second autologous HSCT versus low-dose consolidation therapy after relapse (NCT00747877)
- Risk-adapted therapy (NCT00546988)
- Tandem transplantation (NCT00670631)
- Single autologous HSCT and maintenance versus tandem autologous HSCT and maintenance therapy (NCT01109004)
- Autologous versus allogeneic HSCT (Phase II/III; NCT00998270)

- Single versus tandem autologous HSCT (NCT01208766)
- Conventional-dose induction therapy followed by maintenance versus high-dose therapy with autologous HSCT in the initial treatment of myeloma (NCT01191060)
- Comparison of the drug combination of lenalidomide, bortezomib and dexamethasone with or without HSCT in newly diagnosed myeloma (NCT01208662).

Clinical Input Received through Physician Medical Societies and Academic Medical Centers (December 2009)
In response to requests, input was received from 2 academic medical centers while this policy was under review in 2009. 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. 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 HSCT is investigational for salvage therapy was a late addition to the policy and was not sent for clinical input.)

POEMS Syndrome

A comprehensive source of information on treatment of POEMS is a Cochrane review that was published in 2012. (10) The authors performed a broad literature search, including CENTRAL (2012, Issue 2), MEDLINE (January 1966 to February 2012), EMBASE (January 1980 to February 2012), and CINAHL Plus (January 1937 to February 2012). They identified no randomized controlled trials (RCTs), no quasi-RCTs, no historically controlled trials or trials with concurrent controls that met their study selection criteria. The Cochrane authors included 6 small series of patients (total n=57) who underwent autologous HSCT. Two-year survival rates ranged from 94-100%. The review authors indicated that if all published experience with autologous HSCT was pooled, transplant-related mortality would be 3 of 112 (2.7%). They caution that long-term outcomes with autologous HSCT have not been elucidated 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/m^2. (4) 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 HSCT are unclear given the sparse numbers. However, 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. (47)

Summary
No RCTs of hematopoietic stem-cell transplantation (HSCT) have been performed in patients with POEMS syndrome, nor is it likely such studies will ever be performed given the rarity of this condition. Available case reports and series are subject to selection bias and are heterogeneous with respect to treatment approaches and peri-transplant support. However, for autologous HSCT, a chain of indirect evidence suggests improved health outcomes, as several case studies have reported good clinical responses. In addition, certain contextual factors and strong clinical consensus support that autologous HSCT may be considered medically necessary for disseminated POEMS syndrome. Allogeneic and tandem HSCT are considered investigational to treat POEMS syndrome.

National Comprehensive Cancer Network (NCCN) Practice Guidelines 2013
As of March 29, 2013, the NCCN has not proffered recommendations for the treatment of POEMS syndrome.

National Cancer Institute PDQ® Clinical Trial Database

A search of the National Cancer Institute's online database of clinical trials on March 29, 2013 identified no clinical trials specifically addressing HSCT and a comparator in the treatment of POEMS syndrome.

Clinical Input Received through Physician Medical Societies and Academic Medical Centers (July 2013)

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. 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. There was near-consensus that autologous HSCT is medically necessary for POEMS syndrome, and near-consensus that allogeneic and tandem HSCT is investigational for POEMS syndrome.

References

1. Kyle RA, Rajkumar SV. Multiple myeloma. Blood 2008; 111(6):2962-72.
2. Palumbo A, Rajkumar SV. Treatment of newly diagnosed myeloma. Leukemia 2009; 23(3):449-56.
3. Dispenzieri A. Long-term outcomes after autologous stem cell transplantation in patients with POEMS syndrome. Clin Adv Hematol Oncol 2012; 10(11):744-6.
4. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol 2012; 87(8):804-14.
5. Bardwick PA, Zvaifler NJ, Gill GN et al. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine (Baltimore) 1980; 59(4):311-22.
6. Dispenzieri A, Kyle RA, Lacy MQ et al. POEMS syndrome: definitions and long-term outcome. Blood 2003; 101(7):2496-506.
7. Nasu S, Misawa S, Sekiguchi Y et al. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 2012; 83(5):476-9.
8. Dispenzieri A, Moreno-Aspitia A, Suarez GA et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. Blood 2004; 104(10):3400-7.
9. Singh D, Wadhwa J, Kumar L et al. POEMS syndrome: experience with fourteen cases. Leuk Lymphoma 2003; 44(10):1749-52.
10. Kuwabara S, Dispenzieri A, Arimura K et al. Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome. Cochrane Database Syst Rev 2012; 6:CD006828.
11. Dispenzieri A. How I treat POEMS syndrome. Blood 2012; 119(24):5650-8.
12. Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. Br J Haematol 1998; 102(5):1115-23.
13. Fermand JP, Katsahian S, Divine M et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005; 23(36):9227-33.
14. Reece DE. Recent trends in the management of newly diagnosed multiple myeloma. Curr Opin Hematol 2009; 16(4):306-12.
15. Reece D, Harousseau JL, Gertz MA. Myeloma Management 2009: Nontransplant therapy of myeloma, high-dose therapy for myeloma, and apersonalized care plan for treatment of myeloma. 2009 American Society of Clinical Oncology Annual Meeting Educational Handbook/ 2009:502-9.
16. Fonseca R. Strategies for risk-adapted therapy in myeloma. Hematology Am Soc Hematol Educ Program 2007:304-10.
17. Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011; 86(1):57-65.
18. Larocca A, Palumbo A. Evolving paradigms in the treatment of newly diagnosed multiple myeloma. J Natl Compr Canc Netw 2011; 9(10):1186-96.

19. van de Donk NW, Lokhorst HM, Dimopoulos M et al. Treatment of relapsed and refractory multiple myeloma in the era of novel agents. Cancer Treat Rev 2011; 37(4):266-83.
20. Nishihori T, Alsina M. Advances in the autologous and allogeneic transplantation strategies for multiple myeloma. Cancer Control 2011; 18(4):258-67.
21. Attal M, Harousseau JL. The role of high-dose therapy with autologous stem cell support in the era of novel agents. Semin Hematol 2009; 46(2):127-32.
22. Attal M, Harousseau JL, Stoppa AM et al. A prospective randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996; 335(2):91-7.
23. Barlogie B, Kyle RA, Anderson KC et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial 9321. J Clin Oncol 2006; 24(6):929-36.
24. Blade J, Rosinol L, Sureda A et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish Cooperative Group PETHEMA. Blood 2005; 106(12):3755-9.
25. Child JA, Morgan GJ, Davies FE et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348(19):1875-83.
26. Fermand JP, Ravaud P, Chevret S et al. High-dose therapy and autologous peripheral blood stem-cell transplantation in multiple myeloma: upfront or rescue treatment? Results of a multicenter sequential randomized trial. Blood 1998; 92(9):3131-6.
27. Palumbo A, Bringhen S, Petrucci MT et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50-70: results of a randomized controlled trial. Blood 2004; 104(10):3052-7.
28. Koreth J, Cutler CS, Djulbegovic B et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials. Biol Blood Marrow Transplant 2007; 13(2):183-96.
29. Bensinger WI. Role of autologous and allogeneic stem cell transplantation in myeloma. Leukemia 2009; 23(3):442-8.
30. Olin RL, Vogl DT, Porter DL et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant 2009; 43(5):417-22.
31. Hahn T, Wingard JR, Anderson KC et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. Biol Blood Marrow Transplant 2003; 9(1):4-37.
32. Qazilbash MH, Saliba R, De Lima M et al. Second autologous or allogeneic transplantation after the failure of first autograft in patients with multiple myeloma. Cancer 2006; 106(5):1084-9.
33. Attal M, Harousseau JL, Facon T et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003; 349(26):2495-502.
34. Stadtmauer EA. Multiple myeloma, 2004--one or two transplants? N Engl J Med 2003; 349(26):2551-3.
35. Cavo M, Tosi P, Zamagni E et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol 2007; 25(17):2434-41.
36. Garban F, Attal M, Michallet M et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04) trial in high-risk de novo multiple myeloma. Blood 2006; 107(9):3474-80.
37. Moreau P, Garban F, Attal M et al. Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous transplantation in high-risk de novo multiple myeloma. Blood 2008; 112(9):3914-5.
38. Bruno B, Rotta M, Patriarca F et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007; 356(11):1110-20.
39. Rosinol L, Perez-Simon JA, Sureda A et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood 2008; 112(9):3591-3.

40. Lokhorst H, Mutis, I. Allogeneic transplantation and immune interventions in multiple myeloma. Hematology Education: the education program for the annual congress of the European Hematology Association, 2008; 2:106-14.
41. Bjorkstrand B, Iacobelli S, Hegenbart U et al. Autologous stem cell transplantation (ASCT) versus ASCT followed by reduced-intensity conditioning allogeneic SCT with identical sibling donor in previously untreated multiple myeloma: preliminary analysis of a prospective controlled trial by the EBMT. Bone Marrow Transplant 2008; 41:S38.
42. Gahrton G, Bjorkstrand B. Allogeneic transplantation in multiple myeloma. Haematologica 2008; 93(9):1295-300.
43. Krishnan A, Pasquini MC, Logan B et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol 2011; 12(13):1195-203.
44. Harousseau JL. The allogeneic dilemma. Bone Marrow Transplant 2007; 40(12):1123-8.
45. Crawley C, Iacobelli S, Bjorkstrand B et al. Reduced-intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. Blood 2007; 109(8):3588-94.
46. Lokhorst H, Einsele H, Vesole D et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. J Clin Oncol 2010; 28(29):4521-30.
47. D'Souza A, Lacy M, Gertz M et al. Long-term outcomes after autologous stem cell transplantation for patients with POEMS syndrome (osteosclerotic myeloma): a single-center experience. Blood 2012; 120(1):56-62.

Billing Coding/Physician Documentation Information

38204 Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206 Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207 Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209 Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210 Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211 Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212 Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213 Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214 Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215 Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38220 Bone marrow; aspiration only
38221 Bone marrow; biopsy, needle or trocar
38240 Bone marrow or blood-derived peripheral stem cell transplantation; allogenic
38241 Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242 Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
S2140 Cord blood harvesting for transplantation, allogeneic
S2142 Cord blood-derived stem cell transplantation, allogeneic
S2150 Bone marrow or blood-derived stem cells (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.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

12/1/01	New policy. Added to Surgery and Lab sections
12/1/02	Added primary amyloidosis as an investigational indication; removed from Lab section and added to Transplant section.
12/1/03	No policy statement changes; changed title name to: Single or Tandem High-dose Chemotherapy with Hematopoietic Stem Cell Support for Multiple Myeloma and Primary Amyloidosis
12/1/04	Removed primary amyloidosis from the policy; added information regarding tandem transplants and mini-transplants; added policy statement regarding repeat autotransplants for relapse after initial autotransplant; changed name of title to: Single or Tandem High-dose Chemotherapy with Hematopoietic Stem Cell Support for Multiple Myeloma
12/1/05	No policy statement change
4/1/06	Considerations section revised to include general criteria.
12/1/06	No policy statement changes.
12/1/07	Policy statement revised to include language regarding tandem transplants in newly diagnosed multiple myeloma. Responsive multiple myeloma clarified.
12/1/08	Policy updated with literature search, reference numbers 38-43 added. “High-dose chemotherapy” removed from policy title and policy statements. “Stem-cell transplantation” (SCT) now used instead of “stem cell support” (SCS) in policy and policy statements. Intent of current policy statements unchanged. New policy statement added regarding situations when autologous SCT may be indicated for patients with primary progressive myeloma.
12/1/09	No policy statement changes.
12/1/10	Policy statements updated to reflect current practice. Allogeneic HSCT as salvage therapy added to policy statement as investigational.
12/1/11	Minor change to policy statements (added phrase “in the tandem sequence” to the medically necessary tandem autologous-autologous statement).
12/1/12	No policy statement changes.
12/1/13	Policy title changed. Policy updated with literature search through mid-March 2013; no change in multiple myeloma policy statements. POEMS syndrome added, with a medically necessary statement for autologous HSCT for disseminated disease; allogeneic and tandem HSCT for POEMS are investigational.