Protocol

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

(80117)

Medical Benefit		**Effective Date**: 01/01/14	**Next Review Date**: 09/17
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 05/10, 05/11, 05/12, 05/13, 09/13, 09/14, 09/15, 09/16	

Preauthorization is required and must be obtained through Case Management.

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

Populations	Interventions	Comparators	Outcomes
Individuals: • With newly diagnosed multiple myeloma	Interventions of interest are: • Autologous HSCT • Tandem autologous-autologous HSCT • Tandem autologous-allogeneic HSCT • Allogeneic HSCT	Comparators of interest are: • Conventional chemotherapy with or without novel therapies	Relevant outcomes include: • Overall survival • Treatment-related morbidity
Individuals: • With relapsed or refractory multiple myeloma	Interventions of interest are: • Autologous HSCT • Tandem autologous-autologous HSCT • Tandem autologous-allogeneic HSCT • Allogeneic HSCT	Comparators of interest are: • Conventional chemotherapy with or without novel therapies	Relevant outcomes include: • Overall survival • Treatment-related morbidity
Individuals: • With POEMS syndrome	Interventions of interest are: • Autologous HSCT • Tandem autologous-autologous HSCT • Tandem autologous-allogeneic HSCT • Allogeneic HSCT	Comparators of interest are: • Conventional chemotherapy with or without novel therapies	Relevant outcomes include: • Overall survival • Treatment-related morbidity

HSCT: hematopoietic stem cell transplantation.

Description

Multiple myeloma (MM) is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable. POEMS syndrome is a rare, paraneoplastic disorder secondary to a plasma-cell dyscrasia. The acronym POEMS reflects the hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

Summary of Evidence

Multiple Myeloma

The evidence for autologous hematopoietic stem cell transplantation (HSCT) for upfront treatment in patients who have newly diagnosed multiple myeloma includes several prospective, randomized controlled trials (RCTs) that compared conventional chemotherapy with high-dose chemotherapy with autologous HSCT. Relevant outcomes include overall survival (OS) and treatment-associated morbidity. In general, the evidence suggests OS rates are improved with autologous HSCT compared with conventional chemotherapy in this setting. Limitations

of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for autologous HSCT for treatment of relapsed MM following autologous HSCT or refractory disease includes one RCT and a systematic review that summarized data from four clinical series of patients who relapsed after a first autologous HSCT. Relevant outcomes include OS and treatment-related morbidity. In general, the evidence suggests OS rates are improved with autologous HSCT compared with conventional chemotherapy in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for tandem autologous HSCT in patients who have MM who fail to achieve at least a near complete or very good partial response after the first transplant in the tandem sequence (i.e., refractory disease) includes three RCTs. Relevant outcomes include OS and treatment-related morbidity. The evidence shows tandem autologous HSCT improves OS rates in this setting. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for tandem autologous HSCT followed by reduced-intensity conditioning (RIC) allogeneic HSCT in patients who have newly diagnosed MM includes several RCTs comparing RIC-allogeneic HSCT following a first autologous HSCT with autologous transplants, single or in tandem (these studies were based on "genetic randomization," i.e., patients with an HLA-identical sibling were offered an RIC allogeneic HSCT following the autologous HSCT, whereas the other patients underwent either one or two autologous transplants). Relevant outcomes include OS and treatment-related morbidity. Although the body of evidence shows inconsistencies in terms of OS and DFS rates, some studies have shown a survival benefit with tandem autologous-RIC allogeneic HSCT, 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 quantitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for allogeneic HSCT with myeloablative or nonmyeloablative conditioning for upfront or salvage treatment in patients who have MM includes nonrandomized studies. Relevant outcomes include OS and treatment-related morbidity. Limitations of the published evidence include patient heterogeneity; variability in treatment protocols; short follow-up periods; inconsistency in reporting important health outcomes; and, inconsistency in reporting or collecting outcomes. Nonmyeloablative allogeneic HSCT as first-line therapy is associated with lower transplant-related mortality but a greater risk of relapse; convincing evidence is lacking that allogeneic HSCT improves survival compared with autologous HSCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

POEMS Syndrome

The evidence for HSCT of any type in patients who have POEMS syndrome includes case reports and series. Relevant outcomes include OS and treatment-related morbidity. No RCTs of HSCT 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 indirect evidence and contextual factors related to the disease and MM, suggests improvement in health outcomes with autologous HSCT. The evidence is sufficient to determine qualitatively that autologous HSCT results in a meaningful improvement in the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

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 Policy Guidelines.)

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.

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

Autologous hematopoietic stem cell transplantation may be considered **medically necessary** to treat disseminated POEMS syndrome. (See Policy Guidelines)

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

Policy Guidelines

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

A complete response has been defined by the International Myeloma Working Group of the International Myeloma Foundation as negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and > 5% plasma cells in bone marrow. Other response criteria have been determined by them for these categories: stringent complete response, very good partial response, partial response, and stable disease.[43]

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

Medicare Advantage

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

Background

Hematopoietic 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 radiotherapy. 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 "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous 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 antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the class I and class II loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

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 before 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 before engraftment, but not GVHD.

RIC 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 nonrelapse 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 alloge-

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

Multiple Myeloma

MM is a systemic malignancy of plasma cells that represents approximately 10% of all hematologic cancers. It is treatable but rarely curable. At the time of diagnosis, most patients have generalized disease, and the selection of treatment is influenced by patient age, general health, prior therapy, and the presence of complications of the disease.[1-3]

The disease is staged by estimating tumor mass, based on various clinical parameters such as hemoglobin, serum calcium, number of lytic bone lesions, and the presence or absence of renal failure. MM usually evolves from an asymptomatic premalignant stage (termed monoclonal gammopathy of undetermined significance). Treatment is usually reserved for patients with symptomatic disease (usually progressive myeloma), whereas asymptomatic patients are observed, as there is little evidence that early treatment of asymptomatic MM prolongs survival when compared with therapy delivered at the time of symptoms or end-organ damage.[1, 2] In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized and referred to as smoldering MM. The overall risk of disease progression from smoldering to symptomatic MM is 10% per year for the first five years, approximately 3% per year for the next five years, and 1% for the next 10 years.[1, 2]

POEMS Syndrome

POEMS syndrome (also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takatsuki syndrome) is a rare, paraneoplastic disorder secondary to a plasma-cell dyscrasia.[4, 5] This complex, multiorgan disease was first described in 1938, but the acronym POEMS was coined in 1980, reflecting hallmark characteristics of the syndrome: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.[6] No single test establishes the presence of POEMS syndrome. Its pathogenesis is undefined, although some evidence suggests it is mediated by imbalance of proinflammatory cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α; vascular endothelial growth factor may also be involved.[5, 7] However, specific criteria have been established, and the syndrome may entail other findings in the constellation of signs and symptoms, as shown in Table 1. Both major criteria and at least one of the minor criteria are necessary for diagnosis.[7]

Table 1: Criteria and Associations

Major Criteria	Minor Criteria	Known Associations	Possible Associations
Polyneuropathy			
	Sclerotic bone lesions	Clubbing	Pulmonary hypertension
Monoclonal plasma-proliferative disorder			
	Castleman disease	Weight loss	Restrictive lung disease
	Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)	Thrombocytosis	Thrombotic diatheses
	Edema (edema, pleural effusion, ascites)	Polycythemia	Arthralgias
	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)	Hyperhidrosis	Cardiomyopathy (systolic dysfunction)
	Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)		Fever
	Papilledema		Low vitamin B12 values

Major Criteria	Minor Criteria	Known Associations	Possible Associations
			Diarrhea

The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.[8] Other large series have been described in the United States[5, 7, 9] and in India.[10] In general, patients with POEMS have a superior OS compared with that of MM, nearly 14 years in a large series from Mayo Clinic.[7] However, given the rarity of POEMS, no randomized controlled trials (RCTs) of therapies have been reported.[11] Numerous approaches have included ionizing radiation, plasmapheresis, intravenous immunoglobulin, interferon-α, corticosteroids, alkylating agents, azathioprine, tamoxifen, transretinoic acid, and high-dose chemotherapy with autologous HSCT support.[5, 7] Optimal treatment involves eliminating the plasma cell clone, for example, by surgical excision or local radiotherapy for an isolated plasmacytoma, or systemic chemotherapy in patients with disseminated disease, such as medullary disease or multiple plasmacytomas. Given the underlying plasma cell dyscrasia of POEMS, newer approaches to MM, including bortezomib, lenalidomide, and thalidomide, are also under investigation.[5, 12]

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, parts 1270 and 1271.[13] Hematopoietic stem cells are included in these regulations.

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

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

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

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