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Medical Policy Manual

Topic: Hematopoietic Stem-Cell Transplantation for Multiple Myeloma and POEMS Syndrome

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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).

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 (conventional) regimens.

Multiple Myeloma

Multiple myeloma is a systemic malignancy of plasma cells that represents a small but significant proportion of all hematologic cancers. It is treatable but rarely curable, with estimated new cases and deaths in 2012 in the U.S. of 21,700 and 10,710, 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.

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.[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-1β (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 the table below. Both major criteria and at least one of the minor criteria are necessary for diagnosis.[7]

Criteria For The Diagnosis Of POEMS Syndrome[5,7]

Major Criteria	Minor Criteria	Known Associations	Possible Associations
• Polyneuropathy • Monoclonal plasma-proliferation disorder	• Sclerotic bone lesions • Castleman disease • Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Edema (edema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails) • Papilledema	• Clubbing • Weight loss • Thrombocytosis • Polycythemia • Hyperhidrosis	• Pulmonary hypertension • Restrictive lung disease • Thrombotic diatheses • Arthralgias • Cardiomyopathy (systolic dysfunction) • Fever • Low vitamin B12 values • 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 overall survival compared with that of multiple myeloma; with one study reporting a median survival of nearly 14 years, in a large series from the Mayo Clinic.[7] However, given the rarity of POEMS, no randomized controlled trials of therapies have been reported.[11] 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.[5,7] 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.[5,12]

MEDICAL POLICY CRITERIA

I. Autologous HSCT

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

II. Tandem HSCT

A. Tandem autologous-autologous HSCT may be considered **medically necessary** to treat newly diagnosed (i.e., previously untreated) multiple myeloma.

B. Tandem transplantation with an initial autologous HSCT followed by reduced-intensity conditioning allogeneic HSCT may be considered **medically necessary** to treat newly diagnosed (i.e., previously untreated) multiple myeloma.

III. Allogeneic HSCT

A. Myeloablative allogeneic HSCT is considered **investigational** as initial therapy of newly diagnosed (i.e., previously untreated) multiple myeloma or as salvage therapy (after a failed prior course of autologous HSCT).

B. Nonmyeloablative (reduced intensity conditioning) allogeneic HSCT is considered **investigational** as initial therapy of newly diagnosed (i.e., previously untreated) multiple myeloma or as salvage therapy (after a failed prior course of autologous HSCT).

IV. POEMS Syndrome

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

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

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

SCIENTIFIC EVIDENCE

The principal outcomes associated with treatment of hematologic malignancies are typically measured in units of survival past treatment: disease-free survival (DFS), a period of time following treatment where the disease is undetectable; progression-free survival (PFS), the duration of time after treatment before the advancement or progression of disease; and overall survival (OS), the period of time the patient remains alive following treatment. Risk of graft-versus-host disease is another primary outcome among patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Ideally, in order to understand the impact of HSCT for treatment of multiple myeloma, comparative clinical trials that compare this therapy to standard medical treatment, such as standard conditioning regimens, are needed. Further, for treatment of hematologic malignancies, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits associated with treatment to understand the net treatment effect.

Single Autologous HSCT

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.

Meta-Analysis

A meta-analysis of 2,411 patients enrolled in randomized controlled trials compared standard dose chemotherapy versus myeloablative chemotherapy with single autologous HSCT.[13] The authors of the meta-analysis concluded that myeloablative therapy with autologous HSCT increased the likelihood of PFS (hazard of progression=0.75; 95% 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 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.

Randomized Controlled Trials (RCTs)

Currently, data from 7 randomized studies are available.[14-20] In all but 1 study, the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HSCT arm.[19] This study published final results of the S9321 trial, which was initiated in 1993, and randomized 516 patients with multiple myeloma to receive either standard therapy or myeloablative conditioning with melphalan 140 mg/m^2 plus total body irradiation followed by autologous HSCT.[19] The authors reported virtually no difference in outcomes, including response rates, progression-free survival, and OS.

In 5 of the 7 studies, the superior CR rate translated into a significant increase in progression-free survival (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.[20] Three of the 7 studies showed superior OS in the autologous HSCT group.[14,15,17]

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.[14] The group that underwent autologous HSCT had significantly improved response rates, event-free and overall survival. Seven years later, the British Medical Research Council published similar results.[15]

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

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 multiple myeloma. 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 a role. However, it will require further follow-up to determine if these newer induction regimens will translate into improved survival.[21]

Salvage Transplantation

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 multiple myeloma 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.[22] No clear standard of care exists.

Repeat Autologous HSCT for Relapse After Initial Autologous HSCT

Systematic Review

An evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from 4 relevant clinical series.[23] 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.

Non-randomized Trials

Olin et al. reported their experience with 41 patients with multiple myeloma who received a second salvage autologous HSCT for relapsed disease.[22] 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.

Although not conclusive, available evidence on the use of autologous transplant following relapse is sufficient to suggest treatment benefit.

Allogeneic HSCT for Relapse After Initial Autologous HSCT

Qazilbash et al. reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant.[24] 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. 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).

Evidence on the use of allogeneic transplant as salvage treatment after initial autotransplant is not suggestive of increased treatment benefit compared with autologous transplant.

Tandem Transplant

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 (i.e., previously untreated) myeloma to single or tandem autologous transplants.[25] 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 (3rd) 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%, p=0.03), relapse-free (RFS; 23% vs. 13%; p<0.01), and overall (OS; 42% vs. 21%, 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 complete (CR) or very good partial response (VGPR) after one transplant (OS at 7 years: 43% vs. 11%, p<0.001), however the methodological shortcomings limit reliability of this finding (comparing outcomes in subgroups was not one of the study objectives, study was not adequately

powered for subgroup analyses).

An accompanying editorial by Stadtmauer raised concerns that these results might be specific to the regimens used for myeloablative therapy in IFM-94.[26] Patients in the single transplant arm received 140 mg/m^2 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/m^2 melphalan plus TBI may be less effective and more toxic than myeloablative therapy than 200 mg/m^2 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, compared single with double autologous HSCT (n=321).[27] Patients undergoing tandem autologous HSCT were more likely than those with a single autologous HSCT to attain at least a near complete response (47% vs. 33%; p=0.008), to prolong relapse-free survival (median, 42 vs. 24 months; p<0.001), and extend event-free survival (median, 35 vs. 23 months; p=0.001). There was no significant difference between the groups in treatment-related mortality (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 transplant, 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 study, in that the benefit of a second transplant was seen only in patients that did not achieve at least a very good partial response with the first transplant.[25] However, the methodological shortcomings limit reliability of this finding.

Results from available randomized controlled trials demonstrate small but significant clinical improvements with tandem autologous transplants among treatment naïve patients; such evidence may be suggestive of a treatment benefit. However, methodological limitations demonstrate the need for additional clinical trials.

Tandem Autologous/Reduced-Intensity Conditioning (RIC) Allogeneic HSCT

Several randomized controlled trials 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 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.

- The first published study by Garban et al. included high-risk patients (including deletion of chromosome 13).[28] Sixty-five patients were in the autologous/RIC-allogeneic group and 219 in the autologous/autologous group. 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 et al.[29] 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, p=0.88), with a trend toward superior

OS in favor of double autologous HSCT (median OS 57 vs. 41 months; p=0.08), due to a longer survival after relapse in the tandem autologous transplant arm.

- One study by Bruno et al. included 80 patients with an HLA-identical sibling and who were allowed to choose 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).[30] The results among those completing tandem transplantation showed a higher complete response 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 graft-versus-host disease.

- Rosinol et al. reported the results of a prospective study of 110 patients with multiple myeloma 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.[31] The autologous/RIC-allogeneic group had a higher CR rate (40% vs. 11%; p=0.001) and a trend toward a longer PFS (median 31 months vs. not reached, 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%; p=0.07) and a 66% chance of chronic graft-versus-host disease.

- 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).[32] 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% [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.

Although the results differ among the Garban/Moreau study[28,29] and the other studies[30-32] the authors of the Moreau study suggest that this is due to different 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 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 study. The authors suggest that the subgroup of high-risk patients with de novo multiple myeloma 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 multiple myeloma, RIC allograft may be an option.

Currently, the final results of 2 recently completed prospective Phase III trials comparing double autologous with single autologous followed by RIC-allogeneic transplant are awaited.[33,34] 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.[33] An interim analysis of a European Group for Blood and Marrow Transplant (EBMT) study was recently presented with somewhat different inclusion criteria.[34] 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 a 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.

Although not conclusive, available evidence on tandem autologous and RIC allogeneic HSCT indicates potential for treatment benefit; however, risk of harm associated with second transplant has been poorly characterized.

Allogeneic HSCT

Even though myeloablative allogeneic HSCT may be the only curative treatment in multiple myeloma (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.[35]

Mortality can be reduced through the use of RIC regimens, and can be considered for older patients up to 65 years of age. However, when RIC-allogeneic transplant 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.[35] Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HSCT.[35]

Evidence on the use of allogeneic HSCT as a first-line or salvage therapy does not suggest that potential treatment benefit outweighs risk of harm.

POEMS Syndrome

In 2012, Kuwabara and colleagues performed a Cochrane review of HSCT treatment of POEMS syndrome which identified no randomized controlled trials (RCTs), no quasi- RCTs, no historically controlled trials or trials with concurrent controls that met their study selection criteria.[11] The 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 indicated case series suggest most patients achieve at least some neurologic and functional improvement using conditioning doses of melphalan ranging from 140 to 200 mg/m2.[5] Responses have been reported as durable but relapse occurs. Symptomatic progression has typically been reported as rare, with most progressions identified as rising vascular endothelial growth factor (VEGF) and radiographic. This author also reports that long-term outcomes with autologous 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.[36]

It is unlikely that randomized controlled trials of HSCT in patients with POEMS syndrome will be feasible, given the rarity of the condition. The current evidence regarding HSCT in patients with POEMS Syndrome consists mainly of small case series[9,37-41] (n<60) and review articles.[42-45] In addition, the criteria for diagnosing and treating the multiple potential symptoms associated with POEMS, has not been well defined. However, for autologous HSCT, a chain of indirect evidence suggests improved health outcomes, as several case studies have reported good clinical responses in patients diagnosed with POEMS syndrome. Without larger treatment studies, the efficacy of allogenic and tandem HSCT for patients with POEMS is unknown.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

Current guidelines from the NCCN address the use of autologous and allogenic hematopoietic stem cell transplantation (HSCT) as follows:[46]

- Autologous Single Transplant

  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.

  A repeat autologous HSCT as salvage therapy may be considered in patients with progressive disease following an initial autologous HSCT (with or without primary therapy) and in patients with progressive disease who initially had a response to treatment with a single or tandem autologous HSCT.

- Tandem Autologous-Autologous Transplant

  NCCN recommends collecting enough stems cells for all patients eligible for HSCT. 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 very good partial response after the initial autologous HSCT (a category 2A recommendation).

- Allogeneic Transplant

NCCN guidelines consider myeloablative allogeneic HSCT as an accepted option in the setting of a clinical trial (category 2A) in patients with responsive or primary progressive disease. Salvage therapy may include nonmyeloablative allogeneic HSCT following an autologous HSCT (category 2A) or myeloablative allogeneic HSCT on a clinical trial (off trial category 3).

No clinical practice guidelines could be identified which address the use of HSCT as a treatment for patients with POEMS syndrome.

Summary

Autologous Single Transplant

Several prospective, randomized trials have been conducted comparing conventional chemotherapy with high-dose therapy and autologous hematopoietic stem cell transplant (HSCT) for patients with newly diagnosed multiple myeloma. Superior complete response rates and prolongation of progression-free and overall survival have been demonstrated with autologous HSCT. Therefore, autologous HSCT may be considered medically necessary as a first-line or salvage treatment.

Tandem Autologous-Autologous

Randomized trials comparing a single autologous to a tandem autologous HSCT have shown improved survival with the use of tandem HSCT, but 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 use of tandem autologous-autologous transplant is therefore considered medically necessary among previously untreated patients.

Tandem Autologous Followed by Reduced-Intensity Conditioning and Allogeneic HSCT Transplant

The results of trials comparing tandem autologous-reduced-intensity conditioning (RIC) allogeneic HSCT to tandem autologous-autologous transplant have shown conflicting results, although most studies have not shown a survival benefit with tandem autologous-RIC allogeneic transplant, 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 different criteria for advancing to a second transplant. The future of tandem autologous-RIC allogeneic transplants in treating myeloma will depend on additional trials with longer follow-up data. However, current evidence is sufficient to suggest potential for treatment benefit among previously untreated patients; therefore, use of this technique is considered medically necessary among these patients.

Allogeneic Transplant

The use of allogeneic HSCT with myeloablative conditioning may cure a minority of patients but is associated with 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 with autologous HSCT. Therefore, allogeneic HSCT in treating myeloma is considered investigational (except as a component of a tandem autologous-RIC allogeneic HSCT).

POEMS Syndrome

Given the relatively low prevalence and lack of specific diagnostic criteria for POEMS Syndrome, it is unlikely that RCTs will be available to evaluate the use of HSCT in patients with 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, several small studies indicated improved health outcomes and overall survival. Therefore, autologous HSCT may be considered medically necessary for disseminated POEMS syndrome.

Although available case series on the use of allogeneic and tandem HSCT as a treatment for POEMS syndrome contribute to the body of literature, they are not sufficient to determine relative treatment risk versus benefit balance favoring these treatments. Therefore, allogeneic and tandem HSCT are considered investigational to treat POEMS syndrome.

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CODES	NUMBER	DESCRIPTION
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Bone marrow; aspiration only
	38221	Bone marrow; biopsy, needle or trocar
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	;autologous transplantation
	38243	;HPC boost

CODES	NUMBER	DESCRIPTION
	38242	Allogeneic lymphocyte infusions
HCPCS	J9000–J9999	Chemotherapy drugs code range
	Q0083–Q0085	Chemotherapy administration code range
	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)