Hematopoietic Cell Transplantation for Multiple Myeloma and POEMS Syndrome

Effective: January 1, 2018

Next Review: August 2018
Last Review: December 2017

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

POEMS syndrome, also known as osteosclerotic myeloma, is a complex multiorgan disease which includes a variety of symptoms including polyneuropathy. Transplantation for these patients as well as multiple myeloma patients is performed to restore bone marrow function following bone-marrow-toxic doses of chemotherapy.

MEDICAL POLICY CRITERIA

Note: See Appendix I for a glossary of terms.

I. Autologous hematopoietic cell transplant may be considered medically necessary to treat multiple myeloma or POEMS syndrome for either of the following (A. or B.):
   A. Single initial or second (salvage) transplant to treat multiple myeloma.
   B. Patients with disseminated POEMS syndrome. Patients with disseminated POEMS syndrome may have diffuse sclerotic lesions or disseminated bone marrow involvement.
II. Tandem hematopoietic cell transplant may be considered **medically necessary** to treat newly diagnosed (i.e., previously untreated) multiple myeloma for either of the following (A. or B.):

A. Autologous-autologous tandem hematopoietic cell transplant
B. Tandem transplantation with an initial autologous hematopoietic cell transplant followed by reduced-intensity conditioning allogeneic hematopoietic cell transplant

III. Hematopoietic cell transplant is considered **investigational** in the treatment of multiple myeloma or POEMS syndrome for any of the following (A.-D.):

A. Tandem hematopoietic cell transplant for POEMS syndrome
B. Myeloablative allogeneic hematopoietic cell transplant as initial therapy for newly diagnosed (i.e., previously untreated) multiple myeloma or as salvage therapy (after a failed prior course of autologous hematopoietic cell transplant)
C. Nonmyeloablative (reduced intensity conditioning) allogeneic hematopoietic cell transplant as an initial therapy for newly diagnosed (i.e., previously untreated) multiple myeloma or as salvage therapy (after a failed prior course of autologous hematopoietic cell transplant)
D. Allogeneic hematopoietic cell transplant to treat POEMS syndrome

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.

**CROSS REFERENCES**

1. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03
2. [Placental and Umbilical Cord Blood as a Source of Stem Cells](#), Transplant, Policy No. 45.16

**BACKGROUND**

**HEMATOPOIETIC CELL TRANSPLANTATION**

Hematopoietic cell transplantation (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the 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 cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte 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 HCT

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

REDUCED-INTENSITY CONDITIONING FOR ALLOGENEIC HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less-intensive regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For 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 (MM)
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 2017 in the U.S. of 30,280 and 12,590, respectively. 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. 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. In some patients, an intermediate asymptomatic but more advanced premalignant stage is recognized, and referred to as smoldering multiple myeloma. 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.

POEMS SYNDROME

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

Criteria for the Diagnosis of POEMS Syndrome

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<th>Known Associations</th>
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<td>Polyneuropathy</td>
<td>Sclerotic bone lesions</td>
<td>Clubbing</td>
<td>Pulmonary hypertension</td>
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<td>Monoclonal plasma-proliferation disorder</td>
<td>Castleman disease</td>
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<td>Edema (edema, pleural effusion, or ascites)</td>
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The prevalence of POEMS syndrome is unclear. A national survey in Japan showed a prevalence of about 0.3 per 100,000.[8] Other large series have been described in the United States[5,7,9] and in India.[10] In general, patients with POEMS have a superior 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 HCT 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]

EVIDENCE SUMMARY

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 cell transplantation (HCT). Ideally, in order to understand the impact of HCT for treatment of multiple myeloma or POEMS syndrome, 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 HCT

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

Systematic Reviews

A meta-analysis of 2,411 patients enrolled in randomized controlled trials compared standard dose chemotherapy versus myeloablative chemotherapy with single autologous hematopoietic stem cell transplant (HCT).[13] The authors of the meta-analysis concluded that myeloablative therapy with autologous HCT 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

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treatment-related mortality was 3.01 (95% CI: 1.64–5.50) in the group with autologous HCT. However, the effects of myeloablative chemotherapy and autologous HCT may have been diluted by the fact that up to 55% of patients in the standard chemotherapy group received myeloablative chemotherapy with autologous HCT 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**

One RCT was identified that compared autologous HCT to standard chemotherapy plus lenalidomide, a newer agent for treatment of MM.[14] The study was an open label RCT from 59 centers in Europe and Australia that used a 2x2 factorial design to compare 4 groups 1) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide alone, 2) standard consolidation therapy plus HCT, followed by maintenance with lenalidomide and prednisone 3) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide alone, and 4) consolidation with chemotherapy plus lenalidomide, followed by maintenance with lenalidomide plus prednisone. The primary outcome for this study was progression-free survival (PFS), and mean followup at the time of publication was 52 months. Median PFS was superior for the HCT group compared to chemotherapy plus lenalidomide (43.3 months, 95% CI 33.2-52.2 months vs 28.6 months, 95% CI 20.6-36.7 months, p<0.0001). The rate of grade 3 or 4 adverse events was higher for the HCT group compared to chemotherapy for hematological events (84% vs 26%), gastrointestinal complications (20% vs 5%), and infections (19% vs 5%).

Data are available from seven randomized trials of autologous HCT following induction therapy that were designed and implemented prior to the availability of thalidomide, lenalidomide, and bortezomib.[15-21] 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 HCT 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.[22]

In all but one of the seven studies, the complete response (CR) rate was superior in the high-dose chemotherapy/autologous HCT arm.[20] 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/m² plus total body irradiation followed by autologous HCT.[20] The authors reported virtually no difference in outcomes, including response rates, progression-free survival, and OS. In five of the seven studies, the superior CR rate translated into a significant increase in progression-free survival (PFS). However, in the two studies that did not show an improved PFS with autologous HCT, randomization was not performed at diagnosis, but only after induction treatment, possibly introducing selection bias.[21] Three of the seven studies showed superior OS in the autologous HCT group.[15,16,18] The Intergroupe Francophone du Myélome (IFM) showed the superiority of high-dose chemotherapy and autologous HCT compared to conventional chemotherapy in a randomized trial of 200 patients younger than 65 years of age.[15] The group that underwent autologous HCT had significantly improved response rates, event-free and overall survival. Seven years later, the British Medical Research Council published similar results.[16]
The reasons for the discrepant results among these randomized studies are uncertain, but may be related to the conditioning regimens or patient age.

**SALVAGE TRANSPLANTATION**

Despite the success in improved survival with autologous HCT versus conventional chemotherapy, nearly all patients will relapse and require salvage therapy. Therapeutic options for patients with relapsed multiple myeloma after a prior autologous HCT 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 HCT. No clear standard of care exists.

**Repeat Autologous HCT for Relapse after Initial Autologous HCT**

**Systematic Reviews**

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.

**Randomized Controlled Trials**

In 2014, Cook and colleagues published a multicenter, randomized, open-label, phase 3 study from 51 centers across the United Kingdom, that included patients aged at least 18 years with MM who needed treatment for first progressive or relapsed disease at least 18 months after a previous autologous HCT.\(^{[24]}\)

Before randomization, eligible patients received bortezomib, doxorubicin, and dexamethasone (PAD) induction therapy and then underwent peripheral blood stem cell mobilization and harvesting, if applicable. Eligible patients were randomly assigned (1:1) to receive either high-dose melphalan 200 mg/m\(^2\) plus salvage autologous HCT or oral cyclophosphamide (400 mg/m\(^2\)/wk for 12 weeks). The primary end point was time to disease progression, analyzed by intention to treat. A total of 297 patients were enrolled, of whom 293 received PAD reinduction therapy. Among the latter, 174 patients with sufficient harvest of peripheral blood stem cells were randomly allocated to undergo salvage HCT (n=89) or receive cyclophosphamide (n=85). After a median follow-up of 31 months, median time to progression was significantly longer in the salvage HCT group than in the cyclophosphamide group (19 months [95% CI, 16 to 25] vs 11 months [95% CI, 9 to 12]; hazard ratio=0.36 [95% CI, 0.25 to 0.53]; p<0.001). Frequently reported (>10% of patients) grade 3-4 morbidity with PAD induction, salvage HCT, and cyclophosphamide were: neutropenia (125 [43%] of 293 patients after PAD and 63 [76%] of 83 patients in the salvage HCT group vs 11 [13%] of 84 patients in the cyclophosphamide group), thrombocytopenia (150 [51%] after PAD, and 60 [72%] vs four [5%, respectively), and peripheral neuropathy (35 [12%] after PAD, and none vs none, respectively). This study provides additional evidence for a net benefit of high-dose melphalan plus salvage HCT when compared with cyclophosphamide in patients with relapsed MM eligible for intensive therapy.
Final survival data for the trial was reported in 2016.[25] The HCT group had superior overall median survival compared to the chemotherapy group (67 months, 95% CI 55mths-not estimable vs 52 months, 95% CI 42-60mths, p<0.0001). Time to disease progression continued to favor the HCT group at the longer followup (19 months, 95% CI 16-26mths vs 11 months, 95% CI 9-12mths, p=0.02). There were no further adverse events related to the HCT procedure reported during longer followup. The cumulative incidence of second malignancies was 5.2% (95% CI 2.1-8.2%).

Nonrandomized Studies

Olin et al. reported their experience with 41 patients with multiple myeloma who received a second salvage autologous HCT for relapsed disease.[26] 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 HCT for Relapse after Initial Autologous HCT

Nonrandomized Studies

Schneidawind (2017) reported on consecutive patients (N=41) who received an allogeneic HCT for the treatment of relapsed or refractory multiple myeloma from 2001 to 2015. Ninety five percent of patients had previously received autologous HCT (18 tandem; 21 single high-dose chemotherapy followed by autologous HCT). Allogeneic HCT following the single approach was associated with an increased 3-year EFS (24% vs 6%, P=0.04) and OS (64% vs 35%, P=0.09) compared with a tandem autologous approach. Additionally, allogeneic HCT following the tandem autologous approach was associated with an increased relapse/progression rate (72% vs 58%, P=0.30).

Qazilbash et al. reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant.[27] 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).

The European Group for Blood and Marrow Transplant (EBMT) reported an analysis of 413 patients who received a related or unrelated RIC allogeneic HCT for the treatment of relapse or disease progression after a prior autologous HCT.[28] Median age at RIC allogeneic HCT
was 54 years, and 45% of patients had undergone two or more prior autologous transplants. The median OS and PFS from the time of allogeneic transplantation for the entire population were about 25 and 10 months, respectively. Cumulative non-relapse mortality (NRM) at 1 year was about 22%. In a multivariate analysis, cytomegalovirus (CMV) seronegativity of both patient and donor was associated with significantly better PFS, OS and NRM. Patient-donor gender mismatch was associated with better PFS. Fewer than two prior autologous transplants was associated with better OS and shorter time from the first autologous HCT to the RIC allogeneic HCT was associated with lower NRM. Findings suggested patient and donor CMV seronegativity may represent key prognostic factors for outcome after RIC allogeneic HCT in cases of relapse or progression following one or more autologous transplants.

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 HCT**

**Randomized Controlled Trials**

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.[29] 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=0.01) 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.[30] 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, compared single with double autologous HCT (n=321). Patients undergoing tandem autologous HCT were more likely than those with a single autologous HCT to attain at least a near 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. However, the methodological shortcomings limit reliability of this finding.

Results from available RCTs demonstrated 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 HCT**

Several randomized controlled trials have been published comparing RIC-allogeneic HCT following a first autologous HCT 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 HCT following the autologous HCT, whereas the other patients underwent either one or two autologous transplants.

The first published study by Garban et al. included high-risk patients (including deletion of chromosome 13). Sixty-five patients were in the autologous/RIC-allogeneic group and 219 in the autologous/autologous group. 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. Comparing the results of the 166 patients who completed the whole tandem autologous HCT 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 HCT (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). 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 HCT and were scheduled to receive a second autologous transplant (n=85) or an RIC-allogeneic transplant (n=25), depending on the availability of an HLA-identical sibling donor. The autologous/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 HCT (auto-auto group) versus tandem autologous-RIC allogeneic HCT (auto-allo group) in patients from 37 transplant centers in the U.S., who between 2003 and 2007, had received an autologous HCT (n=710). 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 HCT 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 HCT after autologous HCT is not more effective than tandem autologous HCT for patients with standard-risk myeloma.

Although the results differ among the Garban/Moreau study and the other studies the authors of the Moreau study suggested that this is due to different study designs. The Moreau study update 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.
Interim Study Findings

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.\cite{37,38} 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.\cite{37}

An interim analysis of a European Group for Blood and Marrow Transplant (EBMT) study was recently presented with somewhat different inclusion criteria.\cite{38} Previously untreated patients received vincristine, doxorubicin, dexamethasone (VAD) or VAD-like induction treatment, and had a response status of at least stable disease (i.e., complete or partial remission or stable disease) at the time of autologous transplantation, which was also the time point for study inclusion. Patients with an HLA-identical sibling proceeded to RIC-allogeneic transplantation, while those without a matched sibling received no further treatment or a second autologous 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.

At 96 months in the EBMT trial, progression-free survival (PFS) and overall survival (OS) were 22% and 49% versus 12% (P = .027) and 36% (P = .030) with autologous/RIC-allogeneic (auto/RICallo) and autologous HCT, respectively.\cite{39} The corresponding relapse/progression rate (RL) was 60% versus 82% (P = .0002) and the non-relapse mortality at 36 months was 13% versus 3% (P = .0004) with auto/RICallo and autologous HCT respectively. In patients with the del(13) abnormality corresponding PFS and OS were 21% and 47% in the auto/RICallo group versus 5% (P = .026), and 31% (P = .154) in the autologous only group. Long-term outcome in patients with multiple myeloma was better with auto/RICallo HCT as compared with autologous only and the auto/RICallo approach seemed to overcome the poor prognostic impact of del(13) observed after autologous transplantation. Authors called for longer follow-up periods of at least 5 years in order to better characterize the role of auto/RICallo HCT in patients with multiple myeloma.

ALLOGENEIC HCT

Even though myeloablative allogeneic HCT 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.\cite{40} 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.\cite{40} Therefore, RIC-allogeneic transplantation is currently used after tumor mass reduction with high-dose chemotherapy and autologous HCT.\cite{40}
The role of allogeneic HCT remains controversial, in particular because of conflicting data from cooperative group trials, but also because of confounding factors which may have influenced positive outcomes such as those observed with proteasome inhibitors, new immune modulatory agents, and the use of post-transplant maintenance therapy.[41,42] Overall the evidence on the use of allogeneic HCT as a first-line or salvage therapy does not suggest that potential treatment benefit outweighs risk of harm.

POEMS SYNDROME

Systematic Reviews

In 2012, Kuwabara and colleagues performed a Cochrane review of HCT 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 HCT. Two-year survival rates ranged from 94-100%. The review authors indicated that if all published experience with autologous HCT was pooled, transplant-related mortality would be 3 of 112 (2.7%). They caution that long-term outcomes with autologous HCT 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 HCT 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.[43]

It is unlikely that randomized controlled trials of HCT in patients with POEMS syndrome will be feasible, given the rarity of the condition. The current evidence regarding HCT in patients with POEMS Syndrome consists mainly of small case series[9,44-51] (n<60) and review articles.[52-55] In addition, the criteria for diagnosing and treating the multiple potential symptoms associated with POEMS, has not been well defined. However, for autologous HCT, 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 HCT for patients with POEMS is unknown.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

*All recommendations are category 2A unless otherwise noted. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (MM) address the following:[56]

Autologous Transplant

For active (symptomatic) myeloma “category 1 evidence supports proceeding straight after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell
transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant.” Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Additional treatment post-autologous cell transplant may include additional autologous cell transplant. “Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression. Retrospective studies suggest a 2–3 y minimum length of remission for consideration of a second autologous stem cell transplant for salvage therapy (category 2B).” Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Tandem Transplant**

For active (symptomatic) myeloma, additional treatment recommendations for response or stable disease includes second tandem transplant with or without maintenance therapy.

**Allogeneic Transplant**

For active (symptomatic) myeloma, the recommendation states: “Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably in a clinical trial. Current data do not support miniallografting alone.”

The same recommendation is applied to post-autologous cell transplant scenarios for progressive disease and response or stable disease. For patients treated with or without a prior transplant, allogeneic cell transplant is also a recommended option for transplant candidates with relapse or progressive disease.

**AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION**

In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) published evidence-based guidelines for the use of HCT in patients with MM. The guidelines are generally consistent with the conclusions in the above review of the literature. ASBMT recognizes that much of the RCT evidence summarized in the 2015 guidelines comes from trials that predate the advent of novel triple therapy induction regimens. Furthermore, advances in supportive care and earlier disease detection has increasingly influenced decision making and allows individual tailoring of therapy.

**AMERICAN SOCIETY FOR BLOOD AND MARROW TRANSPLANTATION, EUROPEAN SOCIETY OF BLOOD AND MARROW TRANSPLANTATION, BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK, AND INTERNATIONAL MYELOMA WORKING GROUP**

Following a 2014 meeting of multiple myeloma experts representing the above four groups, consensus guidelines were published regarding salvage autologous HCT, and the role of allogeneic HCT in relapsed myeloma. Among the recommendations, the authors conclude that well-designed prospective trials are necessary to extensively explore therapy in the salvage setting. While the guidelines state that both autologous and allogeneic HCT should be considered as a clinical option, this is based on a Likert survey of agreement, and the role of allografting for relapsing after autologous HCT had much less consensus than the autologous setting.
SUMMARY

MULTIPLE MYELOMA

There is enough research to show single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants for those with multiple myeloma may improve overall health outcomes. Outcomes include, but are not limited to partial or complete response rates, and prolongation of progression-free and overall survival. Practice guidelines based on research have specific recommendations for these regimes in specific patient populations. Therefore, single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants may be considered medically necessary in select patients when policy criteria are met.

There is not enough research to know if allogeneic hematopoietic cell transplant (including allo-HCT with myeloablative conditioning) improves overall health outcomes for those with multiple myeloma. Additionally, there is not enough research to know if single autologous, tandem autologous-autologous, and tandem autologous-reduced-intensity conditioning allogeneic hematopoietic cell transplants improves overall health outcomes when policy criteria are not met. Therefore, these treatment regimes are considered investigational unless policy criteria are met.

POEMS SYNDROME

There is enough research to show that overall survival may be improved with autologous hematopoietic cell transplant for those with disseminated POEMS syndrome. Therefore, this treatment may be considered medically necessary. Due to a lack of evidence, and practice guidelines, allogeneic and tandem hematopoietic cell transplant are considered investigational to treat POEMS syndrome when policy criteria are not met.

REFERENCES


38. Bjorkstrand, B, Iacobelli, S, Hegenbart, U. 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. PMID:


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**CODES**

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APPENDIX I: Glossary of Terms used in this Policy

**consolidation therapy**¹ - Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.

**relapse**² - The return of a disease or the signs and symptoms of a disease after a period of improvement.

**salvage therapy**³ - Treatment that is given after the cancer has not responded to other treatments.

**tandem transplant**⁴ – Refers to a planned second course of high-dose therapy and HCT within six months of the first course.


*Date of Origin: May 2010*