Medical Policy

Subject:	Hematopoietic Stem Cell Transplantation for Multiple Myeloma and Other Plasma Cell Dyscrasias		
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Description/Scope

This document addresses hematopoietic stem cell transplantation in multiple myeloma, amyloidosis and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes).

Note: For additional stem cell transplant information and criteria, see the applicable document(s):

- CG-TRANS-03 Donor Lymphocyte Infusion for Hematologic Malignancies after Allogeneic Hematopoietic Progenitor Cell Transplantation
- TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation
- TRANS.00024 Hematopoietic Stem Cell Transplantation for Select Leukemias and Myelodysplastic Syndrome

Note: For information about Waldenström's Macroglobulinemia, see
TRANS.00028 Hematopoietic Stem Cell Transplantation for Hodgkin Disease and non-Hodgkin Lymphoma

Position Statement

Multiple Myeloma

Medically Necessary:

Autologous hematopoietic stem cell transplantation (AutoHSCT) for treatment of individuals with multiple myeloma is considered **medically necessary** when used as:

A. As a single transplant (AutoHSCT); **or**
B. As a tandem* transplant (two AutoHSCTs separated by 30 to 180 days); **or**
C. As a repeat procedure (AutoHSCT greater than 180 days following a previous AutoHSCT); **or**
D. As a pretreatment for a non-myeloablative allogeneic hematopoietic stem cell transplant; **or**
E. As salvage therapy after:
    1. Primary graft failure; **or**
    2. Failure to engraft; **or**
    3. Rejection following an allogeneic HSCT.

Allogeneic (ablative or non-myeloablative) stem cell transplantation after a previous autologous stem cell transplant for treatment of individuals with multiple myeloma is considered **medically necessary.**

A planned tandem non-myeloablative allogeneic transplantation following an autologous transplantation is considered **medically necessary** for treatment of individuals with multiple myeloma.

A *repeat allogeneic (ablative or non-myeloablative) stem cell transplantation* due to primary graft failure, failure to engraft or rejection is considered **medically necessary.**

*Hematopoietic stem cell harvesting*** for an anticipated but unscheduled transplant is considered **medically necessary** in individuals with multiple myeloma who meet one of the above criteria and for whom the treating physician documents that a future transplant is likely.

Investigational and Not Medically Necessary:

Allogeneic (ablative or non-myeloablative) stem cell transplantation or autologous stem cell transplantation is considered **investigational and not medically necessary** for individuals with multiple myeloma who do not meet the above criteria.

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary** when the criteria above are not met.

A repeat allogeneic (ablative or non-myeloablative) stem cell transplantation due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary.**

Three or more *autologous hematopoietic stem cell transplantations* within a 12-month period are considered **investigational and not medically necessary.**

Amyloidosis

Medically Necessary:

Autologous stem cell transplantation is considered **medically necessary** for individuals with primary amyloidosis (AL) who meet the following criteria:
Note: (If the individual has a preceding diagnosis of multiple myeloma, use the transplant criteria above for multiple myeloma).

A. If the heart is involved with AL, the individual is asymptomatic or has compensated congestive heart failure; **and**
B. Left ventricular ejection fraction (LVEF) greater than or equal to 45%; **and**
C. Must have documented disease on biopsy without a preceding diagnosis of multiple myeloma.

A repeat autologous stem cell transplantation due to primary graft failure or failure to engraft is considered **medically necessary.**

*Hematopoietic stem cell harvesting*** for an anticipated but unscheduled transplant is considered **medically necessary** in individuals with amyloidosis who meet one of the above criteria and for whom the treating physician documents that a future transplant is likely.

Investigational and Not Medically Necessary:

Autologous stem cell transplantation is considered **investigational and not medically necessary** in the treatment of primary amyloidosis in individuals with symptomatic heart failure regardless of the number of organs involved.

Allogeneic (ablative or non-myeloablative) stem cell transplantation is considered **investigational and not medically necessary** for treatment of individuals with amyloidosis.

A tandem autologous stem cell transplantation* is considered **investigational and not medically necessary** for treatment of individuals with amyloidosis.

A repeat autologous stem cell transplantation due to persistent, progressive or relapsed disease is considered **investigational and not medically necessary.**

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary** when the criteria above are not met.

POEMS Syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)

Medically Necessary:

Autologous stem cell transplantation is considered **medically necessary** for treatment of POEMS Syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) when diagnostic criteria for that syndrome are met.

A repeat autologous stem cell transplantation due to primary graft failure or failure to engraft is considered **medically necessary.**

*Hematopoietic stem cell harvesting*** for an anticipated but unscheduled transplant is considered **medically necessary** in individuals with POEMS syndrome who meet one of the above criteria and for whom the treating physician documents that a future transplant is likely.

Investigational and Not Medically Necessary:

Autologous stem cell transplantation for treatment of individuals with POEMS Syndrome is considered **investigational and not medically necessary** when the above criteria are not met.

Allogeneic (ablative or non-myeloablative) stem cell transplantation for treatment of individuals with POEMS Syndrome is considered **investigational and not medically necessary.**

A tandem autologous stem cell transplantation* for treatment of individuals with POEMS Syndrome is considered **investigational and not medically necessary.**

A repeat autologous stem cell transplantation due to persistent, progressive or relapsed POEMS is considered **investigational and not medically necessary.**

Hematopoietic stem cell harvesting for a future but unscheduled transplant is considered **investigational and not medically necessary** when the criteria above are not met.

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

** Hematopoietic stem cell harvesting does not include the transplant procedure.

Rationale

Multiple Myeloma

Multiple myeloma is a malignant disorder characterized by the proliferation of mature plasma cells in the bone marrow that produce monoclonal immunoglobulin proteins. The proliferation of plasma cells leads to destruction of the bone and failure of the bone marrow and may cause nephropathy and neuropathy (Girnius, 2010). Initial standard treatment options are partially dependent upon whether the individual is a candidate for high-dose therapy and transplant, as some of the therapy agents are myelotoxic. While multiple myeloma is not considered curable with the current treatments available, newly diagnosed cases are usually sensitive to a number of cytotoxic drugs and responses are typically durable (National Comprehensive Cancer Network® [NCCN], V1.2024). Median survival rates have improved and now exceed 60 months as a result of newer treatment modalities that include pulse corticosteroids, dexamethasone, thalidomide, bortezomib and lenalidomide along with autologous and allogeneic stem cell transplantation (National Cancer Institute [NCI], 2023). The latest generation of proteasome inhibitors, immunomodulatory agents and monoclonal antibodies has resulted in overall response rates of over 90% (Veltri, 2017). There are ongoing studies to determine the optimal timing, combination and sequence of therapies and long-term benefits of therapy with the newer treatments.

Koreth and colleagues (2007) performed a meta-analysis of randomized controlled trials (RCTs), comparing chemotherapy to high-dose chemotherapy (HDT) with single autologous stem cell transplant. The nine trials that met the selection criteria started enrolling participants (n=2411) in the 1990s and included two studies that did not detect a survival benefit from high-dose chemotherapy. The study concluded that there is no significant difference in overall survival benefit to individuals given up-front HDT. Additionally, the use of peripheral blood stem cells (PBSCs) did not provide an overall survival benefit. However, a significant progression-free survival (PFS) benefit to individuals given up-front HDT was reported. A significantly increased risk of treatment-related mortality for individuals receiving HDT was found (odds ratio 3.01, 95% confidence interval [CI], 1.64-5.50) in the group with autologous stem cell transplant. However, the effects of HDT and autologous stem cell transplant may have been diluted by the fact that up to 55% of individuals in the standard chemotherapy group received HDT with autologous stem cell transplant as salvage therapy when the multiple myeloma progressed. This could account for the lack of a significant difference in overall survival between the two groups in the study.

A multicenter RCT by Cavo (2007) compared single with double autologous stem cell transplants in 321 participants. Individuals undergoing tandem autologous transplantation were significantly more likely than those with a single transplant to attain at least a near complete response (47% vs. 33%), to prolong relapse-free survival

(median, 42 vs. 24 months), and extend event-free survival (median, 35 vs. 23 months). There was no significant difference between the groups in treatment-related mortality (3%-4%).

Few individuals are considered eligible for a second autologous stem cell transplant to treat relapsed multiple myeloma after a complete or partial remission. Thus, it is unlikely that prospective trials will ever be conducted to rigorously compare outcomes of this strategy with alternatives. Nevertheless, retrospective studies report durable complete or partial responses and extended survival for individuals treated this way, particularly when a long disease- or progression-free interval followed the first transplant.

Sibling or unrelated allogeneic transplants have several potential advantages relative to autologous transplants, including no chance that the transplant will reinfuse multiple myeloma cells and the possibility that donor cells may mediate immunologic antitumor effects. Allogeneic transplants may be considered a potentially curative therapy in a limited number of individuals. This may be the result of a graft-vs-myeloma effect that can occur following allogeneic transplantation. A positive response may be attributed to the identification of myeloma-specific cytotoxic T cells in transplant recipients and clinical responses to donor lymphocyte infusions. Allogeneic transplants are associated with considerable risk for toxicity due to graft versus host disease. (Khorochkov, 2021; Schmidt, 2023). Schmidt and colleagues (2023) summarized the use of allogeneic therapy in multiple myeloma noting:

> In conclusion, allogeneic transplant poses a therapeutic dilemma for myeloma clinicians. Particularly as salvage therapy, allo SCT has poor outcomes. It is curative for a small subset of patients, however, the patient, treatment, and disease characteristics that predispose those in this subgroup to favorable long-term outcomes remain ill-defined. Unfortunately, the curative potential of allo SCT is tempered by poor OS, poor PFS, and a high TRM [treatment related mortality] that exceeded the "cure" rate among the rest of the observed patients. The benefit of allo SCT may be tremendously high—a potential cure—but the risk is even higher. With an expanding array of anti-CD38, BiTE, and other novel therapeutics, we would expect better overall outcomes and tolerability of these agents compared to allo SCT and, if available, would prefer them to allo SCT.

A study published by Maloney (2003) included 54 individuals (median age 52 years; range 29-71) with previously treated multiple myeloma (52% refractory or relapsed disease) given an initial autologous stem cell transplant conditioned with 200 mg/m^2 melphalan. Of these, 52 received a subsequent non-myeloablative allogeneic stem cell transplant. Investigators reported 78% overall survival (OS) at a median 552 days after allografting. Treatment achieved a complete remission (CR) in 57% and an overall response rate of 83%. Acute graft-versus-host disease (GVHD) developed in 38% of individuals (grades III/IV in 4 cases; grade II in all others), and chronic GVHD requiring therapy in 46%. Twelve participants died: 1 from viral infection after the initial autologous transplant, 2 from multiple myeloma progression (3 and 23 months post-mini-allogeneic transplant), 7 from GVHD, and 1 each from lung cancer and encephalopathy.

Bruno and colleagues (2007) reported results from a series of 162 participants with newly diagnosed multiple myeloma and who had at least one sibling. All participants received induction chemotherapy and an initial autologous stem cell transplant followed by a subsequent transplant. Forty-six out of 82 eligible participants without an HLA-identically matched sibling received a tandem autologous stem cell transplant. Fifty-eight out of 80 enrolled participants with an HLA-identical sibling received a nonmyeloablative stem cell transplant from the

sibling. At a median follow-up of 45 months, the median overall survival (80 months vs. 54 months, p=0.01) and event-free survival (35 months vs. 29 months, p=0.02) were significantly better for individuals treated with autologous – allogeneic stem cell transplants compared to those treated with two autologous stem cell transplants .

A long-term analysis of autologous stem cell transplant (ASCT) alone versus ASCT followed by reduced-intensity conditioning (RIC) matched-related allogeneic transplant (auto-allo) for treatment of 357 individuals with multiple myeloma was reported by Björkstrand and colleagues (2011). The 249 individuals without an HLA-identical donor were assigned to the ASCT group and 108 who had a matched donor were assigned to the auto-allo group. A total of 91 individuals in the auto-allo cohort received the RIC allogeneic stem cell transplant (alloSCT) as planned. A total of 145 individuals in the ASCT cohort received a single transplant while 104 individuals received a tandem auto transplant. At 60 months after the first ASCT, based upon intention-to-treat (ITT) analysis, PFS of 35% in the auto-allo group was significantly better than 18% in the ASCT group. Long-term OS was also significantly better for the auto-allo cohort at 60 months, 65% versus 58% in the ASCT group. The rate of CR for the auto-allo group was 51% and the ASCT group was 41% (p=0.020). The long-term results support the use of auto-allo transplant as treatment for individuals with previously untreated multiple myeloma who have an HLA-matched sibling (Björkstrand, 2011).

The NCCN Multiple Myeloma Clinical Practice Guideline (V1.2024) notes an ASCT, immediate or delayed, is the standard of care after primary induction therapy and results in high response rates. The guidelines also list the second cycle of a tandem transplant (within 6 months of the initial autologous stem cell transplant) as an option for individuals with partial response or stable disease after their first autologous stem cell transplant. The guidelines state that donor lymphocyte infusions (DLI) may be given to those who do not respond or to those who relapse after an allogeneic stem cell transplant.

In 2022, the American Society for Transplantation and Cellular Therapy (ASTCT) published a clinical practice recommendation regarding the use of transplants and cellular therapy for multiple myeloma. The introduction of multiple novel therapeutic agents has revised treatment. For the past 20 years, the standard treatment has been high-dose therapy followed by autologous stem cell transplant. Although allogeneic HCT has been curative in select individuals, the use of this therapy has remained controversial due to inconsistent results. The ASTCT recommendations include, but are not limited to, the following for front-line therapy:

1. The panel recommends early autologous transplantation as a consolidation therapy in eligible, newly diagnosed myeloma patients after 4-6 cycles of induction. Grading recommendation: A
5. In the absence of clinical trial, the panel recommends early autologous transplantation in myeloma patients with high-risk cytogenetics [t (4;14); t (14;16); t (14;20)], 1p deletion, 1q gain/amplification and 17p deletion. Grading recommendation: B
6. The panel does not recommend tandem autologous transplantation in standard risk myeloma patients after induction, outside in the setting of a clinical trial. Grading recommendation: B.
11. The panel does not recommend allogeneic transplantation except in the context of clinical trial. Grading recommendation: C.
12. The panel does not recommend tandem autologous-allogeneic transplantation except in the context of clinical trial. Grading recommendation: C.

The 2022 ASTCT recommendations for relapsed or refractory multiple myeloma are as follows:

1. The panel recommends autologous transplantation in first relapse in patients who have not received transplant as a first-line therapy. Grading recommendation: A.
2. The panel recommends consideration of autologous transplantation in patients with primary refractory disease. Grading recommendation: C.
3. The panel recommends salvage second autologous transplantation in patients who were in remission for (at least) 36 months with maintenance and 18 months in the absence of maintenance. Grading recommendation: B.
6. The panel encourages allogeneic transplantation in relapsed and/or refractory setting only in the context of clinical trial. Grading recommendation: B.

Grading Recommendations: A = There is good research-based evidence to support the recommendation; B = There is fair research-based evidence to support the recommendation; C = The recommendation is based on expert opinion and panel consensus.

Amyloidosis

In amyloidosis, amyloid fibrils deposit in various organs causing dysfunction (Girnius, 2010). While any organ can be affected, cardiac and renal involvement is the most common (Fotiou, 2020). There are many types of amyloidosis with the most common and rapidly progressive form being immunoglobulin light chain AL (primary) amyloidosis. Secondary amyloidosis can be associated with other chronic conditions such as rheumatoid arthritis, autoinflammatory disorders, or chronic infections. Similar to treatment of multiple myeloma, current regimens for primary (AL) amyloidosis rarely cure individuals- the goal is to induce remission. High-dose chemotherapy with autologous stem cell transplantation for primary (AL) amyloidosis targets the aberrant plasma cell clone to prevent further synthesis and deposition of the amyloid protein. For individuals considered transplant eligible, high dose melphalan coupled with ASCT has resulted in high hematological response rates and durable remission (Fotiou, 2020; Manwani, 2018). While this treatment is one of the most effective, it is associated with high TRM (Fortiou, 2020; NCCN, V1.2024). Due to the significant TRM and a typical advanced stage diagnosis, most individuals are not transplant eligible. If not eligible for transplant at the time of initial diagnosis, an individual can be reassessed after initial systemic therapy. A transplant eligible individual may also elect to collect stem cells and delay transplant to a later line of therapy (NCCN, V1.2024). Cardiac status or involvement is strongly associated with prognosis, and advanced-stage cardiac disease is linked to very poor survival (Fotiou, 2020).

Since results of standard therapies for primary amyloidosis are often unsatisfactory, clinical studies were begun on high-dose chemotherapy (HDC) with autologous stem cell support (AuSCT). Data showing HDC AuSCT improved outcomes for those with myeloma provided an additional rationale for studies on individuals with amyloidosis. The number of organs involved is strongly associated with mortality. Individuals with three or more involved organs are considered poor candidates for transplantation. There is sufficient evidence from case series studies to demonstrate a net health benefit to support the use of HDC AuSCT in individuals with primary amyloidosis that is limited to one or two organs and without symptomatic heart failure. In a review of 92 individuals with amyloidosis treated with autologous stem cell transplant, the TRM was high at 23% (Goodman, 2006). However, when a subset analysis was performed, "the number of organs involved by amyloid correlated strongly with TRM ($p<0.0005$); all 8 patients with 4 or 5 organs involved died by day 100, as did 6 of 17 patients with 3 organs involved." Goodman and colleagues concluded limiting inclusion criteria to "one or two amyloidotic

organs have the potential to reduce TRM to rates approaching those seen in myeloma." With improvements observed in multiple myeloma, newer treatment modalities that include dexamethasone, thalidomide, bortezomib and lenalidomide are being studied as treatments for primary amyloidosis.

Analysis of long-term data collected prospectively on 421 consecutive individuals with AL amyloidosis treated with autologous stem cell transplant at one center was provided by Cibeira (2011). Thirty percent (125 individuals) had AL involvement in one organ, 27% (115 individuals) had two involved organs, and 43% (181 individuals) had AL involvement in three or more organs. One-year survival was not achieved in 81 participants. With a median follow-up of 6.9 years, 43% of the 340 evaluable individuals achieved CR and organ response was noted in 78%. For those in CR, the median event-free survival (EFS) was 8.3 years and the OS was 13.2 years, respectively. Forty individuals initially in CR (28%) experienced a relapse. Fifty-two percent of the 195 individuals that did not obtain CR had median EFS of 2 years and an OS of 5.9 years. Univariate analysis noted that the absence of cardiac involvement (p=0.005) was a significant predictor of CR. The overall treatment-related mortality rate was 5.6% within the last 5 years of the study, and 11.4% overall. The authors noted autologous stem cell transplant results in organ response and CR while improving treatment mortality rates.

Sanchorawala and colleagues (2007) reported long-term survival of 80 participants treated with autologous transplants at a single institution. Seventeen individuals died within the first year as a result of treatment-related complications or progressive disease. Sixty-three individuals were evaluable at 1 year with 32 (51%) in a complete hematologic response. The median survival is 57 months for all 80 participants, and 18 (23%) were alive at 10 or more years after transplant. The survival rate at 10 years was 53% and the median survival for individuals who achieved a complete hematologic response had not yet been reached.

In a case-controlled study of 126 participants with primary systemic amyloidosis by Dispenzieri (2004), data suggested improved outcomes in select individuals with high dose chemotherapy and stem cell transplant compared to treatment with chemotherapy agents. Each cohort consisted of 63 participants. Transplant-related mortality was 13% (8 individuals). Fifty participants in the control group died. Median follow-up for the control group was 8.8 years compared to 3.8 years for the treatment group. Based on 95% confidence intervals, the estimated 4-year survival for the transplant group was 71% compared to 41% for controls.

A retrospective review of the Center for International Blood and Marrow Transplant Research (CIBMTR) database reported results for 107 individuals with comprehensive information available for analysis (Vesole, 2006). All 107 participants were treated with various preparatory regimens and autologous stem cell transplants for primary amyloidosis. Responses at day 100 were noted in at least one organ system in 28 (36%) of 77 individuals for whom organ-specific data were available. Thirty-four of 107 individuals had a hematologic response at 1 year (17 [16%] with complete response; 17 [16%] partial response; 33 [31%] had stable disease and 11 [10%] had progressive disease). The median overall survival for all individuals was 47.2 months. Overall survival at 1 year and at 3 years was 66% and 56%, respectively. Transplant related mortality was 27% (29/107 individuals). Further analysis revealed the year of transplantation to be the only statistically significant predictor (p=0.02) of survival. Those who were treated with transplants more recently had superior outcomes compared to earlier transplants.

According to Girnius and colleagues (2010) approximately 12-15% of individuals with multiple myeloma develop systemic amyloid light-chain amyloidosis. The resulting organ dysfunction resulting from the deposition of amyloid fibrils can occur when the bone marrow has 5-10% clonal plasma cells. These authors reported results

from a retrospective study of individuals with both amyloidosis and multiple myeloma treated with autologous stem cell transplant at a single center and concluded "in terms of response and recurrence, patients with amyloid light chain amyloidosis and myeloma behave more like patients with myeloma only."

The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guideline (V2.2023) indicates that high-dose melphalan followed by autologous stem cell transplant is a therapeutic option for amyloidosis. However, individuals have to be carefully selected because of significant treatment-related mortality. The NCCN panel recommends assessing stem cell candidacy in newly diagnosed individuals. If an individual is not a candidate at initial diagnosis, candidacy should be reassessed following two cycles of systemic therapy. Relapsed or refractory disease therapy includes immune-modulatory drugs or the monoclonal antibody drug daratumumab (Palladini, 2020).

Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) Syndrome

POEMS is an acronym for a rare multisystem disorder associated with plasma cell dyscrasia. Quality of life for individuals with POEMS typically deteriorates as neuropathy progresses. POEMS syndrome is a compound disorder characterized by monoclonal plasma cell proliferative disorder, polyneuropathy and an elevation in vascular endothelial growth factor (VEGF) and other proinflammatory cytokines. The prevalence of POEMS remains uncertain; with an estimated occurrence of 0.3 cases per 100,000 individual. Current treatment options may include chemotherapy, radiation therapy, intravenous immunoglobulin, plasma exchange, corticosteroids, and stem cell transplantation. Treatment with irradiation or surgical resection of solitary plasmacytoma has been used. Systemic chemotherapy similar to regimens used to treat multiple myeloma is recommended for individuals with widespread osteosclerotic lesions or no detectable bone lesion (Chee, 2010; Dispenzieri, 2007; Kuwabara, 2008b). High-dose chemotherapy with autologous stem cell transplantation is recommended for diffuse disease involving multiple bone lesions or an iliac crest biopsy positive for clonal plasma cells, (Kuwabara, 2008b). However, there is no established treatment regimen for this syndrome based on RCTs (Kuwabara, 2008b).

Multiple case series and individual case reports (Kansagra, 2022; Kuwabara, 2008b; Laurenti, 2008) have demonstrated improvement in function and reduction of symptoms following high-dose chemotherapy and autologous stem cell transplant for POEMS. In the largest case series to date, Kuwabara (2008a) and associates reported clinical improvement at 6 months in all 9 individuals with POEMS treated with autologous peripheral blood stem cell transplant (AuPBSCT). Neurologic improvement began at 3 months, and all individuals showed substantial neurologic recovery during the next 3 months. Three initially chairbound individuals regained the ability to walk at 6 months. Nerve conduction studies showed significant increases in conduction velocities and amplitudes within 6 months of treatment. The median follow-up period was 20 months (8-49 months). At the end of follow-up periods, neuropathy was still improving, and no individuals had recurrence of symptoms.

The NCCN Multiple Myeloma guideline (V1.2024) recommends high dose melphalan therapy followed by autologous stem cell transplant as a treatment option for those who are eligible. Autologous stem cell transplant can be used as a sole therapy or as consolidation therapy following induction therapy. Shibimiya and others note that there is no standard therapy for treatment of relapsed POEMs following an autologous HCT and that there is a paucity of evidence regarding the use of a second autologous HCT following relapsed or refractory POEMs (Shibamiya, 2021).

A Cochrane Review (Kuwabara, 2008b) noted the lack of RCTs for POEMS involving "demyelinating and axonal mixed neuropathy with multiorgan involvement." Due to the rarity of this condition, Phase II and III trials have not been conducted. The data from eight retrospective case series were analyzed. The authors noted substantial stabilization or improvement in neurological symptoms as well as other features associated with POEMS with autologous stem cell transplantation. Also, the pooled mortality figure is estimated 2/45 (4%) which appears higher than the 2% TRM in individuals with multiple myeloma, but lower than TRM of 14% in primary amyloidosis. The authors concluded "recent case series and case reports have shown that high-dose chemotherapy with autologous peripheral blood stem cell transplantation is efficacious treatment for POEMS syndrome, although long-term outcomes have not yet been elucidated" (Kuwabara, 2008). In an update of 30 individuals with POEMS who had autologous stem cell transplants, Dispenzieri (2008) noted a higher rate of treatment related morbidity or engraftment syndrome (ES).

Poor Graft Function

Poor graft function or graft failure is one of the major causes of morbidity and mortality after hematopoietic stem cell transplantation. Poor graft function is defined as slow or incomplete recovery of blood cell counts following a stem cell transplant or decreasing blood counts after initially successful hematopoietic engraftment following a stem cell transplant. There are various options for the management of poor graft function. Stem cell "boost" is a non-standardized term that is used to describe an infusion of additional hematopoietic stem cells to an individual who has undergone recent hematopoietic stem cell transplantation and has poor graft function (Larocca, 2006). The infusion of additional hematopoietic stem cells may mitigate graft failure or rejection with or without immunosuppression. This process may include the collection of additional hematopoietic stem cells from a donor and infusion into the transplant recipient. Note that a "boost" is distinct from a repeat transplant and that there may be separate medical necessity criteria for a repeat transplant.

Other Considerations

In 2015, the American Society for Transplantation and Cellular Therapy (ASTCT) (formerly known as the American Society for Blood and Marrow Transplantation (Majhail and colleagues)) issued guidelines on indications for autologous and allogeneic hematopoietic cell transplantation. These guidelines were updated in 2020 (Kanate, 2020). Definitions used for classifying indications were: standard of care (S); standard of care, clinical evidence available (C); standard of care, rare indication (R); Developmental (D); and not generally recommended (N). Indications for hematopoietic cell transplantation in adults (generally 18 years of age or older) include the following classifications for plasma cell disorders:

- Myeloma, initial response (D for allogeneic and S for autologous)
- Myeloma, sensitive relapse (S for allogeneic and S for autologous)
- Myeloma, refractory (C for allogeneic and C for autologous)
- Plasma cell leukemia (S for allogeneic and C for autologous)
- Amyloid light-chain amyloidosis (N for allogeneic and S for autologous)
- POEMS syndrome (N for allogeneic and C for autologous)
- Relapse after autologous transplant (C for allogeneic and C for autologous)

Giralt and colleagues (2015) for the American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in individuals with Relapsed Multiple Myeloma proposed guidelines for the use of salvage hematopoietic stem cell transplantation for the treatment of multiple myeloma. The group's consensus committee agreed on the following guideline statements:

Consensus Guidelines for Salvage Autologous Hematopoietic Stem Cell Transplantation (HCT):

1. In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with autologous HCT as part of salvage therapy should be considered standard.
2. High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months.
3. High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT.
4. The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, IMiDs, and oral proteasome inhibitors.
5. Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short remission (less than 18 months).
6. Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM relapsing after primary therapy comparing to "best non-HCT" therapy.

The committee also stressed the importance of collecting enough hematopoietic stem cells to perform two transplantations early in the course of the disease.

Consensus Guidelines Regarding Role of Allogeneic HCT in Relapsed Myeloma

1. Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT.
2. Whenever possible, allogeneic HCT should be performed in the context of a clinical trial.
3. The role of postallogeneic HCT maintenance therapy needs to be further explored.
4. Prospective randomized trials need to be performed to define the role of salvage allogeneic HCT in patients with MM relapsing after primary therapy.

Shah and colleagues (2015) for the American Society for Blood and Marrow Transplantation issued guidelines for hematopoietic stem cell transplantation for multiple myeloma. The document includes the following statements:

1. We recommend HDC and auto-HCT as consolidative therapy for patients with multiple myeloma (grade A recommendation)
2. Though prospective evidence is lacking, we recommend consideration of a first auto-HCT for patients with refractory disease (grade C recommendation)
3. We recommend serious consideration of a clinical trial for patients with high-risk cytogenetics, particularly del17p or t(4:14) (grade C recommendation)
4. Second auto-HCT is a safe and efficacious treatment modality for relapsed multiple myeloma and should be considered (grade B)
5. Patients with longer progression-free interval after first auto-HCT have better outcomes after salvage second auto-HCT. It is recommended that the minimum length of remission be at least 12 months for consideration of a second auto-HCT as salvage therapy (grade D). The role of maintenance therapy after salvage second-HCT in unclear.
6. Upfront myeloablative allo-HCT is not routinely recommended (grade A). It may be appropriate for further study in young patients with very high-risk MM, in the context of a clinical trial.
7. Planned reduced-intensity conditioning (RIC)-allo HCT after auto-HCT has not been found to be superior in the majority of clinical trials and is, therefore, not recommended over auto-HCT (grade A). Its role in high-risk subgroups requires further study.
8. Allo-HCT salvage therapy for relapsed MM has not been shown to be superior to salvage auto-HCT and is not routinely recommended outside of a clinical trial (grade D). For younger patients with a good performance status, allo-HCT can be considered, ideally in the context of a clinical trial.

Levels of evidence were assessed and a grade assigned to each recommendation following the criteria below:

Levels of Evidence
1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++ High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2- Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3 Nonanalytic studies, eg, case reports or case series.
4 Expert opinion.

Reproduced from: A new system for grading recommendations in evidence based guidelines, Harbour R, Miller J. BMJ 2001; 323:334-336.

Grades of Recommendation

A At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.

C A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2++.

D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+.

Reproduced from: A new system for grading recommendations in evidence based guidelines, Harbour R, Miller J. BMJ 2001; 323:334-336.

Background/Overview

The introduction of targeted therapies, such as CAR T-cel therapy and immunotherapy have been important additions into many cancer treatment plans. These treatments have times become first or second line recommended lines of therapy. HSCT remains an important therapeutic modality for many malignant and nonmalignant hematologic diseases. The number individuals who could benefit from HSCT has increased due to advancements, such as reduced intensity conditioning regimens, which have made HSCT safer (Majhail, 2015). However, the risks associated with transplant-associated morbidity and mortality remain significant. Most transplant centers utilize forums, boards or conferences where the treatment options of individual HSCT candidates are discussed (Majhail, 2015). Okamoto (2017) notes:

> The medical decision-making process for a transplant procedure is complex which requires assessing several factors besides the underlying indication for transplantation. Those include patient/disease factors, and transplant factors such as planed conditioning/graft-versus-host disease (GVHD) prophylaxis and stem cell source. Patient factors include their overall health and comorbidities, prior therapies, and how patients responded to those therapies, age, and disease/disease risk.

There are a number of clinical assessment and prognostic tools which evaluate individuals diagnosed with cancers based upon multiple factors. The earlier, simpler tools, such as the Charlson Comorbidity Index (CCI) were useful in predicting outcomes, but lacked the sensitivity of subsequent tools such as the HCT-specific comorbidity index (HCT-CI). The HCT-CI score has been validated in multiple HSCT settings to independently predict non-relapse mortality (NRM) rates by weighting 17 relevant comorbidities. The HCT-CI was further enhanced by the incorporation of some laboratory biomarkers into an augmented version. The revised International Staging System (ISS) uses the original ISS tool developed in 2005 and incorporates information regarding chromosomal abnormalities to produce a prognostic staging system for individuals newly diagnosed with multiple myeloma (Palumbo, 2015). While these tools provide valuable prognostic information, the decision to transplant is unique to

each individual and needs to include a specific risk-benefit analysis in partnership with the individual's physicians and other caregivers.

There are a number of plasma cell disorders all of which are associated with a monoclonal myeloma protein. These include monoclonal gammopathy of undetermined significance (MGUS), isolated plasmacytoma of bone, extramedullary plasmacytoma and multiple myeloma. Treatment of these conditions vary. Individuals with smoldering myeloma or MGUS are monitored for the development of progressive disease such as myeloma, lymphoma, Waldenström macroglobulinemi or amyloidosis, which requires treatment (Hasib, 2021). Chemotherapy remains the standard treatment and stem cell transplants have been beneficial in those who are eligible. With the availability of new, more effective pharmacological agents which have been shown to produce a deep response, the utility of stem cell transplantation continues to be evaluated (Hasib, 2021).

Multiple Myeloma

Multiple myeloma is a systemic malignancy of plasma cells that accumulate in the bone marrow which results in destruction of bone and failure of the bone marrow. Multiple myeloma is highly treatable but rarely curable. However, when it presents as a solitary plasmacytoma of bone or as an extramedullary plasmacytoma it is potentially curable. In 2023, an estimated 35,730 new cases of multiple myeloma will be diagnosed and approximately 12,590 deaths from the disease will occur (American Cancer Society, 2023). The disease is staged by estimating the myeloma tumor cell mass on the basis of the amount of monoclonal (or myeloma) protein (M-protein) in the serum and/or urine along with various clinical parameters, such as the hemoglobin and serum calcium concentrations, the number of lytic bone lesions, and the presence or absence of renal failure. The stage of the disease at presentation is a strong determinant of survival, but has little influence on the choice of therapy since almost all individuals (except for those with solitary bone tumors or extramedullary plasmacytomas) have generalized disease. The age and general health of the individual, prior therapy and the presence of complications of the disease influence treatment selection. The median survival in the prechemotherapy era was about 7 months. Multiple myeloma has demonstrated chemosensitivity to initial treatment or treatment for relapsed disease. After the introduction of chemotherapy, prognosis improved significantly with a median survival of 24 to 30 months and a 10-year survival of 3%. Drugs such as bortezomib along with immunomodulatory derivatives, thalidomide and lenalidomide, have been used as a treatment for multiple myeloma and have contributed to advances in therapy and prognosis (Cavo, 2011; NCCN, V1.2024; NCI, 2023).

Amyloidosis

Primary amyloidosis, or light chain amyloidosis (AL), is a disorder in which insoluble immunoglobulin light chain protein fibrils are deposited in tissues and organs, impairing their function. The cause of primary amyloidosis is unknown, but the condition is related to the abnormal production of immunoglobulins by a type of immune cell called plasma cells. The symptoms depend on the organs affected by the deposits, which can include the tongue, intestines, skeletal and smooth muscles, nerves, skin, ligaments, heart, liver, spleen, and kidneys. The deposits infiltrate the affected organs, causing them to lose resilience and become stiff, which decreases their ability to function. Multiple myeloma, including other plasma cell neoplasms, may cause amyloidosis (NCI, 2023). Amyloidosis is approximately one-fifth as common as multiple myeloma (Hasib, 2021). There are an estimated 40.5 cases per million in 2015. The incidence of amyloidosis has been on the rise, possibly due to growing awareness of the disease and its symptoms as well as improved treatments which have lowered the mortality rate

(Baker, 2022). Treatment depends upon the location and extent of damage and the underlying associated plasma cell dyscrasia (NCI, 2023). When diagnosed at a late stage, the median survival is as short as 5 months with infection or cardiac or hepatic failure being the most common cause of death (Baker, 2022).

POEMS Syndrome

POEMS is an acronym for the dominant presentations of the syndrome which may also be called Crow-Fukase Syndrome and Takatsuki syndrome (Dispenzieri, 2007). POEMS is rare paraneoplastic syndrome which is associated with an underlying plasma cell neoplasm. There are additional clinical features that are not included in the acronym, which include elevated levels of VEGF, sclerotic bone lesions, Castleman Disease, papilledema, peripheral edema, ascites, effusions, thrombocytosis, polycythemia, fatigue and clubbing for this syndrome where etiology is uncertain (Dispenzieri, 2007).

POEMS syndrome:
- Peripheral neuropathy-A disease or degenerative state of the peripheral nerves in which motor, sensory, or vasomotor nerve fibers may be affected as evidence by tingling, numbness and weakening of hands and feet
- Organomegaly- An abnormal enlargement of organs like the liver, spleen and lymph nodes
- Endocrinopathy- Dysfunction of the endocrine gland causing abnormality in the hormone levels
- Monoclonal plasma proliferative disorder- A collection of abnormal bone marrow cells called the plasma cells

The modality used to treat POEMS syndrome is dependent on the individual's underlying blood cell disorder. Based on the presentation and complexity of the syndrome, a variety of specialists (e.g., neurologist, hematologist, dermatologist, and endocrinologist) are used with several different treatment regimens. Treatment of POEMS syndrome is utilized to halt the production of bone marrow cells that can create complications in other parts of the body. A standard treatment has not been identified; options such as radiation therapy, chemotherapy, corticosteroids, immunoglobulin therapy, plasma exchange and AuPBSCT have been utilized for this condition.

Hematopoietic Stem Cell Transplant

Hematopoietic stem cell transplantation is a process which includes mobilization, harvesting, and transplant of stem cells after the administration of HDC and/or radiotherapy. High-dose chemotherapy involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (e.g., opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. Autologous - Stem cells can be harvested from the individual's own bone marrow prior to the cytotoxic therapy

2. Allogeneic - Stem cells harvested from a healthy, histocompatible donor. (**Note:** this document does not require that a specific level of histocompatibility be present as part of the medical necessity evaluation).

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy, hematopoietic growth factors, or both. Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease. The most appropriate stem cell source depends upon the type of disease, treatment history, and the availability of a compatible donor. The most appropriate stem cell source must balance the risks of graft failure and re-infusion of malignant cells in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

While the intensity of the regimens used for conditioning in conventional HDC varies, collectively they have been termed "myeloablative." Several less intense conditioning regimens have been developed recently and rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells. These regimens, collectively termed "non-myeloablative", also vary in intensity with substantial overlap between the ranges for "myeloablative" and "non-myeloablative" regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. This manifests as a stable mixed donor-host hematopoietic chimerism. Once chimerism has developed, a further infusion of donor leukocytes may be given to eradicate malignant cells by inducing a graft vs. tumor effect. Non-myeloablative allogeneic transplants, also referred to as "mini-transplant" or "transplant lite", are thought to be potentially as effective as conventional HDC followed by an allogeneic stem cell transplantation (AlloBMT), but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen. Consequently, for individuals with malignancies who are eligible for conventional HDC/AlloBMT, conditioning with milder, non-myeloablative regimens (NM-AlloBMT) represents a technical modification of an established procedure.

Tandem high-dose or non-myeloablative chemotherapy with autologous and/or allogeneic stem cell support is the planned administration of two cycles of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of residual tumor cells can be achieved using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

Definitions

Ablative: A very high dose of a treatment, calculated to kill a tumor or malignant cells.

Allogeneic hematopoietic stem cell transplantation: Infusion of hematopoietic stem cells obtained from a genetically different individual ("donor").

Autologous hematopoietic stem cell transplantation: Infusion of previously harvested hematopoietic stem cells to the same individual from whom they were harvested.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism: Cell populations derived from different individuals, which may be mixed or complete.

Complete response/remission (CR): The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured.

Cytotoxic: Destructive to cells.

Failure to engraft: When the hematopoietic stem cells infused during a stem cell transplant do not grow and function adequately in the bone marrow.

Graft-versus-host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells; may also be called reduced intensity conditioning.

Partial response: A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment; also called partial remission.

Primary graft failure: When the hematopoietic stem cells infused during a stem cell transplant do not grow and function adequately in the bone marrow.

Primary refractory disease: Cancer that does not respond at the beginning of treatment; also called resistant disease.

Relapse: After a period of improvement, the return of signs and symptoms of cancer.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met for autologous transplants:

CPT	
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; when specified for autologous transplant]
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition [when specified as autologous]
ICD-10 Procedure	
	Autologous transplantation
30233G0-30243G0	Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]
30233Y0-30243Y0	Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]
	Pheresis [when specified as autologous]
6A550ZV	Pheresis of hematopoietic stem cells, single [when specified as autologous]
6A551ZV	Pheresis of hematopoietic stem cells, multiple [when specified as autologous]
ICD-10 Diagnosis	
C90.00-C90.32	Multiple myeloma, plasmacytoma, immunoproliferative neoplasms
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
E85.0-E85.9	Amyloidosis
E88.09	Other disorders of plasma-protein metabolism, not elsewhere classified [when specified as POEMS syndrome]

When services are Investigational and Not Medically Necessary:

For the procedure and diagnosis codes listed above, when criteria are not met; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When services may be Medically Necessary when criteria are met for allogeneic transplants:

CPT	
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215; when specified for allogeneic transplant]
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38243	Hematopoietic progenitor cell (HPC); HPC boost
HCPCS	
S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition [when specified as allogeneic]
ICD-10 Procedure	
	Allogeneic transplantation
30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]
30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]
	Pheresis [when specified as allogeneic]
6A550ZV	Pheresis of hematopoietic stem cells, single [when specified as allogeneic]
6A551ZV	Pheresis of hematopoietic stem cells, multiple [when specified as allogeneic]

ICD-10 Diagnosis	
C90.00-C90.32	Multiple myeloma, plasmacytoma, immunoproliferative neoplasms
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above, when criteria are not met; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When services are also Investigational and Not Medically Necessary:
For the procedure codes listed above for allogeneic transplants, for the following diagnosis codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

ICD-10 Diagnosis	
E85.0-E85.9	Amyloidosis
E88.09	Other disorders of plasma-protein metabolism, not elsewhere classified [when specified as POEMS syndrome]

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Document History

Status	Date	Action
Revised	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Removed duplicate asterisk notes within the position statements. Updated Rationale and References sections.
Reviewed	11/10/2022	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	11/11/2021	MPTAC review. Updated Rationale and References sections.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Reviewed	11/05/2020	MPTAC review. Updated Description, Rationale, Background, References and Websites sections.
Reviewed	11/07/2019	MPTAC review. Updated Rationale, Background, References and Websites sections.
	10/01/2019	Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.
Reviewed	11/08/2018	MPTAC review.
Reviewed	10/31/2018	Hematology/Oncology Subcommittee review. Updated Rationale, Background References and Websites sections.
Revised	11/02/2017	MPTAC review.
Revised	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from "Current Effective Date" to "Publish Date". Removed individual selection criteria. Updated Rationale, Background, References and Websites sections.
Revised	11/03/2016	MPTAC review.
Revised	11/02/2016	Hematology/Oncology Subcommittee review. Multiple occurrences of "transplant" replaced with "transplantation" in position statement. Formatting updated in position statement. Rationale, Background, Definitions, Reference and Index sections updated.
	10/01/2016	Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.

Reviewed	11/05/2015	MPTAC review.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Updated Rationale, Background and Reference sections. Removed ICD-9 codes from Coding section.
Reviewed	11/13/2014	MPTAC review.
Reviewed	11/12/2014	Hematology/Oncology Subcommittee review. Updated Rationale, References, Definitions and Websites.
Revised	11/14/2013	MPTAC review.
Revised	11/13/2013	Hematology/Oncology Subcommittee review. Clarified medically necessary criterion for planned tandem transplantation in multiple myeloma. POEMS – clarified existing investigational and not medically necessary criterion and added a separate criterion for allogeneic stem cell transplant. Updated Rationale, References, Definitions and Websites.
Revised	11/08/2012	MPTAC review.
Revised	11/07/2012	Hematology/Oncology Subcommittee review. Clarified Position Statements for multiple myeloma and amyloidosis. Added investigational and not medically necessary indication for three or more autologous stem cell transplants within a twelve-month period for multiple myeloma. Removed number of involved number of organs criterion for amyloidosis. Updated Rationale, References, Definitions and Websites.
Revised	11/17/2011	MPTAC review.
Revised	11/16/2011	Hematology/Oncology Subcommittee review. Clarified medically necessary indication for primary (AL) amyloidosis. Added medically necessary stem cell harvest Position Statement for POEMS. Clarified investigational and not medically necessary stem cell harvest criteria. Updated Rationale, Background, References and Websites. Updated Coding section with 01/01/2012 CPT changes.
Revised	11/18/2010	MPTAC review.
Revised	11/17/2010	Hematology/Oncology Subcommittee review. Title changed to Hematopoietic Stem Cell Transplantation for Multiple Myeloma and Other Plasma Cell Dyscrasias. Clarified medically necessary indications for multiple myeloma. Addition of medically necessary indication for POEMS Syndrome and graft failure or failure to engraft. Addition of not medically necessary statements for treatments of POEMS Syndrome with allogeneic transplant, tandem transplant, transplant for progressive/relapsed disease and stem cell harvest only without a planned future transplant. Rationale, Background, Coding, References and Websites updated.
Revised	11/19/2009	MPTAC review.
Revised	11/18/2009	Hematology/Oncology Subcommittee review. Title changed. Removed "suitably matched" language from criteria. Added medical necessity criteria for hematopoietic stem harvest for multiple myeloma and amyloidosis. Clarified investigational and not medically necessary statement for prophylactic stem cell harvest for multiple myeloma and amyloidosis. Rationale, background, references and websites updated.
	05/21/2009	Updated rationale to include information about stem cell "boosts".

Revised	11/20/2008	MPTAC review.
Revised	11/19/2008	Hematology/Oncology Subcommittee review. Updated rationale, references, coding and websites. Clarified Individual Selection Criteria.
	10/01/2008	Updated Coding section with 10/01/2008 ICD-9 changes.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007.
Revised	11/29/2007	MPTAC review.
Revised	11/28/2007	Hematology/Oncology Subcommittee review. Updated references, websites. Removed separate medical necessity statement for tandem autologous stem cell transplant. Clarified medical necessity statements for tandem transplants. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary."
	05/17/2007	Added note to cross reference TRANS.00016 Umbilical Cord Blood Progenitor Cell Collection, Storage and Transplantation.
Revised	12/07/2006	MPTAC review.
Revised	12/06/2006	Hematology/Oncology Subcommittee review. Addition of medically neccessary statement for primary graft failure.
Revised	06/08/2006	MPTAC review.
Revised	06/07/2006	Hematology/Oncology Subcommittee review. Revision to general patient selection criteria.
Revised	12/01/2005	MPTAC review.
Revised	11/30/2005	Hematology/Oncology Subcommittee. Revision to general patient selection criteria and clarification to multiple myeloma criteria.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Reviewed	07/14/2005	MPTAC review.
Revised	04/28/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organization	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	10/28/2004	TRANS.00002	Stem Cell Transplant following Chemotherapy for Malignant Diseases
WellPoint Health Networks, Inc.	12/02/2004	7.11.02	Autologous Bone Marrow Transplantation or Peripheral Blood Stem Cell Support (PBSCS) for Malignancies
	12/02/2004	7.11.03	Allogeneic Bone Marrow or Stem Cell Transplantation
	12/02/2004	7.11.05	Mini-Transplants

	06/24/2004	7.11.06	Second Autologous Bone Marrow Transplantation for Peripheral Blood Stem Cell Support (PBSCS) in Multiple Myeloma
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for Multiple Myeloma
	12/02/2004	Clinical Guideline	Bone Marrow Transplant for Amyloidosis
	12/02/2004	Clinical Guideline	Second (Repeat) Bone Marrow/Stem Cell Transplant