

Subject: Hematopoietic Stem Cell Transplantation for Multiple Myeloma		Original Effective Date: 12/12/2012
Policy Number: MCP-122	Revision Date(s): 8/12/2015	
Review Date: 12/16/2015, 12/14/2016, 6/22/2017, 9/13/2018		
MCPC Approval Date: 6/22/2017, 9/13/2018		

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.¹

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Multiple Myeloma

Multiple Myeloma (MM) is a hematological cancer affecting plasma cells. Plasma cells develop from B lymphocytes when foreign substances (antigens) enter the body and are responsible for producing antibodies (immunoglobulin) to fight infection and disease. MM is characterized by an overproduction of abnormal plasma cells that adhere to the bone marrow and continue to proliferate, invading hard bone tissue and leading to bone destruction. Multiple lesions affecting the large bones of the body are common. Additionally, myeloma cells produce large numbers of inactive antibodies that crowd out normal functioning antibodies, and levels of functioning antibodies are often depressed in patients with MM. The clinical manifestations of MM include increased infection, diffuse osteoporosis, hypercalcemia, and renal damage. MM is generally considered a treatable but incurable disease. The diagnosis of myeloma requires 10% or more plasma cells on bone marrow examination (or biopsy-proven plasmacytoma), M protein in the serum or urine (except in patients who have true nonsecretory myeloma), and evidence of organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) believed secondary to the underlying plasma cell disorder.²⁷⁻²⁸

There are two staging systems used for Multiple Myeloma, the Durie-Salmon staging system and the International Staging System (ISS). The following table outlines the criteria for the staging²⁴:

Stage	Durie-Salmon Staging Criteria	International Staging System (ISS) Criteria
I	All of the following: <ul style="list-style-type: none"> Hb > 10g/dL normal calcium 	Serum beta-2 microglobulin <3.5mg/L Serum Albumin ≥ 3.5g/dL

	<ul style="list-style-type: none"> • Skeletal survey: normal or single plasmacytoma or osteoporosis • Low M component production rate: <ul style="list-style-type: none"> ➢ Serum paraprotein level IgG < 5 g/dL ➢ Serum paraprotein level IgA < 3 g/dL • Urinary light chain excretion < 4 g/24h 	
II	Neither stage I or III	Neither stage I or III
III	One or more of the following: <ul style="list-style-type: none"> • Hb < 8.5g/dL • high calcium > 12 mg/dL • Skeletal survey: Three or more lytic bone lesions • Low M component production rate: <ul style="list-style-type: none"> ➢ Serum paraprotein level IgG > 7g/dL ➢ Serum paraprotein level if IgA, > 5 g/dL • Urinary light chain excretion > 12g/24h 	Serum beta-2 microglobulin <5.5mg/L
Note	Sub-classification criteria: A: Normal renal function: serum creatinine < 2 mg/dL B: Abnormal renal function: serum creatinine > 2 mg/dL	

Multiple Myeloma is also described as symptomatic or smoldering. Symptomatic multiple myeloma is defined as:²⁴

- Calcium > 11.5 mg/dL
- Renal insufficiency: creatinine > 2 mg/dL
- Anemia: hemoglobin < 10 g/dL or 2 g/dL < normal
- Bone disease: lytic or osteopenic

Smoldering or asymptomatic multiple myeloma is defined by serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10 to 60 and the absence of myeloma defining events or amyloidosis.²⁴

Stem Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person’s own stem cells) or allogeneic (using stem cells from a donor). In allogeneic HSCT, it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

Tandem Transplantation:

Tandem transplantation refers to a planned second transplant or a subsequent second 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 that is used as salvage therapy after failure of initial transplantation or relapsed disease.

RECOMMENDATION 1 23-29 30-37

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Members must meet UNOS guidelines for transplantation and the diagnosis must be made by a *Specialist in the Disease* and or Transplant Surgeon.

Pre-Transplant Evaluation: 27 36

Criteria for transplant evaluation include all of the following:

- History and physical examination
- Psychosocial evaluation and clearance:
 - No behavioral health disorder by history or psychosocial issues:
 - if history of behavioral health disorder, no severe psychosis or personality disorder
 - mood/anxiety disorder must be excluded or treated
 - member has understanding of surgical risk and post procedure compliance and follow-up required
 - Adequate family and social support
- EKG
- Chest x-ray
- Cardiac clearance in the presence of any of the following:
 - chronic smokers
 - > 50 years age
 - those with a clinical or family history of heart disease or diabetes
- Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- Neurological exam and clearance for transplant: [ONE]
 - Normal exam by H&P
 - Abnormal neurological exam with positive findings: [ONE]
 - Lumbar puncture normal cytology
 - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance
- Performance Status : [ONE]
 - Karnofsky score 70-100%; or
 - Eastern Cooperative Oncology Group (ECOG) grade 0-2

- Lab studies:
 - *Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
 - *Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
 - If HIV positive all of the following are met:
 - CD4 count >200 cells/mm-3 for >6 months
 - HIV-1 RNA undetectable
 - On stable anti-retroviral therapy >3 months
 - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasm)
 - If abnormal serology need physician plan to address and/or treatment as indicated
 - UDS (urine drug screen) if patient is current or gives a history of past drug abuse
- *Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated
- *GYN examination with Pap smear for women ≥21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant
- *Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- *PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

**Participating Centers of Excellence may waive these criteria*

Criteria for Hematopoietic Autologous Stem Cell transplantation (AuSCT) Transplantation:

1. **Hematopoietic Autologous stem cell transplantation** may be considered medically necessary when the member has Durie-Salmon Stage II or III multiple myeloma ²⁴ and: [ALL of the following]
 - All pre-transplant criteria are met; and
 - Age < 78 years ¹
 - Treatment Response [ONE]
 - Partial response to post induction chemotherapy sustained for one month defined as: [ALL]
 - ◆ >50% reduction in serum M protein; and
 - ◆ >90% reduction in M (Bence Jones) urine protein; and
 - ◆ No evidence of new bone lesions
 - Relapsed disease post induction therapy defined as:
 - ◆ increased M proteins in serum and urine

Note: normal M protein is zero

- Refractory disease post induction chemotherapy defined as disease that is unresponsive to post induction chemotherapy³²

AND

- The requesting transplant recipient should not have any of the following **absolute contraindications**:
 - Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
 - Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
 - Systemic and/or uncontrolled infection
 - AIDS (CD4 count < 200cells/mm³)
 - Unwilling or unable to follow post-transplant regimen
 - ◇ Documented history of non-compliance
 - ◇ Inability to follow through with medication adherence or office follow-up
 - Chronic illness with one year or less life expectancy
 - Limited, irreversible rehabilitation potential
 - Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
 - No adequate social/family support
- The requesting transplant recipient should be evaluated carefully and potentially treated if the following **relative contraindications** are present:
 - Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
 - Smoking, documentation supporting free from smoking for 6 months
 - Active peptic ulcer disease
 - Active gastroesophageal reflux disease
 - CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
 - Obesity with body mass index of >30 kg/m² may increase surgical risk
 - Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
 - Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

Criteria for Subsequent Hematopoietic Stem Cell Transplantation:

2. **Hematopoietic Autologous Stem Cell Transplantation** may be considered medically necessary after the *first prior autologous stem cell transplantation* has occurred only one time, for members with multiple myeloma who meet all of the above criteria for transplant and have the following:[ONE]

- Relapsed disease occurring > 6 -12 months after the first stem cell transplant

3. **Tandem Hematopoietic Autologous Stem Cell Transplantation** may be considered medically necessary after the first prior autologous stem cell transplantation for members with multiple myeloma who meet all of the above criteria for transplant and meet the following: [ONE]

- Failed to achieve at least a very good partial response < 6 months after the first stem cell transplant

4. **Hematopoietic Allogenic Stem Cell Transplantation** may be considered medically necessary after the first prior autologous stem cell transplantation for members with active symptomatic multiple myeloma who meet all of the above criteria for transplant and have the following: ²⁴ [ONE]

- In progressive disease as salvage therapy

CONTINUATION OF THERAPY

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
 - Presence of no absolute contraindication as listed above;
 - History and physical within the last 12 months;
 - Kidney profile within the last 12 months;
 - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
 - Psychosocial evaluation or update within the last 12 months;
 - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.
- If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
 - Authorization letter/documentation from previous insurer;
 - Presence of no absolute contraindication as listed above;
 - History and physical within the last 12 months;
 - Cardiac update if history of cardiac disease within two years (≥ 50 years of age);
 - Psychosocial evaluation or update within the last 12 months;
 - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

COVERAGE EXCLUSIONS

1. Autologous (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant

The published medical evidence and outcomes for hematopoietic stem cell transplantation for multiple myeloma in children and adults in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information. Additional studies are outlined below.

Chemotherapy versus Autologous Stem Cell Transplantation

Koreth and colleagues performed a meta-analysis of 2,411 patients enrolled in randomized controlled trials compared standard dose chemotherapy versus myeloablative chemotherapy with single autologous HSCT. Myeloablative high-dose therapy and single autologous stem cell transplantation (HDT) is frequently performed early in the course of multiple myeloma, supported by some randomized controlled trials (RCTs) indicating overall survival (OS) and progression-free survival (PFS) benefit compared with non-myeloablative standard-dose therapy (SDT). Other RCTs, however, suggest variable benefit. The primary objective was to quantify overall survival (OS) benefit with single autologous HSCT. In total, 3407 articles were accessed, and 10 RCTs prospectively comparing upfront HDT with SDT, with > or =2-year follow-up, and reporting OS benefit on an intent-to-treat basis were identified. The authors of the meta-analysis concluded that myeloablative therapy with autologous HSCT increased the likelihood of PFS (hazard of progression=0.75; 95% CI: 0.59–0.96) but not OS (hazard of death=0.92; 95% CI: 0.74–1.13). However, the overall risk of developing treatment-related mortality with HDT was increased significantly (odds ratio, 3.01; 95% CI: 1.64–5.50) in the group with autologous HSCT. Therefore, evaluating alternative therapeutic options upfront may also be reasonable.

Another meta-analysis by Faussner and colleagues²² was performed to compare myeloablative high-dose chemotherapy (HDT) followed by single autologous stem cell transplantation with standard dose therapy (SDT) in 2,600 patients. 10 randomized controlled trials (RCTs) were identified comparing HDT with SDT on an intention-to-treat-basis. Treatment characteristics and outcomes of overall survival (OS) and progression free survival (PFS) were reported. Statistical heterogeneity and publication bias and subgroup analyses were performed. Patients undergoing HDT with stem cell transplantation had a significant PFS benefit (hazard ratio=0.73; 95% CI=0.56-0.95; p=0.02) but no OS benefit (HR 0.90; 95% CI 0.74-1.10; p=0.32) as compared to patients undergoing SDT. The authors concluded that although there is only a trend of OS benefit with HDT, it is currently still the first line treatment. Additional data from ongoing clinical trials and new studies using novel agents such as thalidomide, lenalidomide and bortezomib are warranted to finally evaluate the role of HDT in the treatment management of patients with newly diagnosed MM.⁶

Repeat Autotransplant for Relapse after Initial Autotransplant

An evidence-based systematic review sponsored by the American Society for Blood and Marrow Transplantation (ASBMT) summarized data from 4 relevant clinical series. Investigators reported that some myeloma patients who relapsed after a first autotransplant achieved durable complete or partial remissions after a second autotransplant as salvage therapy. Factors that apparently increased the likelihood of durable remissions and extended survival included a chemosensitive relapse, younger age, a long disease-free or progression-free interval since the initial autotransplant, and fewer chemotherapy regimens prior to the initial autotransplant.²⁵

Olin and colleagues reported their experience with 41 patients with multiple myeloma who received a second salvage autologous HSCT for relapsed disease. 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 progression free survival (PFS) of 8.5 months and median overall survival (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. The authors concluded that in well-selected patients salvage auto-SCT is safe and effective for relapsed myeloma.⁸

Allogeneic transplant for Relapse after Initial Autotransplant^{9-11 14}

The Eastern Cooperative Oncology Group conducted a Phase II trial of autologous HSCT followed by Nonmyeloablative allogeneic transplantation (NST) to provide maximal tumor cytoreduction to allow for a subsequent GVM effect. Patients received melphalan 200 mg/m² with autologous HSCT, followed by fludarabine 30 mg/m² in 5 daily doses and cyclophosphamide 1 g/m² in 2 daily doses with matched sibling donor NST. Graft-versus-host disease (GVHD) prophylaxis included cyclosporine and corticosteroids. The primary endpoints were TRM, graft failure, acute GVHD, progression-free survival (PFS), and overall survival (OS). Thirty-two patients were enrolled into the study; 23 patients completed both transplantations (72%). Best responses post-NST were 7 (30%) complete remission (CR), 11 (48%) partial remission (PR), 2 (9%) no response, and 3 (13%) not evaluable. Acute grade III-IV GVHD was observed in 4 patients (17%), and chronic GVHD was seen in 13 patients (57%; 7 limited, 6 extensive). Chronic GVHD resulted in the following responses: 3 (23%) CR, 1 continuing CR, and 6 (46%) PR. Two patients (8.7%) had early TRM. With a median follow up of 4.6 years, the median PFS was 3.6 years, and the 2-year OS was 78%. Our findings indicate that autologous HSCT followed by NST is feasible, with a low early TRM in a cooperative group setting. The overall response rate was 78%, including 30% CR, similar to other reports for autologous HSCT-NST. Because a plateau in PFS or OS was not observed with this treatment approach even in patients achieving CR, we suggest that future studies use post-transplantation maintenance therapy.⁹

Qazilbash and colleagues reported their experience with salvage autologous or allogeneic transplantation after a failed first autologous transplant. 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 authors concluded that both autografting and allografting are feasible as salvage therapy for myeloma patients who develop disease recurrence after the first autograft, although disease progression remains the major cause of failure. Because of limited efficacy, high cost, and treatment-related complications, salvage autologous and allogeneic transplants should be performed only in the setting of a clinical trial, preferably in comparison with conventional nontransplant approaches using newer agents such as bortezomib or lenalidomide.¹⁰

Tandem Autologous HSCT

Several randomized controlled trials, prospective studies, and meta-analysis reports have evaluated the relative efficacy of double versus single autologous HCT in previously untreated patients. Among the randomized trials, consistent benefits have primarily been reported among those with less than a very good partial response (VGPR) to the initial transplant procedure. The evidence supports tandem HDC/autograft when used as part of first-line therapy for newly diagnosed MM in patients with good performance status and adequate cardiac, pulmonary, and hepatic function.¹⁵⁻²²

Professional Society Guidelines: Several professional society organizations have recommended that Autologous SCT is the preferred method of treatment following primary therapy for eligible patients and is an option for treatment of primary progressive or refractory disease post induction treatment.²³⁻²⁹

- **The National Marrow Donor Program:** The NMDP recommends that individuals with multiple myeloma referred for consultation for HSCT when the following characteristics are present: After initiation of therapy and at first progression.²⁷
- **The National Comprehensive Cancer Network Guidelines (NCCN Guidelines):**²⁴ The guidelines recommend that high dose therapy with stem cell support is a critical component in the treatment plan for eligible newly diagnosed MM patients and that all types of stem-cell transplantations are appropriate in different clinical settings. Autologous HSCT results in high response rates and remains the standard of care following primary therapy for eligible patients and is an option for treatment of primary progressive or refractory disease post induction treatment. A tandem transplant can be considered for all patients who are candidates for stem cell transplant and is an option for patients who do not achieve at least a very good partial response after the first autologous stem cell transplant. Allogeneic HSCT may be an accepted option in the setting of a clinical trial in patients responding to primary therapy or primary progressive disease, or as salvage therapy in patients with progressive disease following an initial autologous HSCT. The algorithms also identify two situations where a repeat salvage autologous HSCT may be considered either on or off clinical trial:
 - In patients initially treated with primary therapy alone, followed by an autologous HSCT when the disease relapsed, who now have progressive disease following a first autologous HSCT
 - In patients who develop progressive disease after first autologous transplant

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
38243	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic hematopoietic cellular transplant boost

HCPCS	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

ICD-10	Description: [For dates of service on or after 10/01/2015]
C90.0	Multiple Myeloma

RESOURCE REFERENCES

Government Agency

- Centers for Medicare & Medicaid Services. NCD for Stem Cell Transplantation (Formerly 110.8.1) 110.23. Effective date 1/27/2016. Accessed at: <http://www.cms.gov/medicare-coverage-database/>
- National Marrow Donor Program. Multiple Myeloma Transplant Outcomes. Accessed at: http://marrow.org/Physicians/When_to_Transplant/Outcomes_by_Disease.aspx

Peer Reviewed Publications

3. Lokhorst H, Einsele H, Vesole D, et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *J Clin Oncol*. 2010;28(29):4521-4530.
4. Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78 p. Accessed at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc_stemcell.pdf
5. Bird JM, Owen RG, D'Sa S, Snowden JA, Pratt G, Ashcroft J, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. *Br J Haematol*. 2011 Jul;154(1):32-75. Accessed at: <http://iaclid.ir/DL/ravesh/guidelinesforthediagnosisandmanagementofmultiplemyeloma2011.pdf>
6. Koreth, J, Cutler, CS, Djulbegovic, B, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. *Biol Blood Marrow Transplant*. 2007 Feb;13(2):183-96. PMID: 17241924. Accessed at: http://www.medicine.ufl.edu/hemonc/fellowship/Reading_List/2006-2007%20BMT%20ARTICLES/BMT%20for%20Multiple%20Myeloma/Koreth%20et%20al.pdf
7. Faussner F, Dempke WC. Multiple myeloma: myeloablative therapy with autologous stem cell support versus chemotherapy: a meta-analysis. *Anticancer Res*. 2012 May; 32(5):2103-9.
8. Olin, RL, Vogl, DT, Porter, DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. *Bone Marrow Transplant*. 2009 Mar;43(5):417-22. PMID: 18850013 accessed at: <http://www.nature.com/bmt/journal/v43/n5/full/bmt2008334a.html>
9. Vesole DH, Zhang L, Flomenberg N, Greipp PR, Lazarus HM, ECOG Myeloma and BMT Committees. A phase II trial of autologous stem cell transplantation followed by mini-allogeneic stem cell transplantation for the treatment of multiple myeloma: an analysis of Eastern Cooperative Oncology Group ECOG E4A98 and E1497. *Biol Blood Marrow Transplant*. 2009 Jan;5(1):83-91.
10. Qazilbash, MH, Saliba, R, De Lima, M, et al. Second autologous or allogeneic transplantation after the failure of first autograft in patients with multiple myeloma. *Cancer*. 2006 Mar 1;106(5):1084-9. PMID: 16456814. Accessed at: <http://onlinelibrary.wiley.com/doi/10.1002/ncr.21700/full>
11. Björkstrand B Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. *J Clin Oncol*. 2011; 29(22):3016-3022.
12. C Mackall, T Fry, R Gress, K Peggs, J Storek and A Toubert. Background to hematopoietic cell transplantation, including post-transplant immune recovery. *Bone Marrow Transplant* 44: 457-462; doi:10.1038/bmt.2009.255 Accessed at: <http://www.nature.com/bmt/journal/v44/n8/full/bmt2009255a.html>
13. Eastern Cooperative Oncology Group (ECOG) Performance Status. Accessed at: http://www.ecog.org/general/perf_stat.html
14. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356:1110-1120. Accessed at: <http://www.nejm.org/doi/full/10.1056/NEJMoa065464#t=articleTop>
15. Kumar A et al. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2009;101:100.
16. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood*. 2006;107(9):3474-3480. Accessed at: <http://bloodjournal.hematologylibrary.org/cgi/content/full/107/9/3474>

17. Rosiñol L, Pérez-Simón JA, Sureda A, et al.; Programa para el Estudio y la Terapéutica de las Hemopatías Malignas y Grupo Español de Mieloma (PETHEMA/GEM). A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008;112(9):3591-3593. Accessed at: <http://bloodjournal.hematologylibrary.org/cgi/content/full/112/9/3591>
18. Barlogie B, Tricot GJ, van Rhee F, Anghuaco E, et al. Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. *Br J Haematol*. 2006 Oct;135(2):158-64. Epub 2006 Aug 25.
19. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. *J Natl Cancer Inst* 2009; 101:100. Accessed at: <http://jnci.oxfordjournals.org/content/101/2/100.full.pdf>
20. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol* 2007; 25:2434. Accessed at: <http://jco.ascopubs.org/content/25/17/2434.full>
21. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003; 349:2495
22. Armeson KE, Hill EG, Costa LJ. Tandem autologous vs autologous plus reduced intensity allogeneic transplantation in the upfront management of multiple myeloma: meta-analysis of trials with biological assignment. *Bone Marrow Transplant*. 2012 Sep 10. doi: 10.1038/bmt.2012.173.

Professional Society Guidelines

23. National Marrow Donor Program[®] (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) referral guidelines: Recommended Timing for Transplant Consultation. Accessed at: <https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Referral-Timing-Guidelines/>
24. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Multiple Myeloma. V1.2019. Accessed at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
25. The American Society for Blood and Marrow Transplantation (ASBMT). Position Statement of the American Society for Blood and Marrow Transplantation. The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Treatment of Multiple Myeloma. *Biol Blood Marrow Transplant*. 2003. Accessed at: <http://www.asbmt.org/?page=GuidelineStatements>
26. The American Society for Blood and Marrow Transplantation (ASBMT). The Role of Cytotoxic Therapy with Hematopoietic Stem Cell Transplantation in the Therapy of Multiple Myeloma: An Evidence-Based Review, *Biology of Blood and Marrow Transplantation*, Vol. 9, No. 1: January 2003. Accessed at: <http://www.asbmt.org/?page=GuidelineStatements>
27. National Marrow Donor Program[®] (NMDP). Patient Eligibility for HCT. Accessed at: <https://bethematchclinical.org/Transplant-Indications-and-Outcomes/Eligibility/>
28. National Cancer Institute. Plasma Cell Neoplasms including Multiple Myeloma Treatment PDQ 2018. Accessed at: <http://www.cancer.gov/cancertopics/pdq/treatment/myeloma/healthprofessional>
29. National Bone Marrow Donor Program. Measuring Engraftment. Accessed at: http://marrow.org/Patient/Transplant_Process/Days_0-30/Measuring_Engraftment.aspx

Other Resources

30. Hayes Health Technology Brief. Autologous Stem Cell Transplantation Followed by Nonmyeloablative Allogeneic Stem Cell Transplantation for Treatment of Multiple Myeloma. Updated Oct 23, 2012. Archived Nov, 2013.

31. Hayes Medical Technology Directory Report. High-Dose Chemotherapy with Peripheral Stem Cell/Autologous Transplantation Treatment for Multiple Myeloma. Winifred Hayes Inc. Sept 2006, updated Sept 2010 and archived Oct 2011.
32. McKesson InterQual Criteria for Procedures: Adult 2017 InterQual Transplantation, Autologous Stem Cell; 2017.
33. DynaMed LLC [website]. EBSCO Publishing 1998-2018. Multiple Myeloma.
34. MD Consult [website]. Kuter DJ, Losman JAL. Multiple Myeloma. Revised Aug 2007.
35. MD Consult [website]. Rajkumar SV, Dispenzieri A. Multiple Myeloma and Related Disorders. Abeloff's Clinical Oncology, 4th ed. 2008 Churchill Livingstone.
36. UpToDate. [website]. Waltham, MA: Walters Kluwer Health; 2018.
 - Holmberg LA, Deeg HJ et al. Determining Eligibility for autologous/allogeneic hematopoietic cell transplantation.
 - Rajkumar SV. Allogeneic hematopoietic cell transplantation in multiple myeloma.
 - Rajkumar SV. Autologous Hematopoietic Cell Transplantation in Multiple Myeloma.
 - Rajkumar SV. Overview of the management of multiple myeloma.
37. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Internal Medicine, Oncology, Hematology. October 18, 2012

Review/Revision History

12/12/2012: Policy created

8/12/2015: Policy reviewed and updated with revisions made to the pre-transplant criteria, minor revision to the criteria to include upper age limit of 78, and criteria for Allogeneic Stem Cell Transplantation was added.

Guideline and reference sections were updated.

12/14/16, 6/22/17: Policy reviewed, no changes

9/13/18: Policy reviewed, no criteria changes, reference section updated.