This Medical Guidance 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 exclusions 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 following website: http://www.cms.hhs.gov/center/coverage.asp.

Centers for Medicare and Medicaid Services (CMS)

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 medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does have a NCD called Stem Cell Transplantation (110.8.1) and effective October 1, 2000 a single AuSCT is covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
- Have adequate cardiac, renal, pulmonary, and hepatic function.

CMS does not cover the following for multiple myeloma:

- Tandem transplantation: a planned second transplant or a subsequent second transplant that is performed within 6 months of the initial transplant
- Allogeneic HSCT

CMS indicates that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood...
stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

**INITIAL COVERAGE CRITERIA**

All transplants must be approved by the Medical Director prior to authorization

Members must meet the criteria outlined below for transplantation and the diagnosis must be made by a Hematologist, Oncologist and/or transplant surgeon.

Pre-Transplant Evaluation:

1. General requirements for transplant evaluation include all of the following:

   - History and physical examination
   - **Psychosocial evaluation and clearance:** This must be completed and documentation submitted for review before any additional transplant work-up or testing is initiated.
   - Dietary consult and clearance for transplant
   - Disease evaluation **may** include all the following:
     - Bone marrow biopsy and/or bone marrow aspiration: must show adequate response to therapy
     - CT scan
     - PET scan
   - Cardiac Echocardiogram: Ejection fraction > 50%
   - EKG
   - Chest X-ray
   - Skeletal survey X-ray: if findings show equivocal lytic lesions additional imaging studies may be needed in the following order:
     - CT scan
     - MRI
   - Performance Status: [ONE]
     - Karnofsky score 70-100%
     - **Eastern Cooperative Oncology Group (ECOG) grade 0-2**
   - Pulmonary function testing: [ALL]
     - Diffusion capacity (DLCO) >60%
     - Forced expiratory volume (FEV) >60%
     - Forced capacity (FVC) >60%
   - Lab studies:
     - Complete blood cell count, liver function tests, kidney profile, coagulation profile (prothrombin time, partial thromboplastin time)
     - HIV testing
- Hepatitis A (HAV), Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis D, Ebstein-Barr virus (EBV), cytomegalovirus (CMV) serology, syphilis, toxoplasmosis, herpes simplex virus
- HLA Antibody
- Blood type
- Serum creatinine: <1.5mg%
- creatinine clearance: > 60 ml/min
- Bilirubin < 2mg%
- quantification of monoclonal protein in serum and urine
- beta-2 microglobulin
- Calcium

Within the last 12 months the following may be required:

- Colonoscopy (indicated > age 50 with removal of any polyps if applicable)
- Dental examination (contact plan for coverage criteria)
- GYN examination with Pap smear (indicated > age 18) with complete workup and treatment of abnormal results as indicated
- Mammogram (indicated > age 40) with complete workup and treatment of abnormal results as indicated

<table>
<thead>
<tr>
<th>Karnofsky Performance Score*</th>
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<tr>
<td>Able to carry on normal activity, no evidence of disease</td>
<td>100%</td>
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<tr>
<td>Able to carry on normal activity, minor signs or symptoms of disease</td>
<td>90%</td>
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<tr>
<td>Normal activity with effort, some signs and symptoms of disease</td>
<td>80%</td>
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<tr>
<td>Cares for self, unable to carry on normal activity or to work</td>
<td>70%</td>
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<tr>
<td>Requires occasional assistance from others but able to care for most needs</td>
<td>60%</td>
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<tr>
<td>Requires considerable assistance from others and frequent medical care</td>
<td>50%</td>
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<tr>
<td>Disabled, requires special care and assistance</td>
<td>40%</td>
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<tr>
<td>Severely disabled, hospitalization indicated, death not imminent</td>
<td>30%</td>
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<tr>
<td>Very sick, hospitalization indicated, active support treatment necessary</td>
<td>20%</td>
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<tr>
<td>Moribund</td>
<td>10%</td>
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<tr>
<td>Dead</td>
<td>0%</td>
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<tr>
<th>Eastern Cooperative Oncology Group (ECOG) Scale**</th>
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<tr>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
<td>0</td>
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<tr>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
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<tr>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
<td>2</td>
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<tr>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
<td>3</td>
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<tr>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
<td>4</td>
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<tr>
<td>Dead</td>
<td>5</td>
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Criteria for Hematopoietic Autologous Stem Cell transplantation (AuSCT) Transplantation:

1. **Hematopoietic Autologous stem cell transplantation** may be authorized when the member has Durie-Salmon Stage II or III multiple myeloma* and: [ALL of the following]
   - Age < 70 years
   - Treatment Response
     - Partial response to post induction chemotherapy sustained for one month defined as: [ONE]
       - >50% reduction in serum M protein; and
       - >90% reduction in M (Bence Jones) urine protein
       - 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 chemotherapy

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<thead>
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AND

- None of the following **absolute contraindications** are present: [NONE]
Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)

- Irreversible brain damage or active central nervous system disease
- Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
- No behavioral health disorder by history or psychosocial issues: [One]
  - 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

*Note:* Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

- No adequate social/family support

**Criteria for Subsequent Hematopoietic Stem Cell Transplantation:**

2. **Hematopoietic Autologous Stem Cell Transplantation** may be authorized 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 15-20:[ONE]

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

3. **Tandem Hematopoietic Autologous Stem Cell Transplantation** may be authorized 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 16 31: [ONE]

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

**CONTINUATION OF THERAPY**

A review for any stem cell transplantation procedure is valid for one year from the time the request was approved. Due to potential lengthy organ donor waiting time, an annual review of clinical information should be conducted to evaluate any changes in the member’s clinical status.

**COVERAGE EXCLUSIONS** 1-2: 10

1. Autologous (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Allogeneic stem cell transplantation alone or after autologous stem cell transplantation is considered investigational 16
3. Tandem stem cell transplantation is not covered for Medicare members.
4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant is not covered.
5. The following absolute contraindications to stem cell transplantation are not covered:
   - Active alcohol and/or other substance abuse including smoking (to remove as a contraindication there must be 6 months of documented abstinence through participation in a structured alcohol/substance abuse program with regular meeting attendance and negative random drug testing)
   - Documented history of non-compliance or inability to follow through with medication adherence or office follow-up
   - Irreversible brain damage or active central nervous system disease
   - Significant or advanced heart, lung, liver, kidney, gastrointestinal or other systemic or multi-system disease that is likely to contribute to a poor outcome after transplantation
   - No behavioral health disorder by history or psychosocial issues: [One]
     - if history of behavioral health disorder, no severe psychosis or personality disorder
     o mood/anxiety disorder must be excluded or treated
   - member has understanding of surgical risk and post procedure compliance and follow-up required

   **Note:** Patient’s need to understand the importance of adherence to medication schedules and follow-up appointments/noncompliance is a major cause of graft failure.

   - No adequate social/family support

6. Relative contraindications to stem cell transplantation include all of the following:
   - poor cardiac function (ejection fraction < 50%)
   - poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal)
   - poor renal function (creatinine clearance < 60ml/min)
   - poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
   - active central nervous system involvement
   - presence of human immunodeficiency virus (HIV)
   - an active infection with any ONE of the following:
     - hepatitis B virus (HBV)
     - hepatitis C virus (HCV)
   - Karnofsky rating <70% ; OR
   - Eastern Cooperative Oncology Group (ECOG) performance status >2

**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.  

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 staging:

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<th>International Staging System (ISS) Criteria</th>
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<tr>
<td>Serum beta-2 microglobulin &lt;3.5mg/L</td>
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<tr>
<td>Serum Albumin ≥ 3.5g/dL</td>
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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:

• 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 the presence of a serum IgG or IgA M protein level of 3 g/dL or greater and/or bone marrow plasma cells 10% or more, and absence of anemia, hypercalcemia, lytic bone lesions, or renal failure that can be attributed to the plasma cell proliferative disorder.

**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.

**Donor Lymphocyte Infusion**

Following an allogeneic hematopoietic stem cell transplant, donor lymphocyte infusion is a form of adoptive immunotherapy and may be requested to induce a graft versus leukemia, or graft versus tumor, response without requiring the recipient to undergo additional high-dose chemotherapy. Donor lymphocytes are collected from the original donor through leukapheresis. This collection is an outpatient procedure for the donor. The lymphocytes are then either infused via vein into the recipient or are frozen for a more clinically appropriate time.

**Pretransplant Evaluation**

The goal of the pretransplant evaluation is to assess the ability of a patient to tolerate the surgery, post-operative immunosuppression, and transplant care. An extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation is standard. Specific testing varies depending upon the patient's age, medical history, and transplant center practice. In addition, while a certain battery of tests may initiate the work up, more testing may be indicated depending upon the condition of the patient or the initial test results. In addition to a standard medical evaluation the initial assessment should include a psychological and social support evaluation to identify issues that may impair a successful outcome after transplantation. These include a lack of information about the nature of the transplant procedure and post-transplant care, drug or alcohol dependence, compliance with complex medical and behavior regimens. The assessment includes education of the family and the support network of the patient because compliance with complex medical and behavior treatment is critical after any organ transplant procedure. Recipients must be able to incorporate complicated
medications, follow-up appointments, and frequent laboratory visits into their schedules. Having an adequate support network aware of these requirements will encourage patient compliance and long-term success.

### GENERAL INFORMATION

**Summary of Medical Evidence**

**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-analyses by Faussner and colleagues 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.

**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.

Olin and colleagues reported their experience with 41 patients with multiple myeloma who received a second salvage autologous HSCT for relapsed disease.\textsuperscript{23} 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 that in well-selected patients salvage auto-SCT is safe and effective for relapsed myeloma.

**Allogeneic transplant for Relapse after Initial Autotransplant**

Dey and colleagues\textsuperscript{24} evaluated the outcome of HLA-matched related donor alloSCT following nonmyeloablative preparative therapy in 13 patients (median age, 38 years) with relapsed hematologic malignancies (Hodgkin's disease, n = 4; Hodgkin's disease and advanced myelodysplastic syndrome, n = 1; non-Hodgkin's lymphoma, n = 6; multiple myeloma, n = 2) after initial autoSCT. Median time from autoSCT to alloSCT was 12 months (range, 3-24 months); 6 patients had chemotherapy-refractory disease following autoSCT, 6 were in untreated relapse, and 1 had a partial response from salvage chemotherapy. Preparative therapy consisted of cyclophosphamide, 150-200 mg/kg; peri-transplantation anti-thymocyte globulin; thymic irradiation (in patients who had not received previous mediastinal irradiation); and a very short course of cyclosporine as GVHD prophylaxis. All patients achieved initial mixed chimerism as defined by greater than 1% donor peripheral white blood cells. Seven patients, who had no evidence of GVHD, received prophylactic DLI beginning 5 to 6 weeks after transplantation for conversion of mixed chimerism to full donor hematopoiesis and to optimize a graft-versus-tumor effect. Six patients showed conversion to full donor chimerism and 1 lost the graft. Grade II or greater acute GVHD occurred in 9 patients. Seven patients achieved a complete response; 6 had no response. The median survival time of the 13 patients is currently 10 months (range, 3-39 months), with an overall survival probability at 2 years of 45% (95% confidence interval [CI], 19%-73%) and a disease-free survival probability at 2 years of 37.5% (95% CI, 12%-65%). Thus, this novel nonmyeloablative alloSCT strategy followed by prophylactic DLI was well tolerated and can result in durable disease-free survival among patients with advanced hematologic malignancies after a failed autoSCT. The authors concluded that further follow-up and evaluation of additional patients are required to conclusively establish the role of this strategy in the treatment of hematologic malignancies after an autologous transplantation.

Qazilbash and colleagues\textsuperscript{25} 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 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.

Tandem autologous/reduced-intensity conditioning (RIC) allogeneic HSCT

A meta-analysis by Armesen and colleagues was conducted to compare tandem autologous (TA) hematopoietic SCT (auto-HSCT) or single auto-HSCT followed by reduced intensity conditioning (RIC), allogeneic (AR) hematopoietic SCT in the upfront management of patients with multiple myeloma (MM). A comprehensive search strategy of published and unpublished reports utilized the following entry criteria: newly diagnosed patients, first autologous transplantation in both arms, use of an RIC regimen and assignment to TA or AR based exclusively on the availability of an HLA matched donor. Six trials were identified yielding 1192 subjects in TA and 630 in AR. Patients in AR had higher likelihoods of treatment related mortality (TRM) (relative risk (RR)=3.3, 95% confidence interval (CI)=2.2-4.8) and CR (RR=1.4, 95% CI=1.1-1.8). Overall survival (OS) was not different in the first 36 months (hazard ratio (HR) =1.15, 95% CI=0.91-1.45) or after (HR=0.74, 95% CI=0.53-1.04) 36 months from assignment. Similar findings were seen for progression free survival (PFS). When compared with TA in the upfront management of MM, AR is associated with higher TRM and CR without improvement in PFS or OS.

Tandem Autologous HSCT

Garban and associates (2006) compared 46 patients who received auto-allo SCT with 166 patients who received auto-auto SCT based on the presence or absence of an HLA-matched sibling. All patients had newly diagnosed MM stages I to III and were aged < 65 years, but were considered at high risk because of high β2 microglobulin or chromosome 13 deletions. All patients initially underwent induction with vincristine, doxorubicin, and dexamethasone (VAD), followed by G-CSF—stimulated peripheral blood stem cell (PBSC) collection. Patients were conditioned for the first autograft using melphalan. In the second stage, allograft recipients were conditioned using busulphan, fludarabine, and antithymocyte globulin, and autograft recipients using melphalan and dexamethasone with or without anti—interleukin-6 monoclonal antibody. At a median follow-up of 24 months, the median OS was 35.0 months for auto-allo SCT patients compared with 47.2 months for auto-auto SCT (P=0.07). Median EFS (disease progression, relapse, or death) was 31.7 for auto-allo SCT compared with 35.0 months for auto-auto SCT (P=0.35). The incidence of acute GVHD was 32.6% and extensive chronic
GVHD was 35.7% in auto-allo SCT recipients, and transplant-related deaths occurred in 10.9% of auto-allo SCT compared with 5.0% of auto-auto SCT recipients.³²

Bruno and colleagues (2007) compared 58 patients receiving auto-allo SCT with 46 receiving auto-auto SCT, based on presence or absence of an HLA-matched sibling. Patients had newly diagnosed MM stage II or III and were 65 years of age or younger. Induction therapy was performed with VAD and patients were conditioned for initial autograft with melphalan following G-CSF—stimulated PBSC collection. Allograft recipients were then conditioned using nonmyeloablative total body irradiation (TBI) and tandem autograft recipients were conditioned with melphalan. At a median follow-up of 46 months (range, 22 to 88), median OS was not reached in auto-allo SCT recipients compared with 58 months in auto-auto SCT recipients (hazard ratio [HR] 0.46; 95% confidence interval [CI] 0.23-0.93; P=0.03). Median EFS was 43 months for auto-allo SCT patients versus 33 months for auto-auto SCT patients (HR, 0.63; CI, 0.39-1.04; P=0.07). The cumulative incidence of treatment-related mortality at 2 years was 10% for auto-allo SCT versus 2% for auto-auto SCT (P=0.09). The incidence of disease-related mortality was 7% for auto-allo SCT versus 43% for auto-auto SCT (P<0.001). The cumulative incidence of acute GVHD in auto-allo SCT recipients was 43%, with grade IV in 4%, and at 2 years the cumulative incidence of extensive chronic GVHD was 32%.³³

Rosiñol and associates (2008) compared 25 patients who received auto-allo SCT with 85 who received auto-auto SCT for newly diagnosed MM stages I to III. Patients were aged < 70 years. Induction therapy consisted of vincristine, carmustine (known as BCNU), melphalan, cyclophosphamide, prednisone (VBMCP) or vincristine, carmustine, adriamycin, dexamethasone (VBAD) followed by a first autograft. Patients failing to achieve a complete remission or near-complete remission after the first autograft were scheduled for a second autograft (in the absence of an HLA-matched sibling aged < 65 years) or an allograft (in those with an HLA-matched sibling). Auto-allo SCT recipients were conditioned using fludarabine and melphalan, and tandem autograft recipients with cyclophosphamide, etoposide, and carmustine (CVB) or higher-dose melphalan. At a median follow-up of 5.2 years median OS was not reached for auto-allo SCT patients compared with 58 months for auto-auto SCT patients (P=0.9). EFS was 19.6 months for auto-allo SCT versus 26 months for auto-auto SCT (P=0.4). Treatment-related mortality was 16% for auto-allo SCT compared with 5% for auto-auto SCT (P=0.09). Grades II to IV acute GVHD developed in 32% of auto-allo SCT recipients and chronic GVHD in 66%.³⁴

Barlogie and colleagues (2006) compared the long-term outcome results of the first tandem autotransplant trial for multiple myeloma. Total Therapy 1, the first tandem autotransplant trial for newly diagnosed patients with multiple myeloma, was designed to increase the frequency of complete response (CR) and thereby extend survival. With a median follow-up of 12 years, 62 of 231 initially enrolled patients are alive (17% at 15 years); 31 remain event free (7% at 15 years) including 16 of 94 (41%) that initially achieved CR. Currently alive patients less frequently had cytogenetic abnormalities (CAs) at baseline (P = 0.002), post enrollment (P < 0.001) and at relapse (P = 0.004); elevations of serum C-reactive protein (CRP) (P = 0.003) and lactate dehydrogenase (P = 0.029), anemia (P = 0.029) and they more often completed two transplants within 12 months (P = 0.019). Post enrollment overall survival (OS) and event-free survival (EFS) were superior in the absence of CA of the hypodiploidy or deletion 13 variety (P < 0.001 and 0.037 respectively) and in the presence of low CRP at baseline (P = 0.001 and 0.017 respectively). Post relapse survival was longer in the absence of CA at relapse (P
Cavo and associates (2007) performed a prospective, randomized study of single (arm A) versus double (arm B) autologous stem-cell transplantation (ASCT) for younger patients with newly diagnosed multiple myeloma (MM). A total of 321 patients were enrolled onto the study and were randomly assigned to receive either a single course of high-dose melphalan at 200 mg/m^2 (arm A) or melphalan at 200 mg/m^2 followed, after 3 to 6 months, by melphalan at 120 mg/m^2 and busulfan at 12 mg/kilogram (arm B). As compared with assignment to the single-transplantation group (n = 163 patients), random assignment to receive double ASCT (n = 158 patients) significantly increased the probability to attain at least a near complete response (nCR; 33% v 47%, respectively; P = .008), prolonged relapse-free survival (RFS) duration of 18 months (median, 24 v 42 months, respectively; P < .001), and significantly extended event-free survival (EFS; median, 23 v 35 months, respectively; P = .001). Administration of a second transplantation and of novel agents for treating sequential relapses in up to 50% of patients randomly assigned to receive a single ASCT likely contributed to prolong the survival duration of the whole group, whose 7-year rate (46%) was similar to that of the double-transplantation group (43%; P = .90). Transplantation-related mortality was 3% in arm A and 4% in arm B (P = .70). The authors concluded that in comparison with a single ASCT as up-front therapy for newly diagnosed MM, double ASCT effected superior CR or nCR rate, RFS, and EFS, but failed to significantly prolong overall survival. Benefits offered by double ASCT were particularly evident among patients who failed at least nCR after one autotransplantation.

Attal and colleagues (2003) conducted a randomized trial of the treatment of multiple myeloma with high-dose chemotherapy followed by either one or two successive autologous stem-cell transplantations. At the time of diagnosis, 399 previously untreated patients under the age of 60 years were randomly assigned to receive a single or double transplant. A complete or a very good partial response was achieved by 42 percent of patients in the single-transplant group and 50 percent of patients in the double-transplant group (P=0.10). The probability of surviving event-free for seven years after the diagnosis was 10 percent in the single-transplant group and 20 percent in the double-transplant group (P=0.03). The estimated overall seven-year survival rate was 21 percent in the single-transplant group and 42 percent in the double-transplant group (P=0.01). Among patients who did not have a very good partial response within three months after one transplantation, the probability of surviving seven years was 11 percent in the single-transplant group and 43 percent in the double-transplant group (P<0.001). Four factors were significantly related to survival: base-line serum levels of beta2-microglobulin (P<0.01) and lactate dehydrogenase (P<0.01), age (P<0.05), and treatment group (P<0.01). The authors concluded that as compared with a single autologous stem-cell transplantation after high-dose chemotherapy, double transplantation improves overall survival among patients with myeloma, especially those who do not have a very good partial response after undergoing one transplantation.
Hayes does have a Health Technology Brief called Autologous Stem Cell Transplantation Followed by Nonmyeloablative Allogeneic Stem Cell Transplantation for Treatment of Multiple Myeloma. This report was updated in 2012 and indicates that the available evidence is insufficient to recommend auto-allo SCT as a routine therapy for patients with MM, but is promising enough to support continued exploration in clinical trials. Among the three prospective studies that compared tandem autologous-autologous SCT with auto-allo SCT for patients with MM, the data were conflicting. Two studies reported no statistically significant benefit in terms of overall survival (OS) or event-free survival (EFS) for auto-allo SCT compared with autologous-autologous SCT, but one study reported an OS and EFS advantage in favor of auto-allo SCT. Four additional, non-comparative studies demonstrated that auto-allo SCT is feasible and effective for some patients with MM; but due to the limited study designs, no definitive conclusions could be reached based on those studies. Whether an allogeneic SCT should be offered after autologous SCT as part of a first-line treatment plan or only as salvage therapy for relapsed or refractory patients remains an unresolved issue of controversy. The optimal timing between autologous SCT and allogeneic SCT is also unknown.

Hayes does have a Medical Technology Directory report called High-Dose Chemotherapy with Peripheral Stem Cell/Autologous Transplantation Treatment for Multiple Myeloma. This report was last updated in 2010 and recommends the use of single or 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. Tandem HDC/autograft when used as part of salvage therapy for relapsed or refractory MM is not recommended.

UpToDate:

In a report called Determining Eligibility for Autologous Hematopoietic Cell Transplantation, the authors indicate that there are few strict rules about who is or is not an appropriate candidate for auto-HCT. Clinical judgment should be used for the majority of patients as to whether the risks with the transplant outweigh the benefits. Risk factors include and are based on performance status, comorbidity, age, compliance, extent and status of disease, as well as the sensitivity of the tumor to standard therapy. All of these factors should be considered when determining appropriateness of auto-HCT for an individual and the final decision on transplant eligibility should be made based on a risk-benefit assessment. Generally patients are eligible for auto-HCT if they meet the following criteria:

- A disease-related indication: An underlying hematologic disease at a stage likely to benefit from auto-HCT.
- Functional capacity: An ECOG performance status ≤2 or Karnofsky performance status ≥70 Renal function
- Serum creatinine: <2 mg/dL (177 micromol/L) or Cr CL >50, unless auto-HCT is for plasma cell dyscrasia.
- Cardiac reserve: Left ventricular ejection fraction (LVEF) ≥40 percent if using the BEAM conditioning regimen and a LVEF ≥50 percent using chemotherapy regimens with known cardiac toxicity.
Pulmonary function: A corrected DLCO ≥50 percent.
Liver function: Both myeloma and lymphoma patients with frank cirrhosis of the liver are excluded from auto-HCT because of excessive mortality and morbidity.
Support structure: Adequate psychosocial and financial support.
Other factors: Seropositivity for HIV does not exclude patients from undergoing auto-HCT.

In a report called Determination of Initial Therapy in Patients with Multiple Myeloma the authors indicate that patients with multiple myeloma and the following risk factors are not eligible for auto-HCT in most centers in the United States:

- Age >77 years
- Direct bilirubin >2.0 mg/dL (34.2 µmol/liter)
- Serum creatinine >2.5 mg/dL (221 µmol/liter) unless on chronic stable dialysis
- Eastern Cooperative Oncology Group (ECOG) performance status 3 or 4 unless due to bone pain
- New York Heart Association functional status Class III or IV

Additionally, secondary to conflicting results, high treatment-related mortality, and toxicity, nonmyeloablative allogeneic HCT is not advised for patients with newly diagnosed myeloma outside of a clinical trial setting, except perhaps in those with high-risk prognostic factors. A second (tandem) HCT is recommended only for patients who do not have at least a very good partial response with the first transplant.

Patients who fail to achieve a complete response (CR) or very good partial response (VGPR) with their first autologous HCT may benefit from a second HCT. In such patients, if a second HCT is considered it is preferable to perform the procedure within 6 to 12 months of the first transplant. However, patients who achieve CR or VGPR with the first HCT do not appear to benefit from a tandem HCT approach. In such patients, the second transplant can be delayed until relapse.

MD Consult: The diagnosis of multiple myeloma is based on several factors. The most common presenting symptoms are fatigue and bone pain. Osteolytic bone lesions and/or compression fractures are the hallmark of the disease and hypercalcemia is found in one fourth of patients; the serum creatinine is elevated in almost one half of patients. The diagnosis requires 10% or more plasma cells in the bone marrow, M protein in the serum, and/or urine and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) secondary to the underlying plasma cell disorder. Monoclonal (M) proteins can be detected by serum protein electrophoresis and immunofixation in 93% of patients and the addition of urine protein electrophoresis and urine immunofixation or the serum free light-chain assay will increase sensitivity to 97% or higher. Prognosis is based upon staging. that includes the International Staging System that divides patients into three distinct stages and prognostic groups based on the β2-microglobulin and albumin levels in the serum. The presence of any one of the following indicates high-risk myeloma: deletion 13 or hypodiploidy on metaphase cytogenetic studies, deletion 17p or immunoglobulin heavy-chain translocations t(4;14) or t(14;16), or plasma cell labeling index of 3% or higher. Treatment is defined by risk. Newly diagnosed patients are categorized into standard-risk and high-risk myeloma on the basis of specific prognostic factors. Initial therapy for patients with standard-risk disease is dependent on eligibility for autologous stem cell transplantation (ASCT). Patients who are eligible for ASCT are treated with nonalkylating-agent-containing regimens as initial therapy, such as thalidomide-dexamethasone.
or lenalidomide-dexamethasone. They can then pursue early or delayed ASCT. If early ASCT is used, a second ASCT is considered in patients who do not achieve a very good partial response or better with the first ASCT. If delayed ASCT is used, the initial induction is continued until plateau or progression at reduced doses. For patients who are not eligible for ASCT, the current standard is melphalan, prednisone, and thalidomide (MPT); however, if such patients are unable to tolerate (or have access to) thalidomide, melphalan plus prednisone (MP) remains a reasonable alternative. Patients with high-risk myeloma are candidates for novel therapy, since outcome is poor even with tandem ASCT. Considerations include bortezomib-containing initial therapy, routine maintenance therapy if ASCT is utilized, MPT in elderly patients, and consideration of allogeneic approaches in selected patients. Options for relapsed disease include thalidomide, lenalidomide, bortezomib, alkylating agents, anthracyclines, and corticosteroids alone or in combination.

The criteria for response to therapy are summarized by the following:

- **Partial response:** >50% reduction in M protein; and >90% reduction in Bence Jones protein
- **Very Good Partial Response (VGPR):** Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥90% or greater reduction in serum M component plus urine M component <100 mg per 24 hours
- **Complete response:** absence of M protein from serum or urine; and <5% plasma cells in the bone marrow
- Chemotherapy is continued until the patient reaches a plateau state with respect to their level of M protein
- Most patients do not achieve a complete response, but some can have durable partial responses
- Chemotherapy does not cure myeloma but aims to stabilize the disease for weeks to years
- The median duration of remission for patients who have responded to MP is 18 months. The overall median survival of patients with multiple myeloma treated with MP is 3 years

**Professional Organizations**

**The National Cancer Institute (NCI) 2012** \(^{11}\): The NCI outlines several treatment options and discusses the results of various clinical trials. The U.S. Intergroup trial (i.e., SWOG-9321), have shown improved survival for patients who received autologous peripheral stem cell or bone marrow transplantation after induction chemotherapy versus chemotherapy alone, other trials have not shown any survival advantage. Another approach to high-dose therapy has been the use of two sequential episodes of high-dose therapy with stem cell support (i.e., tandem transplant). Regarding the use of allogeneic hematopoietic stem-cell transplantation (HSCT), the NCI indicates that a definite graft-versus-myeloma effect has been demonstrated, including regression of myeloma relapses following the infusion of donor lymphocytes. Allogeneic stem-cell transplantation has highly toxic effects with 15%–40% mortality; however, the possibility of a graft-versus-myeloma reaction makes this therapy attractive. Non-myeloablative allogeneic stem-cell transplantation is under development.

**The American Society for Blood and Marrow Transplantation (ASBMT):**
The ASBMT published a position statement on the role of cytotoxic therapy with HSCT for the treatment of Multiple Myeloma\(^{15}\). Treatment recommendations include:
Stem cell transplantation is more effective than conventional chemotherapy as de novo therapy and is the recommended treatment for patients requiring treatment for multiple myeloma. Survival after stem cell transplantation is equivalent for salvage and de novo therapy. Stem cell transplantation as de novo therapy is preferred, however, because it may avoid the inconvenience, cost and risk of myelodysplasia from conventional alkylating agent therapy.

Autologous stem cell transplantation is currently the standard of care for multiple myeloma and is preferred over allogeneic stem cell transplantation based on available evidence. Studies are ongoing, however, to further evaluate the role of allogeneic transplant.

Autologous peripheral blood stem cell transplantation (PBSCT) is preferred over bone marrow transplantation.

Autologous purged bone marrow transplantation is not recommended as therapy for multiple myeloma.

Melphalan is preferred to melphalan plus total body irradiation as the conditioning regimen for autologous stem cell transplantation.

PBSCT using CD34 selected or CD34 unselected stem cells are recommended as equivalent in efficacy.

No recommendations are made for transplantation techniques that have not been adequately studied, including: stem cell transplantation versus standard chemotherapy as salvage therapy; tandem autologous stem cell transplantation autologous or allogeneic stem cell transplantation as a high-dose sequential regimen; allogeneic bone marrow transplantation versus PBSCT; a preferred allogeneic myeloablative or Nonmyeloablative conditioning regimen; maintenance therapy post-autologous stem cell transplantation.

The British Committee for Standards in Haematology and the United Kingdom (UK) Myeloma Forum (2011)¹²: Guidelines for the diagnosis and management of multiple myeloma (MM) indicate that high-dose chemotherapy (HDC) with autologous HSCT should be part of the primary treatment strategy in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function. HDC with autologous hematopoietic stem-cell transplantation (HSCT) should be considered in those >65 years with good performance status. Planned double (‘tandem’) autologous stem-cell transplantation (ASCT) cannot be recommended on the current evidence. Allogeneic HSCT with human leukocyte antigen-matched sibling donors may also be considered in patients up to the age of 40 years who have achieved at least a partial remission after initial therapy. Reduced-intensity conditioning followed by allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered in patients up to age 70 years with a human leukocyte antigen-matched sibling donor. The procedure would usually follow an initial autologous HSCT, be done early in the disease in individuals with responsive disease, and should always be done as part of a clinical trial.

The National Marrow Donor Program ²: 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. Additionally, autologous transplantation is currently the standard of care for multiple myeloma.

The National Comprehensive Cancer Network Guidelines ³ (NCCN Guidelines): The published Guideline for Multiple Myeloma (V.1. 2013) indicates 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. 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

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.

**International Myeloma Working Group (IMWG)**: The IMWG offered no specific recommendations regarding tandem auto-allo SCT for treatment of MM although it noted that studies evaluating this therapy are in progress. The group concluded that myeloablative allo-SCT may cure a minority of patients, but is associated with a high transplant-related mortality even when applied in the first-line setting; however, since smaller phase II studies suggested an improvement in treatment-related mortality, myeloablative conditioning could be evaluated in well-designed prospective clinical trials. Nonmyeloablative allo-SCT in first-line therapy is associated with a lower treatment-related mortality, but a greater risk of relapse and convincing evidence is still lacking that demonstrates allogeneic transplantation with reduced intensity conditioning improves survival compared with autologous SCT. The IMWG further noted that future studies of allo-SCT in myeloma should aim at improving the graft-versus-tumor effect while reducing the morbidity and mortality of allo-SCT. Novel anti-MM agents in the post allograft setting may favor the graft-versus-myeloma effect. However, exact mechanisms of action as well as the optimal timing and dosage of these agents after transplantation have yet to be determined.

**Toronto (ON) Cancer Care Ontario Program Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group**: Stem Cell Transplantation for adults with Multiple Myeloma is recommended for the following:

- Autologous stem cell transplantation is the recommended treatment option for eligible younger patients (under age 65-70 years) with newly diagnosed MM.
- Tandem (double) autologous stem cell transplantation is an option for patients who obtain less than a complete response to the first autologous transplant.
- Repeat autologous transplantation is an option for patients with MM who relapse after a long remission (> 2 years) to a single autologous transplant.
- Allogeneic transplantation is an option for selected patients with MM including those with high-risk cytogenetics and those whose disease is unresponsive to primary therapy.

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**Resource References**


40. Advanced Medical Review (AMR): Policy reviewed by MD board certified in Internal Medicine, Oncology, Hematology. October 18, 2012