Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis

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Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for HSCT

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

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

Reduced-Intensity Conditioning for Allogeneic HSCT

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

Primary Systemic Amyloidosis

The primary amyloidoses comprise a group of diseases with an underlying clonal plasma cell dyscrasia. They are characterized by the extracellular deposition of pathologic, insoluble protein fibrils with a beta-pleated sheet configuration that exhibit a pathognomonic red-green birefringence when stained with Congo red dye and examined under polarized light. These diseases are classified on the basis of the type of amyloidogenic protein involved, as well as by the distribution of amyloid deposits. In systemic amyloidosis, the unnatural protein is produced at a site that is remote from the site(s) of deposition, whereas in localized disease the protein is produced at the site of deposition. Light-chain amyloidosis (AL), the most common type of systemic amyloidosis, has an incidence similar to that of
Hodgkin’s lymphoma or chronic myelogenous leukemia, estimated at 5 to 12 people per million annually. The median age at diagnosis is around 60 years. The amyloidogenic protein in AL amyloidosis is an immunoglobulin (Ig) light chain or light-chain fragment that is produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in AL amyloidosis is typically low, ranging from 5%–10%, this disease also may occur in association with multiple myeloma in 10%–15% of patients. Deposition of AL amyloidogenic proteins causes organ dysfunction, most frequently in the kidneys, heart, and liver, although the central nervous system and brain may be affected.

Historically, this disease has had a poor prognosis, with a median survival from diagnosis of about 12 months, although outcomes have improved with the advent of combination chemotherapy with alkylating agents and autologous HSCT. Emerging approaches include the use of immunomodulating drugs such as thalidomide or lenalidomide, and the proteasome inhibitor bortezomib. Regardless of the approach chosen, treatment of AL amyloidosis is aimed at rapidly reducing the production of amyloidogenic monoclonal light chains by suppressing the underlying plasma cell dyscrasia, with supportive care to decrease symptoms and maintain organ function. The therapeutic index of any chemotherapy regimen is a key consideration in the context of underlying organ dysfunction.

II. Criteria/Guidelines

A. Autologous hematopoietic stem-cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) to treat primary systemic amyloidosis.

B. Allogeneic hematopoietic stem-cell transplantation is not covered to treat primary systemic amyloidosis as payment determination criteria are not met.

III. Limitations/Exclusions

The patient must be an appropriate candidate for transplant. This is defined as:

A. Adequate cardiopulmonary status

B. Absence of active infection

C. No history of malignancy within 5 years of transplantation, excluding nonmelanomatous skin cancers

D. Documentation of patient compliance with medical management

IV. Administrative Guidelines

Precertification is required for this service as well as for any transplant evaluations. To precertify, please complete HMSA's Precertification Request and mail or fax the form as indicated along with the required documentation.

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VI. Scientific Background

Conventional therapy for primary systemic amyloidosis usually combines oral melphalan with prednisone (MP), which has been shown to yield higher response rates and longer survival than colchicine or prior therapies. (1,2) Median survival after MP (approximately 18 months) is longer than for untreated patients or those given older therapies (10–14 months), but more effective regimens
have been sought. Combination therapy with vincristine, doxorubicin, and dexamethasone (VAD), a well-established regimen for myeloma, has been investigated. (1,2) However, because of its toxicity, VAD therapy usually is limited to patients without peripheral neuropathy or cardiomyopathy, both common complications of amyloidosis. Because conventional regimens rarely cure systemic amyloidosis and because of the close biologic similarity to multiple myeloma, myeloablative chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) was investigated for this disease.

Initial results of autologous HSCT in uncontrolled patient series were published in 1998. (3-5) Clinical response rates (50% to 60%) were nearly twice those reported for conventional therapy, and 2-year survival reportedly ranged from 56% to 68%. (2,5-6) However, procedure-related mortality rates of 15% to 43% were substantially higher than those observed in myeloma patients, usually in cases that involved more than 2 organ systems or had symptomatic cardiac involvement. (4,7-8)

A subsequent retrospective study analyzed outcomes of conventional therapy for primary amyloidosis in patients who would have been eligible for autologous HSCT. (6) Inclusion required age younger than 70 years, cardiac interventricular septal thickness less than 15, left ventricular ejection fraction (LVEF) more than 55%, serum creatinine less than 2 mg/dL, and direct bilirubin less than 2.0 mg/dL. Patients eligible for transplantation but managed conventionally reportedly had median survival of 42 months after conventional treatment, compared to median survival of only 18 months for all patients with primary amyloidosis. Survival of conventionally managed patients (n=229) at 24 months was 61%, which was similar to 56% to 65% survival at 24 months after autologous HSCT.

In the same report, survival of 39 patients given autologous HSCT at their institution was compared with survival of a matched cohort (n=78; 2 controls for each case) selected from their database of conventionally treated amyloidosis patients. (6) Factors used to match patients were limited to age (within 5 years), gender, and number of involved organs. They reported similar survival of cases and controls at 6 (85% versus 83%), 12 (77% versus 74%), and 24 months (68% and 60%, all respectively).

A follow-up report to the matched-pair analysis cited above included a larger group of cases (n=63) treated with autologous HSCT and used parameters measuring severity of organ involvement to select matched controls (n=63). (9) Factors used for matching were age, gender, time to presentation, LVEF, serum creatinine, cardiac septal thickness, nerve involvement, 24-hour urinary protein excretion, and serum alkaline phosphatase. At a median follow-up of 3.5 years from diagnosis for each group, 16 transplanted patients and 44 controls had died. Kaplan-Meier analysis showed significantly greater overall survival (OS) for those given autotransplants (p=0.004). The survival rates for the high dose and standard treatment groups at 1, 2, and 4 years were 89% and 71%; 81% and 55%; and 71% and 41%, respectively.

In addition to longer survival, evidence suggests improvement in symptoms for amyloidosis patients treated with autologous HSCT. In a large retrospective series of amyloidosis patients eligible for transplant (n=394), 63 patients declined treatment and 19 lost eligibility when they progressed before treatment started. (10) Estimated median survival for 312 patients who initiated stem-cell mobilization was 4.6 years, but median follow-up was not reported. Of 181 evaluable patients (alive and followed-
up for 1 year or more), 40% achieved complete hematologic response, defined as no evidence of plasma cell dyscrasia at 1 year after transplant. The authors reported functional improvement in at least 1 affected organ for 44% of evaluable patients: 66% of 73 patients with complete hematologic response, and 30% of 108 patients with an incomplete or no hematologic response. Among 277 patients who completed the transplant protocol, 36 (13%) died of treatment-related toxicity before day 100 post-transplant, 21 (8%) died between day 100 and 1 year, and 39 were alive but had not reached 1 year since transplant. This series included all patients transplanted between July 1994 and June 2002, of which one-half (n=196) had 3 or more organs involved and 43% had some cardiac involvement. Median survival for those with cardiac involvement (n=137) was significantly shorter (1.6 vs. 6.4 years, respectively; p<0.001) than for those without cardiac involvement (n=175).

A subsequent report based on the dataset from the large retrospective series outlined in the preceding paragraph provided an analysis of outcomes of risk-adjusted myeloablative melphalan and autologous HSCT in patients aged 65 years and older versus outcomes in those younger than 65 years, with up to 10 years of follow-up. (11) Patients younger than 65 years with LVEF of 45% or greater and adequate stem-cell yield (n=280; median age 55 years, range 29–64 years) received melphalan 200 mg/m²; those aged 65 years and older, those with reduced LVEF (40–45%), or those with lower stem-cell yield (n=65; median age 68 years, range 65–79 years) received risk-adjusted melphalan 140 mg/m². No difference was observed in early treatment-related mortality (10.3% in patients 65 years or older vs. 13.4% in those younger than 65 years, p=0.665). A trend toward a lower rate of hematologic complete response (CR, defined as the absence of clonal plasma cells in the bone marrow by immunohistochemical staining and of monoclonal gammopathy by immunofixation electrophoresis of serum and urine) was observed in the older patients (27.6% for patients 65 years or older) versus 13.4% in those younger than 65 years (p=0.882). However, the median survival after autologous HSCT did not differ according to age (4.0 years for patients aged 65 years and older vs. 4.85 years for those younger than 65 years; log-rank p=0.28).

A registry analysis of 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers included 37 (35%) patients who received a transplant for initial therapy of amyloidosis, while 27 (25%) received a transplant after 2 or more prior therapies. (12) With a median follow-up of 30 months after transplant, OS at 1 and 3 years was 66% (95% confidence interval [CI]: 56–75%) and 56% (95% CI: 45–66%), respectively. For those with no or 1 organ involved at transplant, survival at 1 year was 72% (95% CI: 61–82%), while for those with 2 or more organs involved, survival at 1 year was 54% (95% CI: 38–70%). Survival at 1 year also was greater for those without (69%; 95% CI: 58–79%) than with (56%; 95% CI: 37–74%) cardiac involvement. Treatment-related mortality at 30 days was 18% (95% CI: 11–26%), mostly among patients with cardiac and/or multiple organ involvement.

Long-term survival and outcomes were evaluated in a series of 80 patients with AL amyloidosis who were treated with myeloablative full-dose or risk-adjusted melphalan according to a risk-based protocol and underwent autologous HSCT. (13) All patients had a histologic diagnosis of amyloidosis with evidence of plasma cell dyscrasia and met eligibility criteria for autologous HSCT in clinical protocols. Patients (median age 56 years, range 29–71 years) received risk-adjusted melphalan 100 mg/m² (n=37) or full-dose melphalan 200 mg/m² (n=43) followed by autologous HSCT 24–72 hours after completion of the conditioning regimen. Treatment-related mortality was reported in 11 (14%)
cases, 6 of whom had received risk-adjusted melphalan, while 5 received the full-dose regimen. Median survival for all 80 patients was 57 months; 18 (23%) were alive 10 or more years after undergoing autologous HSCT. Hematologic CR (defined above and in reference 13) was assessed in 63 (79%) surviving patients at 1 year following treatment. Thirty-two of those patients (51%) achieved a hematologic CR; among those, median survival had not been reached at the time the report was prepared for publication. In contrast, the median survival for patients who failed to achieve a CR was 50 months, with a 6% estimated probability of survival at 10 years (p<.001 vs. patients with complete response).

In a series of 282 consecutive patients with AL amyloidosis who underwent autologous HSCT, investigators sought to determine whether or not a hematologic CR, as determined by normalization of serum and urine monoclonal protein levels, provides an adequate surrogate marker for OS. (14) All patients had AL histologically verified with Congo red tissue stain, and received risk-adjusted melphalan conditioning based on the presence of numbers of organs involved, creatinine level, age, and cardiac involvement. One third (n=93) of the patients received risk-adjusted melphalan (100 or 140 mg/m²) and 67% (n=189) received full-dose melphalan (200 mg/m²). The mortality at day 100 was 11%, with 28% of the cohort dead by the time this report was prepared. Ninety-three (33%) patients achieved a CR, 108 (38%) had a partial response (PR), and 36 (13%) had no response (NR) to autologous HSCT. Kaplan-Meier analysis showed that median survival was reached only in the NR group, compared with the CR and PR groups after more than 80 months of follow-up (log-rank p<0.001 for NR vs. CR and PR). An analysis (landmark analysis) focused on patients who survived for at least 6 months after autologous HSCT included 86 patients in the CR group, 91 who had PR, and 36 NR patients. This analysis showed that the survival curve differences remained significant between response groups as in the overall cohort, with a median survival of 40 months reached only in the NR group.

One randomized multicenter trial involving 8 centers from the Myelome Autogreffe (MAG) and Intergroupe Francophone du Myelome (IFM) Intergroup has been reported in which conventional chemotherapy with melphalan plus dexamethasone was compared with myeloablative melphalan followed by autologous HSCT in patients with AL amyloidosis. (15) Patients between 18 and 70 years of age had a histologic diagnosis of AL amyloidosis and either a complete hematologic response characterization of amyloid deposits or evidence of a monoclonal Ig protein in the serum or urine or a monoclonal staining pattern of bone marrow plasma cells and had received no more than 2 courses of any chemotherapy regimen. They were randomly allocated, stratified according to age (younger than 65 years or 65 years or older) and according to the affected organ system (cardiac, renal, neurological, or other). Of note, approximately two thirds of the patients had 2 or more organs affected. Patients in the melphalan plus dexamethasone group (n=50) received monthly courses of dose-adjusted (according to cytopenic status) oral melphalan, 10 mg/m² of body-surface area, on days 1 to 4 plus oral dexamethasone, 40 mg/day on days 1 to 4, for up to 18 courses if no severe adverse events occurred. In the autologous HSCT patients (n=50), hematopoietic stem cells were obtained from peripheral blood with granulocyte colony-stimulating factor mobilization. Melphalan was administered intravenously on day 0, and stem cells were infused on day 2, with the dose reduced from 200 mg/m² to 140 mg/m² for patients aged 65 years or older and for those with an LVEF less than 30%, a calculated creatinine clearance less than 30 mL/min, or severe liver disease. According to intention-to-treat (ITT) analysis, the hematologic response rate did not differ between groups, with 12 CR (24%) and 14 PR (28%) in the
melphalan-dexamethasone recipients versus 11 CR (22%) and 7 PR (14%) in the autologous HSCT group (p=0.11). At publication of the study, the median follow-up for the entire cohort was 24 months, and for survivors it was 36 months; 20 patients in the melphalan-dexamethasone group had died versus 31 in the autologous HSCT group. Among 65 patients who could be evaluated, the ITT median survival for patients assigned to melphalan plus dexamethasone was 56.9 months, versus 22.2 months in the autologous HSCT group (p=0.04). Survival rates and duration were significantly better in responders (CR plus PR) compared to NR (p<0.0001). Analysis of patients who survived for at least 6 months and who received their assigned treatment, showed no significant difference in survival rates in patients assigned to melphalan plus dexamethasone compared to autologous HSCT, with neither group reaching median survival after 80 months (p=0.38).

These randomized trial data suggest that autologous HSCT may be no more efficacious than conventional chemotherapy in prolonging survival among patients with AL amyloidosis. However, the results are limited by the size of the study, a lack of assessor blinding or allocation concealment, and a large attrition post-randomization. Thus, among 50 patients assigned to autologous HSCT, 13 (26%) did not receive the planned treatment (1 declined, 2 had insufficient stem-cell harvest, 10 died before treatment), whereas 7 of 50 (14%) assigned to melphalan plus dexamethasone did not receive planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received incorrect treatment). Therefore, even though this was a randomized trial, the results are not sufficient to change the policy statement given the body of evidence available from other, albeit nonrandomized, studies. Results from ongoing trials noted below will be important in providing additional information.

Data on the use of allogeneic SCT to treat AL amyloidosis are sparse, with no systematic evaluation in a clinical trial. (16) Concerns about the use of allogeneic SCT include high treatment-related mortality (more than 40%), morbidity secondary to graft-versus-host (GVH) disease, and questions about the efficacy of a proposed graft-versus-malignancy (GVM) effect on low-grade plasma cell dyscrasias.

A literature search through December 2010 identified no evidence sufficient to change the conclusions of this policy.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received from no physician specialty societies and 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was support for the policy statements regarding SCT in the treatment of amyloidosis.

In summary, based on the literature review and clinical input, for the 2011 update the policy statements regarding amyloidosis are unchanged.

National Comprehensive Cancer Network Guidelines
The 2011 National Comprehensive Cancer Network (NCCN) guidelines include autologous HSCT as primary therapy for systemic amyloidosis; however, they caution that the optimal therapy is not established and that such treatment would best be performed in a clinical trial. (17)

**National Cancer Institute Physician Data Query (PDQ®) Database**

A search of the National Cancer Institute clinical trials PDQ database identified one Phase III study to be completed in 2011; it compares hematologic response rate in patients with primary systemic amyloidosis treated with conventional chemotherapy comprising low-dose melphalan and dexamethasone versus high-dose melphalan followed by autologous HSCT and compares the toxicity of these regimens in these patients (MAYO-MC0482 MAYO-IRB-1691-05, MC0482, NCT00477971: Phase III Randomized Study of Low-Dose Melphalan and Dexamethasone Versus High-Dose Melphalan Followed By Autologous Hematopoietic Stem Cell Transplantation in Patients With Primary Systemic Amyloidosis).

**VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

**VII. References**


