Hematopoietic Cell Transplantation for Primary Amyloidosis

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Original Effective Date: 04/01/2008
Line(s) of Business: HMO; PPO
Current Effective Date: 05/26/2017
Section: Transplants
Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation (HCT) 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 HCT) or from a donor (allogeneic HCT).

For individuals who have primary amyloidosis who receive autologous HCT, the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined to less than 14% in current studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Evidence on the use of allogeneic HCT is sparse and shows high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.
Clinical input and national and international clinical guidelines support the use of autologous HCT as a treatment of amyloidosis. For primary amyloidosis, allogeneic HCT is not recommended. Thus, autologous HCT may be considered medically necessary for primary amyloidosis and allogeneic HCT for primary amyloidosis is considered investigational.

Background

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 and 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 amyloid light chain (AL) protein is produced at the site of deposition. Primary or AL amyloidosis, the most common type of systemic amyloidosis, has an incidence similar to that of Hodgkin lymphoma or chronic myelogenous leukemia, estimated at 5 to 12 people per million annually. The median age at diagnosis is 60 years. The amyloidogenic protein in primary amyloidosis is an immunoglobulin light chain or light-chain fragment produced by a clonal population of plasma cells in the bone marrow. While the plasma cell burden in primary amyloidosis is typically low, ranging from 5% to 10%, this disease also may occur in association with multiple myeloma in 10% to 15% of patients. Deposition of primary 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 approximately 12 months, although outcomes have improved with combination chemotherapy using alkylating agents and autologous hematopoietic cell transplantation (HCT). Emerging approaches include the use of immunomodulating drugs (eg, thalidomide, lenalidomide) and the proteasome inhibitor bortezomib. Regardless of the approach, treatment of primary amyloidosis aims 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.

HEMATOPOIETIC CELL TRANSPLANTATION
Hematopoietic cell transplantation refers to the infusion of hematopoietic stem cells to restore bone marrow function in cancer patients who receive bone marrow toxic doses of drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” 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 HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing
human leukocyte antigen (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 HCT**

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect 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 HCT, 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 HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

**Reduced-Intensity Conditioning for Allogeneic HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less 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 nonrelapse mortality 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 nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.
II. Policy
Autologous hematopoietic cell transplantation is covered (subject to Limitations/Exclusions and Administrative Guidelines) to treat primary systemic amyloidosis.

III. Policy Guidelines
In 2003, CPT centralized codes describing allogeneic and autologous HCT services to the hematology section (38204-38242). Not all codes are applicable for each stem-cell transplant procedure. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38208-38215).

CPT 38208 and 38209 describe thawing and washing of cryopreserved cells
CPT 38210-38214 describe certain cell types being depleted
CPT 38215 describes plasma cell concentration

IV. Limitations
Allogeneic hematopoietic cell transplantation is not covered to treat primary systemic amyloidosis as is not known to be effective in improving health outcomes.

V. Administrative Guidelines
Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA’s Precertification Request and mail or fax the form, or use iExchange as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38209</td>
<td>;thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>;specific cell depletion with harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>;tumor-cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>;red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>;platelet depletion</td>
</tr>
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</table>
### Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38214</td>
<td>Plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>Autologous transplantation</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
</tbody>
</table>

### HCPCS Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Q0083 - Q0085</td>
<td>Chemotherapy administration code range</td>
</tr>
<tr>
<td>J9000 - J9999</td>
<td>Chemotherapy drugs code range</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)</td>
</tr>
</tbody>
</table>

ICD-10 codes are provided for your information.

### ICD-10-CM

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E85.0-E85.9</td>
<td>Amyloidosis code range (this policy would exclude E85.3 secondary systemic and E85.4 organ limited as they are not primary systemic)</td>
</tr>
</tbody>
</table>

### ICD-10-PCS

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>30243G0, 30243X0, 30243Y0</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
<tr>
<td>30243G2, 30243X2, 30243Y2</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, allogeneic related, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
<tr>
<td>30243G3, 30243X3, 30243Y3</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, allogeneic unrelated, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
</tbody>
</table>
VI. Scientific Background

The policy has been updated with a search of the MEDLINE and EMBASE databases. The most recent literature search was performed through October 13, 2016.

Chemotherapy for the treatment of light-chain amyloidosis was introduced in 1972 in the form of melphalan and prednisone.1 This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies.1-3 Survival after oral melphalan with prednisone (typically 12-18 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.2,3 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 transplantation (HCT) is being investigated for this disease. Following is a summary of key literature to date.

**Autologous HCT**

Initial results of autologous HCT in uncontrolled patient series were published in 1998. Clinical response rates (50% to 60%) were nearly twice those reported for conventional therapy, and 2-year survival reportedly ranged from 56% to 68%. Kaplan-Meier analysis of a matched comparison study (63 pairs) showed greater overall survival (OS) for those given autotransplants (71% at 4 years) than for patients who were eligible for transplantation but managed conventionally (41%; p=0.004). 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.

**Randomized Controlled Trials**

One randomized multicenter trial from the Myelome Autogreffe and Intergroupe Francophone du Myelome Intergroup compared conventional chemotherapy (melphalan plus dexamethasone, n=50) to myeloablative melphalan followed by autologous HCT (n=50). Randomization was stratified by age (<65 years or ≥65 years) and the affected organ system (cardiac, renal, neurologic, other). Of note, approximately two-thirds of patients had 2 or more organs affected. Hematopoietic stem cells were obtained from peripheral blood following granulocyte colony-stimulating factor (G-CSF) mobilization. According to intention-to-treat (ITT) analysis, the
hematologic response rate did not differ between groups, with 12 complete responses (CR; 24%) and 14 partial responses (28%) in the chemotherapy recipients versus 11 CR (22%) and 7 partial responses (14%) in the HCT group (p=0.11). At a median follow-up of 24 months, 20 patients in the chemotherapy group had died versus 31 in the autologous HCT group. Among 65 patients who could be evaluated, the ITT median survival for patients assigned to chemotherapy was 56.9 months, versus 22.2 months in the autologous HCT group (p=0.04). Analysis of patients who survived for at least 6 months and who received their assigned treatment, showed no significant difference in survival rates between treatments.

Although this randomized controlled trial (RCT) suggested that autologous HCT may be no more efficacious than conventional chemotherapy in prolonging survival, the results were limited by the proportion of patients not receiving treatment. Among 50 patients assigned to autologous HCT, 13 (26%) did not receive the planned treatment (1 declined, 2 had insufficient stem cell harvest, 10 died before treatment), while 7 (14%) of 50 assigned to chemotherapy did not receive planned treatment (5 died before treatment, 1 did not tolerate treatment, 1 received incorrect treatment).

Nonrandomized Comparative Studies

A retrospective comparative analysis from a single treatment center published in 2014 provides long-term evidence for improved survival among patients with AL amyloidosis who underwent autologous HCT compared with conventional therapies (CTR).11 Patients underwent autologous HCT (n=80) or CTR (n=65) following induction therapy. Patients were heterogeneous with respect to age, organ involvement, cardiac involvement, renal involvement, and percent of bone marrow blast cells; all were significantly overrepresented in the CTR group compared with the HCT group. Median follow-up was 3 years for the entire cohort, with some survivors followed for up to 14 years postdiagnosis. Median 5-year survival was 63% in the HCT group compared with 38% in the CTR group (p<0.001); median survival at 10 years was 56% in the HCT group and 10% in the CTR group (p<0.001). Among HCT recipients, the transplant-related mortality rate was 7.5% at 100 days and 12.5% within 1 year of transplant.

Observational Studies

The evidence has also suggested improvement in symptoms for amyloidosis patients treated with autologous HCT in addition to survival benefits (see Table 1).

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>N</th>
<th>FU</th>
<th>N at FU</th>
<th>CR Rate</th>
<th>OS Rate</th>
<th>Median Survival</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner et al (2004)</td>
<td>312</td>
<td>≥1 y</td>
<td>181</td>
<td>40%</td>
<td></td>
<td>4.6 y</td>
<td>13%</td>
</tr>
<tr>
<td>Vesole et al (2006)</td>
<td>107</td>
<td>3 y</td>
<td></td>
<td>66%</td>
<td>56%</td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>Cibeira et al (2011)</td>
<td>421</td>
<td>340</td>
<td>34%</td>
<td></td>
<td></td>
<td>6.3 y</td>
<td>11%</td>
</tr>
<tr>
<td>Madan et al (2012)</td>
<td>187</td>
<td></td>
<td>66 mo</td>
<td></td>
<td></td>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Sanchorawala et al (2007)</td>
<td>80</td>
<td>10 y</td>
<td>63</td>
<td>51%</td>
<td>23%</td>
<td>57 mo</td>
<td>14%</td>
</tr>
</tbody>
</table>
In a series of 312 amyloidosis patients eligible for transplant, estimated median survival was 4.6 years. Of 181 evaluable patients (alive and followed-up for ≥1 year), 40% achieved complete hematologic response, defined as no evidence of plasma cell dyscrasia at 1 year after transplant with functional improvement in at least 1 affected organ.

A registry analysis evaluated 107 amyloidosis patients who received transplants between 1995 and 2001 at 48 centers. For those with no or 1 organ involved at transplant, survival at 1 year was 72%, while for those with 2 or more organs involved, survival at 1 year was 54%. Treatment-related mortality at 30 days was mostly among patients with cardiac and/or multiple organ involvement.

Patients with primary amyloidosis and cardiac involvement were treated in a series from a single center. Overall, hematologic and cardiac responses were observed in 66% and 41% of patients, respectively.

A series of 421 consecutive patients treated with HCT at a single referral center compared outcomes for patients with and without a CR. Eighty-one patients died within the first year after HCT and were not evaluable for hematologic and organ response. Of 340 evaluable patients, 43% achieved CR and 78% of them experienced an organ response. Thus, treatment of selected AL amyloidosis patients with autologous HCT resulted in high organ response and longer OS rates, even for those patients who did not achieve CR. These results are compatible with others previously cited.

Several additional retrospective and prospective series have been reported on the use of autologous HCT in patients with primary amyloidosis. Results from these series are consistent with others that have suggested autologous HCT is feasible and beneficial in selected patients with primary amyloidosis.

Long-term survival and outcomes were evaluated in a series of 80 patients. Among the 32 patients who achieved CR, median survival had not been reached at the time of reporting. 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<0.001 vs patients with CR).
A 2015 report from the Center for International Blood and Marrow Transplant Research (CIBMTR) study identified 1536 patients with amyloidosis who had undergone autologous HCT between 1995 and 2012.17 Early mortality and OS were analyzed for 3 time cohorts: 1995 to 2000, 2001 to 2001, and 2007 to 2012. Over this time period, OS improved from 55% to 77%, while early mortality decreased from 20% to 5%. Multivariate analysis showed that cardiac involvement was associated with high mortality and inferior OS. Higher doses of melphalan were associated with a lowered relapse risk.

Section Summary: Autologous HCT

The evidence related to autologous HCT for the treatment of primary amyloidosis includes an RCT, nonrandomized comparative studies, and large case series. The RCT has a number of limitations, and its results are insufficient to determine the effect of the treatment. A retrospective comparison with 10-year follow-up showed a considerable survival advantage for patients treated with HCT. Although retrospective, with evident interstudy patient heterogeneity, this report suggested autologous HCT may yield long-term survival benefits in patients with this disease. Additional case series have shown a CR rate ranging from 34% to 66%, with a clear survival advantage in patients who achieve a CR. Patients who do not achieve a CR may obtain some benefits in organ function. Treatment-related mortality rates from the CIBMTR study have decreased to 5% in recent years, but remain between 11% and 16% in other studies.

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

SUMMARY OF EVIDENCE

For individuals who have primary amyloidosis who receive autologous hematopoietic cell transplantation (HCT), the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and large case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, treatment-related morbidity and treatment-related mortality. Use of autologous HCT for primary amyloidosis rapidly eradicates the amyloid light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This procedure has extended survival rates to a reported 77% at 5 years and 56% at 10 years in patients who respond to treatment. Complete response to treatment has been reported in 34% to 66% of patients, while transplant-related mortality rates have declined to less than 14% in current studies. Therefore, autologous HCT is an important treatment option for patients who are deemed eligible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary amyloidosis who receive allogeneic HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease
status, treatment-related morbidity and treatment-related mortality. Evidence on the use of allogeneic HCT is sparse and shows high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

REGULATORY STATUS
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02257905</td>
<td>Allo SCT in Amyloidosis Non-interventional Study</td>
<td>14</td>
<td>Jul 2015</td>
</tr>
</tbody>
</table>

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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.

In response to requests, input was received from 5 academic medical centers, including 3 transplant centers, while this policy was under review in 2011. There was support for the policy statements on hematopoietic stem transplantation in the treatment of amyloidosis.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation (ASBMT) issued guidelines on the indications for autologous and allogeneic hematopoietic cell transplantation (HCT). ASBMT gave the rating of N (not generally recommended; neither evidence nor clinical practice support the routine use) for the use of allogeneic HCT for the treatment of primary amyloidosis in adults. ASBMT gave a rating of C (standard of care; clinical evidence available) for the use of autologous HCT in the treatment of primary amyloidosis in adults.

British Committee for Standards in Haematology
The British Committee for Standards in Haematology convened a working group to develop guidelines on the management of light chain (primary) amyloidosis. Below is a summary of the recommendations from 2015 guidelines on high-dose melphalan and autologous stem cell transplantation (HDM-ASCT) and allogeneic transplantation as treatments of primary amyloidosis:

- HDM-ASCT recommended as “the preferred first line treatment for patients up to 65-70 years of age with estimated glomerular filtration rate (eGFR) >50 ml/min, low cardiac biomarkers, low level plasma cell infiltration in bone marrow at time of transplant and lacking the contraindications ...(Grade 1c) ...
- with any of the following: Cardiac amyloidosis with N-terminal pro-brain natriuretic peptide >590 pmol/l and/or troponin-T > 0.06 ng/ml, severe autonomic neuropathy, significant gastrointestinal (GI) bleeding due to amyloid, ... recurrent amyloid related pleural effusions or poor Eastern Cooperative Oncology Group performance status (>2) (Grade 1c).”
- “HDM-ASCT may be a treatment for selected patients up to 65-70 years of age with relapsed/refractory disease or with early relapse of plasma cell dyscrasia after chemotherapy (Grade 1c).”
- “Reduced intensity allogeneic transplantation is generally not recommended as an upfront treatment due to high treatment-related mortality (TRM). However, selected fitter younger patients with limited organ involvement who have a matched sibling donor may be considered following relapse of their disease. (Grade 1a).”

National Cancer Institute Physician Data Query (PDQ®) Database

National Comprehensive Cancer Network guidelines (v 2.2017) on multiple myeloma include as a recommended primary treatment option high-dose melphalan followed by autologous stem cell transplant (category 1 evidence). In eligible patients, high-dose chemotherapy along with autologous stem cell support has been associated with higher response rates and improved overall survival compared to standard chemotherapy. The guidelines note that, in select patients, allogeneic stem cell transplant may be considered in relapsed patients, though heavily pretreated patients are unlikely to benefit. The guidelines also caution that the optimal therapy is not established and that such treatment would best be performed in a clinical trial.

MEDICARE NATIONAL COVERAGE

The Centers for Medicare and Medicaid Services has determined that the evidence is adequate to conclude that, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan together with autologous stem cell transplantation can provide a net health benefit for Medicare beneficiaries of any age group with primary amyloidosis. This technique “is reasonable and necessary for patients of any age with primary AL amyloidosis who meet the following criteria:

- amyloid deposition in 2 or fewer organs, and
- cardiac left ventricular ejection fraction (EF) of greater than 45%.
To clarify existing coverage, autologous stem cell transplant must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy and/or radiotherapy used to treat various malignancies.

VII. 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.

VIII. References


27. Centers for Medicare and Medicaid Services. National Coverage Analysis (NCA) for Autologous Stem Cell Transplantation (AuSCT) for AMYLOIDOSIS (CAG-00050R). 2006; http://www.cms.gov/medicare-coverage-database/details/nca-details.aspx?NCAId=126&ExpandComments=n&NcaName=Autologous+Stem+Cell+Transplantation+(AuSCT)+for+Amyloidosis&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=amyloidosis&KeyWordLookUp=Title&KeyWordSearchType=And&from2=search.asp&bc=gAAAABAAAgAAAA%3d%3d&. Accessed December 12, 2016.