Hematopoietic Cell Transplantation for Primary Amyloidosis

Introduction

Primary amyloidosis is a condition in which clumps of abnormal proteins build up in tissues and organs. Treatment may include a stem cell transplant using the patient’s own cells. Stem cells are collected from the patient’s blood and stored. After the patient receives high-dose chemotherapy, stem cells are given back to the patient. Using a person’s own stem cells is known as an autologous stem cell transplant. Using stem cells from a donor is called an allogeneic transplant. Using donor stem cells to treat primary amyloidosis is investigational (unproven) because there is not enough scientific evidence to show that it works for this condition.
Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
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<tr>
<td>Autologous hematopoietic cell transplantation</td>
<td>Autologous hematopoietic cell transplantation may be considered medically necessary to treat primary systemic (AL) amyloidosis.</td>
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<table>
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<tr>
<th>Service</th>
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## Coding

<table>
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<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<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>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
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<tr>
<td>HCPCS</td>
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<td>Cord blood harvesting for transplantation, allogeneic</td>
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<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
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<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis</td>
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### 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 in developed countries, 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 of approximately 12 months from diagnosis, 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 (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). 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). Cord blood is discussed in greater detail in a separate policy. (See Related Policies)

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 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 (eg, 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 medically sufficiently fit 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 non-relapse 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.
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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<tr>
<td>NCT02257905</td>
<td>Allo SCT in Amyloidosis Non-interventional Study</td>
<td>14</td>
<td>Jul 2015</td>
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NCT: National clinical trial
Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may provide appropriate reviewers who collaborate with and make recommendations during this process, 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).\(^\text{24}\) 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.\(^\text{25}\) Below is a summary of the recommendations from their 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 Comprehensive Cancer Network**

National Comprehensive Cancer Network guidelines (v 1.2018) on Systemic Light Chain Amyloidosis 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.

**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.
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+%28AuSCT%29+for+%28amyloidosis&CoverageSelection=Both&AmyloidosisCoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=amyloidosis&KeyWordLocation=And&KeyWordSearchType=And&from2=search.asp&bc=gAAAAABAAAgAAAA%3d%3d&. Accessed January 2018.

### History

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<td>05/12/14</td>
<td>New PR policy replacing 8.01.42. Autologous HSCT may be considered medically necessary to treat primary systemic amyloidosis in carefully selected patients with no more than 2 adverse prognostic characteristics (previously allowed with no qualifying criteria); investigational in all other situations except when enrolled in a clinical trial.</td>
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<td>Annual Review. Policy updated with literature review; not change to policy statements. References 30 – 32 added.</td>
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<td>Coding update. Removed codes that are transplant benefit related.</td>
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<td>Annual Review, approved November 8, 2016. No changes to policy statement.</td>
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<td>Annual Review, approved February 14, 2017. Policy updated with literature review through October 13, 2016; Rationale revised and references 22 and 24-25 added; reference 26 updated. Policy statements unchanged.</td>
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<tr>
<td>08/01/17</td>
<td>Update title of Related Policy 8.01.511.</td>
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<td>10/17/17</td>
<td>Minor update. Updated title of this policy and related policies.</td>
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<td>12/01/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
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<td>02/01/18</td>
<td>Annual Review, approved January 30, 2018. No changes to policy statement.</td>
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U.S. Department of Health and Human Services
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