Hematopoietic Cell Transplantation for Primary Amyloidosis

**Medical Benefit**

**Effective Date:** 04/01/13  
**Next Review Date:** 07/19

**Preauthorization**

Yes  
**Review Dates:** 04/07, 05/08, 01/10, 01/11, 09/11, 07/12, 07/13, 07/14, 07/15, 07/16, 07/17, 07/18

Preauthorization is required and must be obtained through Case Management.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With primary amyloidosis</td>
<td>• Autologous hematopoietic cell transplantation</td>
<td>• Chemotherapy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Change in disease status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related mortality</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>With primary amyloidosis</td>
<td>• Allogeneic hematopoietic cell transplantation</td>
<td>• Chemotherapy</td>
<td>• Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Disease-specific survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Change in disease status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related mortality</td>
</tr>
</tbody>
</table>

**DESCRIPTION**

Hematopoietic cell transplantation (HCT) 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).

**SUMMARY OF EVIDENCE**

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, and treatment-related morbidity and 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 five 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, and treatment-related morbidity and mortality. Evidence on the use of allogeneic HCT is sparse and has shown high treatment-related mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

**POLICY**

Autologous hematopoietic cell transplantation may be considered medically necessary to treat primary systemic amyloidosis.

Allogeneic hematopoietic cell transplantation is considered investigational to treat primary systemic amyloidosis.

**POLICY GUIDELINES**

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

**MEDICARE ADVANTAGE**

If a transplant is needed, we arrange to have the Medicare–approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

**BACKGROUND**

**PRIMARY 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 by 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 protein is produced at the site of deposition. Primary or amyloid light chain amyloidosis, the most common type of systemic amyloidosis, has an incidence similar to that of Hodgkin lymphoma or chronic myelogenous leukemia, estimated at five 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.

**Treatment**

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 (e.g., 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**

HCT 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. 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. The use of cord blood is discussed in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

**AUTOLOGOUS HCT**

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. 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 before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete response. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

**ALLOGENEIC HCT**

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.

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 effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower graft-versus-malignancy 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 events 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 graft-versus-host disease, which also increases susceptibility to opportunistic infections.

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 and to minimize as much as possible treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains variable 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 this protocol, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

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 title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RELATED PROTOCOL

Placental and Umbilical Cord Blood as a Source of Stem Cells

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


