Hematopoietic Stem Cell Transplantation for Primary Amyloidosis

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.

Description

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 radiotherapy.

Summary of Evidence

Chemotherapy for the treatment of light-chain amyloidosis (AL) was introduced in 1972 in the form of melphalan and prednisone. Median survival with this regimen was typically 12 to 18 months, with therapy remaining unchanged until the introduction of autologous hematopoietic stem cell transplantation (HSCT). The use of autologous HSCT for AL amyloidosis rapidly eradicates the amyloidogenic light chain produced by the clonal plasma cell populations, which is the proximal cause of pathology and subsequent death. This has extended survival rates to a reported 53% at 10 years in patients with a complete response to treatment. Transplant-related mortality rates have declined, from as high as 40% to 7% in current studies. Therefore, autologous HSCT is an important option for patients who are deemed eligible, and it is considered medically necessary. Evidence on the use of allogeneic HSCT is sparse and it remains investigational.

Policy

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

Allogeneic hematopoietic stem 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 transplant center review and decide whether the patient is an appropriate candidate for the transplant.

Background

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 radiotherapy. 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 “naive” and thus are associated with a lower incidence of rejection or GVHD. Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

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 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 preengraftment 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 before undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete response (CR). Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections before 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 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 lympho-
ablation, 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 Protocol, the term reduced-intensity conditioning will
refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conven-
tional) 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. AL 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 approximately 60 years. The amyloidogenic protein in AL
amyloidosis is an immunoglobulin 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% to 10%, this disease also may occur in association with multiple myeloma in 10% to 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 approximately 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.

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


