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MEDICAL POLICY – 8.01.42

Hematopoietic Cell Transplantation for Primary Amyloidosis

BCBSA Ref. Policy:	8.01.42
Effective Date:	Apr. 1, 2025
Last Revised:	Mar. 10, 2025
Replaces:	8.01.530

RELATED MEDICAL POLICIES:

8.01.511	Hematopoietic Cell Transplantation for Solid Tumors of Childhood
8.01.531	Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia
10.01.518	Clinical Trials

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

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 individual's own cells. Stem cells are collected from the individual's blood and stored. After the individual receives high-dose chemotherapy, stem cells are given back to the individual. 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

Service	Medical Necessity
Autologous hematopoietic cell transplantation	**Autologous hematopoietic cell transplantation may be considered medically necessary to treat primary systemic (AL) amyloidosis.**

Service	Investigational
Allogeneic hematopoietic cell transplantation	**Allogeneic hematopoietic cell transplantation is considered investigational to treat primary systemic (AL) amyloidosis.**

Documentation Requirements
The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of: • Diagnosis/condition • History and physical examination documenting the severity of the condition • The severity of the condition and prognosis (to included prognostic index scores when applicable)

Coding

Code	Description
CPT	
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem-cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with out-patient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative

Code	Description
	services; and the number of days of pre- and post-transplant care or the global definition.

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

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).

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 exhibits 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 of approximately 9 to 14 cases per

million person-years with approximately 4000 new cases in the US each year.[1] The typical age at diagnosis is about 50 to 65 years.[2] 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 individuals. 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 median survival from diagnosis of approximately 12 months, although outcomes have improved with combination chemotherapy using alkylating agents and autologous HCT. Emerging approaches include the use of immunomodulating drugs (e.g., thalidomide, lenalidomide, pomalidomide) and the proteasome inhibitor bortezomib. The anti-CD38 monoclonal antibody daratumumab/hyaluronidase-fihj received approval in July 2021 for treatment of newly-diagnosed light chain amyloidosis in combination with bortezomib, cyclophosphamide, and dexamethasone. 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.

Chemotherapy for the treatment of light chain amyloidosis was introduced in 1972 in the form of melphalan and prednisone.[3] This chemotherapy regimen has yielded higher response and longer survival rates than colchicine or prior therapies.[3,4] Survival after oral melphalan with prednisone (typically 12 to 18 months) is longer than for untreated individuals or those given older therapies (10 to 14 months), but more effective regimens have been sought. Combination therapy with vincristine, doxorubicin, and dexamethasone, a well-established regimen for myeloma, has been investigated.[3,4] However, because of its toxicity, vincristine, doxorubicin, and dexamethasone therapy is usually limited to individuals 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 HCT is being investigated for this disease.

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 [allo-] HCT). These cells 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 "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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 individual before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete response. Individuals who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

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 individual 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 individual'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 individuals 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 GVHD, which also increases susceptibility of the individual to opportunistic infections.

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 and to minimize as much as possible associated treatment-related morbidity and non-relapse 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 non-relapse 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. Individuals 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 HCT, the evidence includes a network meta-analysis, randomized controlled trials (RCTs), nonrandomized comparative studies, and large case series. The 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 5 years and 56% at 10 years in individuals who respond to treatment. Complete response to treatment has been reported in 34% to 69.6% of individuals, while transplant-related mortality rates have declined significantly in more recent studies. Therefore, autologous HCT is an important treatment option for individuals who are deemed eligible. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06022939	A Phase III, Randomized Study of Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone (Dara-VCD) Induction Followed by Autologous Stem Cell Transplant or Dara-VCD Consolidation and Daratumumab Maintenance in Patients with Newly Diagnosed AL Amyloidosis	338	Oct 2030

Clinical Input Received from 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 five academic medical centers, including three 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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT) issued guidelines on indications for hematopoietic cell transplantation (HCT) and immune effector therapy.[28] ASTCT gave the rating of N (not generally recommended; neither evidence nor clinical practice supports the routine use) for the use of allogeneic HCT in the treatment of primary amyloidosis in adults. ASTCT gave a rating of S (standard of care) for the use of autologous HCT in the treatment of primary amyloidosis in adults.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on systemic light chain amyloidosis (v.1.2025) recommend assessing organ involvement based on amyloidosis consensus criteria in newly diagnosed disease.[1] Next, individuals should be evaluated for stem cell transplant candidacy. The current guidelines prefer the regimen of daratumumab and bortezomib/cyclophosphamide/dexamethasone as initial systemic therapy in most patients.

Medicare National Coverage

The Centers for Medicare & Medicaid Services has determined that the evidence is adequate to conclude that, when recognized clinical risk factors are employed to select individuals 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 (110.23, formerly 110.8.1).[29] This technique "is reasonable and necessary for beneficiaries of any age with primary amyloid light chain (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%."

In addition, autologous HCT "must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy … and/or radiotherapy used to treat various malignancies."

Regulatory Status

The US 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.

References

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History

Date	Comments
05/01/19	New policy, approved April 18, 2019. This policy replaces 8.01.530. Policy created with literature review through October 2018. Autologous hematopoietic cell transplantation may be considered medically necessary to treat primary systemic (AL) amyloidosis. Allogeneic hematopoietic cell transplantation is considered investigational to treat primary systemic AL.
04/01/20	Annual Review, approved March 19, 2020. Policy updated with literature review through November 2019; no references added. Policy statements unchanged. Removed CPT code 38242, does not match criteria.
04/01/21	Annual Review, approved March 2, 2021. Policy updated with literature review through November 25, 2020; references added. Policy statements unchanged. Update Related Policies, removed reference to 8.01.22 and replaced with 8.01.538.

Date	Comments
05/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
04/01/22	Annual Review, approved March 22, 2022. Policy updated with literature review through November 15, 2021; references added. Policy statements unchanged.
10/01/22	Coding update. Removed HCPCS code S2140.
04/01/23	Annual Review, approved March 6, 2023. Policy updated with literature review through December 6, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Annual Review, approved March 25, 2024. Policy updated with literature review through November 13, 2023; no references added. Policy statements unchanged.
10/09/24	Minor update. Removed policy 8.01.538 Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias from the Related Policy section.
04/01/25	Annual Review, approved March 10, 2025. Policy updated with literature review through December 2, 2024; no references added. Policy statements unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.