MASSACHUSETTS

Blue Cross Blue Shield of Massachusetts is an Independent Licensee of the Blue Cross and Blue Shield Association

Medical Policy

Hematopoietic Cell Transplantation for Primary Amyloidosis

Table of Contents

- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 181

BCBSA Reference Number: 8.01.42
NCD/LCD: N/A

Related Policies

- Placental and Umbilical Cord Blood as a Source of Stem Cells, #285

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Autologous hematopoietic stem-cell transplantation to treat primary systemic amyloidosis is considered **MEDICALLY NECESSARY**.

Allogeneic hematopoietic stem-cell transplantation to treat primary systemic amyloidosis is **INVESTIGATIONAL.**

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue[SM]	Prior authorization is **required**.
Medicare PPO Blue[SM]	Prior authorization is **required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

HCPCS Codes

HCPCS codes:	Code Description
S2150	Bone marrow or blood-derived peripheral stem-cell (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications including pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition.

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
30233Y0	Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30263Y0	Transfusion of Autologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
3E03305	Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach
3E04305	Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach
3E05305	Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach
3E06305	Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach

Description

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 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.

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 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
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). 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 policy #285.

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 allo-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 allo-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 the 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 allo-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 allo-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 evidence review, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

Summary

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).

For individuals who have primary amyloidosis who receive autologous HCT, the evidence includes a randomized controlled trial, 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 10years 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 (allo-) HCT, the evidence includes case reports. The relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity and mortality. Evidence on the use of allo-HCT is sparse and has shown 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, allo-HCT is not recommended. Thus, autologous HCT may be considered medically necessary for primary amyloidosis, and allo-HCT for primary amyloidosis is considered investigational.

Policy History

Date	Action
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.

1/2019	Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.
3/2018	New references added from BCBSA National medical policy.
2/2018	Clarified coding information.
1/2017	New references added from BCBSA National medical policy.
9/2015	Clarified coding information.
3/2015	New references added from BCBSA National medical policy.
6/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
5/2014	New references from BCBSA National medical policy.
12/2012	Updated to add new CPT code 38243.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
7/2011	Medical Policy Group – Hematology and Oncology. No changes to policy statements.
5/1/2010	Medical Policy 181 effective 5/1/2010describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Jones NF, Hilton PJ, Tighe JR, Hobbs JR. Treatment of "primary" renal amyloidosis with melphalan. Lancet. Sep 23 1972;2(7778):616-619. PMID 4116774
2. Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation, prognosis, and therapy. Mayo Clin Proc. May 1999;74(5):490-494. PMID 10319082
3. Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood. Jun 15 2002;99(12):4276-4282. PMID 12036853
4. Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. Blood. May 15 1998;91(10):3662-3670. PMID 9573002
5. Moreau P, Leblond V, Bourquelot P, et al. Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. Br J Haematol. Jun 1998;101(4):766-769. PMID 9674753
6. Dispenzieri A, Lacy MQ, Kyle RA, et al. Eligibility for hematopoietic stem-cell transplantation for primary systemic amyloidosis is a favorable prognostic factor for survival. J Clin Oncol. Jul 15 2001;19(14):3350-3356. PMID 11454882
7. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood. May 15 2004;103(10):3960-3963. PMID 14739213
8. Gertz MA, Lacy MQ, Dispenzieri A. Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: a status report. Bone Marrow Transplant. Mar 2000;25(5):465-470. PMID 10713619
9. Saba N, Sutton D, Ross H, et al. High treatment-related mortality in cardiac amyloid patients undergoing autologous stem cell transplant. Bone Marrow Transplant. Oct 1999;24(8):853-855. PMID 10516696
10. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. Sep 13 2007;357(11):1083-1093. PMID 17855669

11. Parmar S, Kongtim P, Champlin R, et al. Auto-SCT improves survival in systemic light chain amyloidosis: a retrospective analysis with 14-year follow-up. Bone Marrow Transplant. Aug 2014;49(8):1036-1041. PMID 24887378
12. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med. Jan 20 2004;140(2):85-93. PMID 14734330
13. Vesole DH, Perez WS, Akasheh M, Boudreau C, Reece DE, Bredeson CN. High-dose therapy and autologous hematopoietic stem cell transplantation for patients with primary systemic amyloidosis: a Center for International Blood and Marrow Transplant Research Study. Mayo Clin Proc. Jul 2006;81(7):880-888. PMID 16835967
14. Cibeira MT, Sanchorawala V, Seldin DC, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem cell transplantation: long-term results in a series of 421 patients. Blood. Oct 20 2011;118(16):4346-4352. PMID 21828140
15. Madan S, Kumar SK, Dispenzieri A, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. Blood. Feb 2 2012;119(5):1117-1122. PMID 22147893
16. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood. Nov 15 2007;110(10):3561-3563. PMID 17673601
17. D'Souza A, Dispenzieri A, Wirk B, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: a Center for International Blood and Marrow Transplant Research study. J Clin Oncol. Nov 10 2015;33(32):3741-3749. PMID 26371138
18. Dispenzieri A, Seenithamby K, Lacy MQ, et al. Patients with immunoglobulin light chain amyloidosis undergoing autologous stem cell transplantation have superior outcomes compared with patients with multiple myeloma: a retrospective review from a tertiary referral center. Bone Marrow Transplant. Oct 2013;48(10):1302-1307. PMID 23604010
19. Girnius S, Seldin DC, Meier-Ewert HK, et al. Safety and efficacy of high-dose melphalan and auto-SCT in patients with AL amyloidosis and cardiac involvement. Bone Marrow Transplant. Mar 2014;49(3):434-439. PMID 24317129
20. Jimenez-Zepeda VH, Franke N, Reece DE, et al. Autologous stem cell transplant is an effective therapy for carefully selected patients with AL amyloidosis: experience of a single institution. Br J Haematol. Mar 2014;164(5):722-728. PMID 24266428
21. Kim SJ, Lee GY, Jang HR, et al. Autologous stem cell transplantation in light-chain amyloidosis patients: a single-center experience in Korea. Amyloid. Dec 2013;20(4):204-211. PMID 23914780
22. Sanchorawala V, Hoering A, Seldin DC, et al. Modified high-dose melphalan and autologous SCT for AL amyloidosis or high-risk myeloma: analysis of SWOG trial S0115. Bone Marrow Transplant. Nov 2013;48(12):1537-1542. PMID 23852321
23. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. Br J Haematol. Feb 2008;140(4):365-377. PMID 18162121
24. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Nov 2015;21(11):1863-1869. PMID 26256941
25. Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. Br J Haematol. Jan 2015;168(2):186-206. PMID 25303672
26. National Comprehensive Cancer Network (NCCN). NCCN Clincal Practice Guidelines in Oncology: Systemic Light Chain Amyloidosis. Version 1.2018. https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf. Accessed December 6, 2018.
27. D'Sa S, Kersten MJ, Castillo JJ, et al. Investigation and management of IgM and Waldenstrom-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel. Br J Haematol. Mar 2017;176(5):728-742. PMID 28198999
28. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&NCAId=9&type=Open&bc=ACAAAAAACAAAAA%3d%3d&. Accessed December 6, 2018.