LifeWise
Health Plan of Washington

MEDICAL POLICY – 8.01.531

Hematopoietic Cell Transplantation for Waldenström Macroglobulinemia

BCBSA Ref. Policy:	8.01.54
Effective Date:	Oct. 1, 2024
Last Revised:	Sept. 23, 2024
Replaces:	8.01.54

RELATED MEDICAL POLICIES:

8.01.29	Hematopoietic Cell Transplantation for Hodgkin Lymphoma
8.01.42	Hematopoietic Cell Transplantation for Primary Amyloidosis
8.01.539	Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
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

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Introduction

Waldenström macroglobulinemia (WM) is a rare type of non-Hodgkin lymphoma termed a lymphoplasmacytic lymphoma (LPL), which is a cancer that starts in a type of white blood cells called lymphocytes. WM causes the body to create a lot of an abnormal protein called macroglobulin. A stem cell transplant using the individual's own cells may be one treatment option. Stem cells are collected from the individual and stored. After the individual receives high-dose chemotherapy, the 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 WM is investigational (unproven). There is not enough scientific evidence to show that it works in this situation.

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 as salvage therapy of chemosensitive Waldenström macroglobulinemia.**

Service	Investigational
Allogeneic hematopoietic cell transplantation	**Allogeneic hematopoietic cell transplantation is considered investigational to treat Waldenström macroglobulinemia.**

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 • Prior treatment (if any) individual has received

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	
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 outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative

Code	Description
	services; and the number of days of pre- and posttransplant care in the global definition

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Related Information

N/A

Evidence Review

Description

Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in individuals 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 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. Cord blood is discussed in greater detail in a separate medical policy (see **Related Policies**).

Background

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is a clonal disorder of B lymphocytes that accounts for 1% to 2% of hematologic malignancies, with an estimated 1500 new cases annually in the United States (US). Symptoms include weakness, headaches, stroke-like symptoms (confusion, loss of coordination), vision problems, excessive bleeding, unexplained weight loss, and frequent

infections. The median age of WM individuals is 63 to 68 years, with men comprising 55% to 70% of cases. Median survival of WM ranges from 5 to 10 years, with age, hemoglobin concentration, serum albumin level, and β_2-microglobulin level as predictors of outcome.

The Revised European American Lymphoma and World Health Organization classification and a consensus group formed at the Second International Workshop on Waldenström's macroglobulinemia recognize WM primarily as a lymphoplasmacytic lymphoma (LPL) with an associated immunoglobulin M (IgM) monoclonal gammopathy. The definition also requires the presence of a characteristic pattern of bone marrow infiltration with small lymphocytes demonstrating plasmacytic differentiation with variable cell surface antigen expression. The Second International Workshop indicated that no minimum serum concentration of IgM is necessary for a diagnosis of WM.

Treatment

The goal of therapy for individuals with WM is to achieve symptomatic relief and reduce organ damage without compromising quality of life. Treatment of WM is indicated only in symptomatic individuals and should not be initiated solely on the basis of serum IgM concentration. Clinical and laboratory findings that indicate the need for therapy of diagnosed WM include a hemoglobin concentration less than 10 g/dL; platelet count less than 100,000/μL; significant adenopathy or organomegaly; symptomatic Ig-related hyperviscosity (>50 g/L); severe neuropathy; amyloidosis; cryoglobulinemia; cold-agglutinin disease; or evidence of disease transformation.

Primary chemotherapeutic options in individuals that may undergo autologous HCT often combine rituximab with other agents (e.g., dexamethasone, cyclophosphamide, bortezomib, bendamustine, Bruton Kinase Inhibitors such as ibrutinib and others). Other agents may also be used including purine analogues (cladribine, fludarabine). Plasma exchange is indicated for acute treatment of symptomatic hyperviscosity.

Conventional Preparative Conditioning for HCT

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 individuals' bone marrow space. While the slower graft-versus-malignancy effect is considered 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 graft-versus-host disease, which also increases susceptibility of the individual to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy 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 remission. Individuals who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not graft-versus-host disease.

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 radiotherapy 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 graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary 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 individual 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 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 WM who receive HCT, the evidence includes case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Several retrospective series have evaluated HCT for WM. Analyses of registry data have found 5 year overall survival rates of 52% after allogeneic HCT and 68.5% after autologous HCT. The total number of individuals studied is small and there is a lack of published controlled studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

There currently are no ongoing trials that might influence this review.

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. Input indicated that autologous hematopoietic cell transplantation may be considered medically necessary as salvage therapy for WM that is chemosensitive. Input was mixed on use of allogeneic hematopoietic cell transplantation, with comments suggesting the procedure be performed as part of a clinical trial.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on WM and lymphoplasmacytic lymphoma (v.1.2021) indicate that, for individuals with previously treated WM, stem cell transplantation may be appropriate in selected cases with either: high-dose therapy with autologous stem cell

rescue or allogeneic cell transplant (myeloablative or nonmyeloablative).[4] The Network noted that allogeneic cell transplantation "should ideally be undertaken in the context of a clinical trial." For potential autologous cell transplantation candidates, the guidelines also provide suggested treatment regimens considered non-stem-cell toxic.

Mayo Clinic Cancer Center

In 2017, the Mayo Clinic Cancer Center updated its guidelines on the diagnosis and management of WM.[5] The guidelines noted that individuals who are potentially eligible for autologous hematopoietic cell transplantation (HCT; < 70 years of age and with chemosensitive disease), should consider harvesting stem cells during first remission after a low tumor burden has been achieved. The guidelines recommended: "Autologous HCT should be considered for first or second relapse in transplant-eligible individuals with chemosensitive disease, especially if the first remission duration is short (< 2 years). Individuals with refractory WM should not be offered [autologous HCT] (level 3, grade B)."

Eighth International Workshop on Waldenström's Macroglobulinemia

In 2016, consensus recommendations from the Eighth International Workshop on WM were published.[6] The panel concluded that autologous HCT is a treatment option for high-risk WM individuals who are eligible for transplant. It further stated that autologous HCT should be offered at early relapses and is not as beneficial once individuals have been exposed to more than three lines of therapy or in those with chemotherapy refractory disease. Regarding allogeneic HCT, it stated that this treatment, "when appropriate, should preferably be considered in the context of clinical trials."

Myeloma Foundation of Australian

In 2017, the Myeloma Foundation of Australia published practice guidelines on the treatment of individuals with WM.[7] The guidelines provided the following treatment recommendation for HCT: "Younger individuals with good physical fitness should be considered for autologous and allogeneic stem cell transplantation at first or second relapse and should avoid stem cell-toxic therapies such as fludarabine (Level III, grade C)."

Medicare National Coverage

There is no national coverage determination.

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

1. Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. May 01 2010; 28(13): 2227-32. PMID 20368570
2. Cornell RF, Bachanova V, D'Souza A, et al. Allogeneic Transplantation for Relapsed Waldenstrom Macroglobulinemia and Lymphoplasmacytic Lymphoma. Biol Blood Marrow Transplant. Jan 2017; 23(1): 60-66. PMID 27789362
3. Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenstrom macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. Nov 20 2010; 28(33): 4926-34. PMID 20956626
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 1.2021. **https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf**. Accessed July 29, 2024.
5. Kapoor P, Ansell SM, Fonseca R, et al. Diagnosis and Management of Waldenstrom Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. JAMA Oncol. Sep 01 2017; 3(9): 1257-1265. PMID 28056114
6. Leblond V, Kastritis E, Advani R, et al. Treatment recommendations from the Eighth International Workshop on Waldenstrom's Macroglobulinemia. Blood. Sep 08 2016; 128(10): 1321-8. PMID 27432877
7. Talaulikar D, Tam CS, Joshua D, et al. Treatment of patients with Waldenstrom macroglobulinaemia: clinical practice guidelines from the Myeloma Foundation of Australia Medical and Scientific Advisory Group. Intern Med J. Jan 2017; 47(1): 35-49. PMID 28076910

History

Date	Comments
05/12/14	New PR policy replacing 8.01.54. Autologous hematopoietic stem-cell transplantation may be considered medically necessary as salvage therapy of chemosensitive Waldenstrom macroglobulinemia in select patients when criteria are met (qualifying criteria added to policy), considered investigational outside of qualifying criteria unless enrolled in a clinical trial.
02/03/15	Update Related Policies. Remove 8.01.23 and 8.01.28.
04/24/15	Annual Review. Policy updated with literature review; no change in policy statements.
11/04/16	Coding Update. Transplant benefit-related codes removed.
12/01/16	Annual review, approved November 8, 2016. No changes to the policy statement.
03/01/17	Annual review, approved February 14, 2017. Policy updated with literature review through October 26, 2016; references 2 and 5 added. Policy statements unchanged.
04/01/17	Update Related Policies; updated two titles.
06/09/17	Coding update; updated description for CPT codes 38240 and 38241.
10/17/17	Minor update. Updated title of this policy and related policy.
12/01/17	Policy moved into new format; no change to policy statements.
07/01/18	Annual Review, approved June 5, 2018. No changes were made to the policy statements.
04/01/19	Annual Review, approved March 5, 2019. Policy updated with literature review through December 2018. No references added, reference 4 updated. Policy statements unchanged.
04/01/20	Coding update. Removed CPT code 38242, does not match criteria.
06/01/20	Annual Review, approved May 21, 2020. Policy updated with literature review through November 2019; no references added. Policy statements unchanged.
04/01/21	Annual Review, approved March 23, 2021. Policy updated with literature review through October 19, 2020; no references added. Policy statements unchanged.
05/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
12/01/22	Annual Review, approved November 7, 2022. No changes to the policy statement. Removed Clinical Trial table as the trials were outdated. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/24	Annual Review, approved December 11, 2023. No changes to the policy statement.
04/11/24	Minor update to related policies. 8.01.21 was replaced by 8.01.539 Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms.
10/01/24	Annual Review, approved September 23, 2024. No changes to policy statements. Added HCPCS code S2150 to match policy criteria.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

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.