MEDICAL POLICY

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR WALDENSTROM MACROGLOBULINEMIA
POLICY NUMBER	MP 9.046

Effective Date:	6/1/2023

I. POLICY

Autologous hematopoietic cell transplantation may be considered **medically necessary** as salvage therapy of chemosensitive Waldenstrom macroglobulinemia.

Allogeneic hematopoietic cell transplantation is considered **investigational** to treat Waldenstrom macroglobulinemia. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. The National Cancer Institute's PDQ (Physician Data Query) is NCI's comprehensive source of cancer information, which includes evidence-based summaries on topics that cover adult and pediatric cancer treatment. These guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital BlueCross when determining medical necessity according to this policy.

Cross-references:

MP-9.042 Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
MP-9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.

II. PRODUCT VARIATIONS TOP

This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO: Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND TOP

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. 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 patients 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 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 no minimum serum concentration of IgM is necessary for a diagnosis of WM.

Treatment

The goal of therapy for patients with WM is to achieve symptomatic relief and reduce organ damage without compromising quality of life. Treatment of WM is indicated only in symptomatic patients 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 patients that may undergo autologous hematopoietic cell transplantation (HCT) often combine rituximab with other agents (e.g., dexamethasone, cyclophosphamide, bortezomib, bendamustine), but 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 patients' 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 patients who are sufficiently fit medically to tolerate substantial adverse events 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 HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the patient 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 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 remission. Patients 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 nonrelapse 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 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 evidence review, the term *reduced-intensity conditioning* 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.

IV. RATIONALE

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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 patients 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.

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V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes							
38205	38230	38240	38242				

Covered when medically necessary:

Procedure Codes							
38204	38206	38207	38208	38209	38210	38211	38212
38213	38214	38215	38232	38241	38243	S2150	

ICD-10-CM Diagnosis Code	Description
C88.0	Waldenstrom macroglobulinemia

IX. REFERENCES

TOP

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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):4926-4934. PMID 20956626*
4. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 1.2023.*
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 1, 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 8, 2016;128(10):1321-1328. 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*
8. *Ansell SM. Epidemiology, Pathogenesis, Clinical Manifestations, and Diagnosis of Waldenström Macroglobulinemia In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated March 29, 2022. Literature review current through: Feb 2023*
9. *Ansell SM. Treatment and Prognosis of Waldenström Macroglobulinemia . UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated May 26, 2022. Literature review current through: Feb 2023*
10. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 8.01.54, Hematopoietic Cell Transplantation for Waldenstrom Magrogloulinemia. March 2021*

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X. POLICY HISTORY

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MP 9.046	**CAC 5/20/14** Minor. Information on HSCT for Waldenstrom Macoglobulinemia was extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. References updated. Rationale section added.
	CAC 6/2/15 Consensus review. No change to policy statements. References and rationale reviewed. Codes reviewed.
	CAC 5/31/16 Consensus review. No change to policy statements. References and rationale reviewed. Coding reviewed.
	Admin update 1/1/17: Product variation section reformatted.
	CAC 5/23/17 Consensus review. Clarification: "hematopoietic stem cell transplantation" changed to "hematopoietic cell transplantation" per NCCN terminology change (title and policy language revised). Policy statements unchanged. Regulatory Status added. Cross References, Description/Background, Rationale and Reference sections updated. Coding reviewed.
	10/24/17 Administrative Update – CPT codes 38220 and 38221 removed from policy as they are not applicable.
	1/1/18 Admin Update: Medicare variations removed from Commercial Policies.
	2/27/18 Consensus. No change to policy statements. Background, rationale, and references updated.
	2/12/19 Consensus review. No change to the policy statements. References reviewed. Rationale revised.
	2/27/20 Consensus review. References reviewed. No change to policy statement or coding.
	2/15/21 Consensus review. No change to policy statement. References updated.
	7/18/2022 Consensus Review. No change in policy statement. References updated and coding reviewed. NCCN statement added.
	3/6/2023 Consensus Review. No change in policy statement. References updated. Coding reviewed.

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